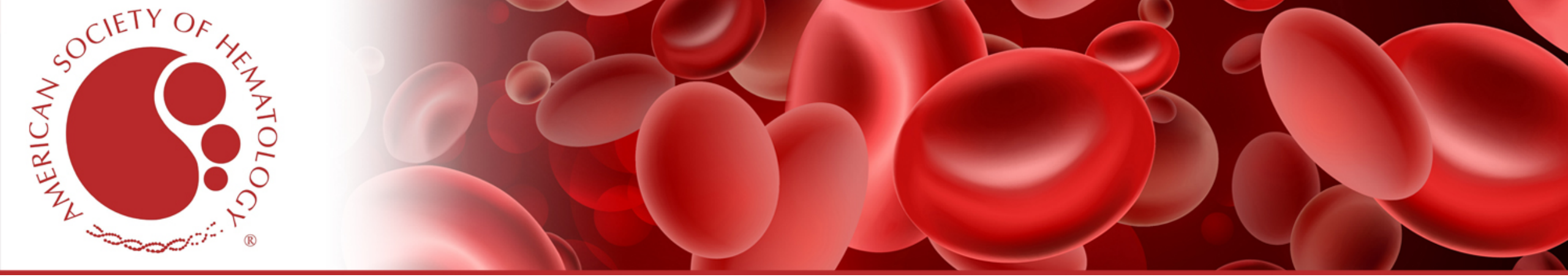

Early Initiation of Treatment with Rivipansel for Acute Vaso-Occlusive Crisis in Sickle Cell Disease (SCD) Achieves Earlier Discontinuation of IV Opioids and Shorter Hospital Stay: RESET Clinical Trial Analysis

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Session Name: 114. Hemoglobinopathies, Excluding Thalassemia

Clinical: Novel Treatments for Sickle Cell Disease
Monday, December 7, 2020

Disclosures

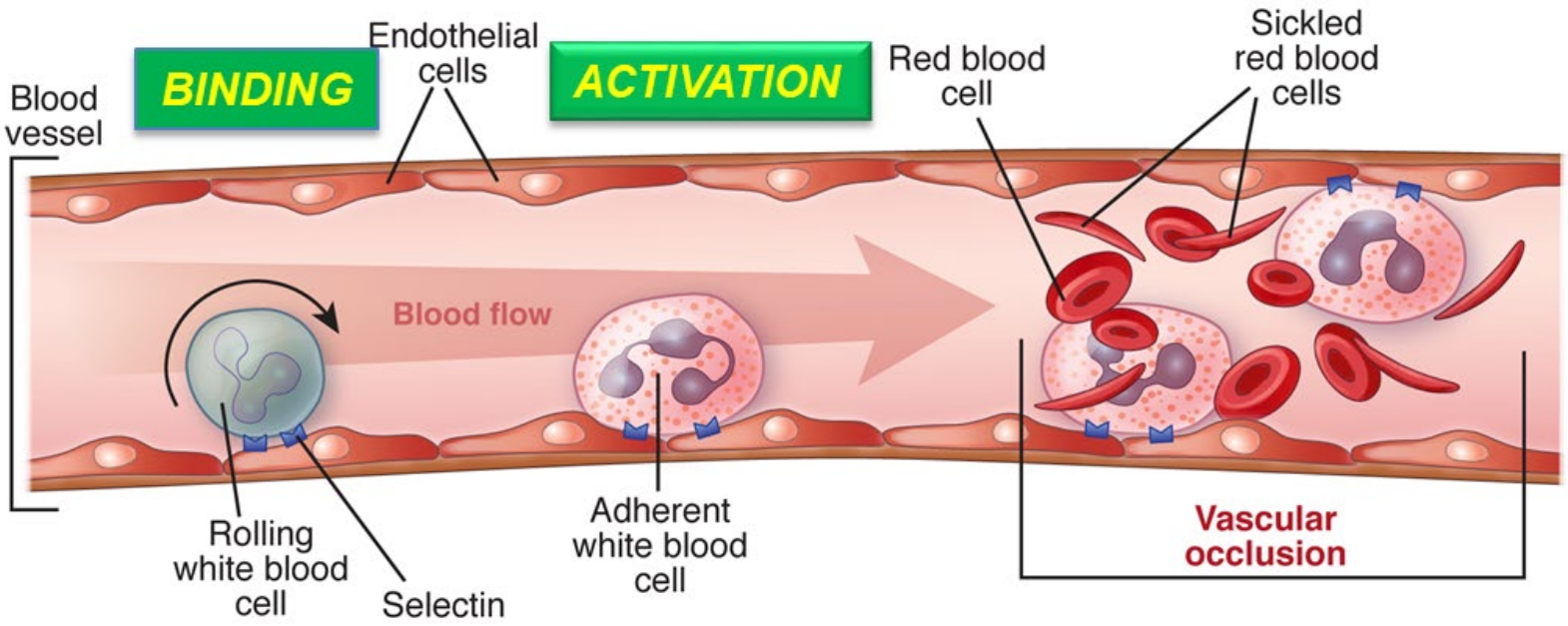
Dr. Wun received research funding from Pfizer to conduct the RESET study.

SCD & Vaso-Occlusive Crisis

- Acute VOC is a major clinical manifestation of SCD, results in frequent hospitalizations, and is associated with chronic morbidity.
- VOC episodes occur despite preventive strategies.
- There remains a need for remittive therapy that will abrogate VOC and reduce the need for hospitalization and opioid use.

E-Selectin and Vaso-Occlusive Crisis

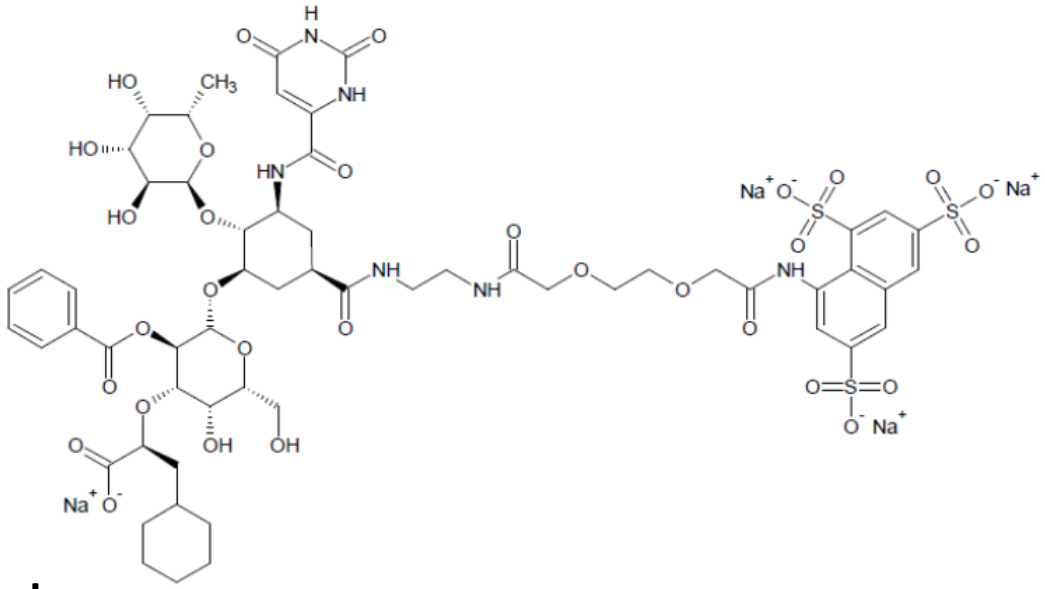
- *Inflammation drives VOC.*
- *Binding to E-selectin activates neutrophils.*
- *Heterotypic Cell-cell aggregation leads to vascular occlusion, ischemia/reperfusion and pain.*



E-selectin mediates <u>early</u> acute inflammation and is critical instigator of <u>acute</u> VOC.
E-selectin inhibition rapidly restores blood flow in SCD mouse models (Chang et al 2010).

Rivipansel and Sickle Cell Disease

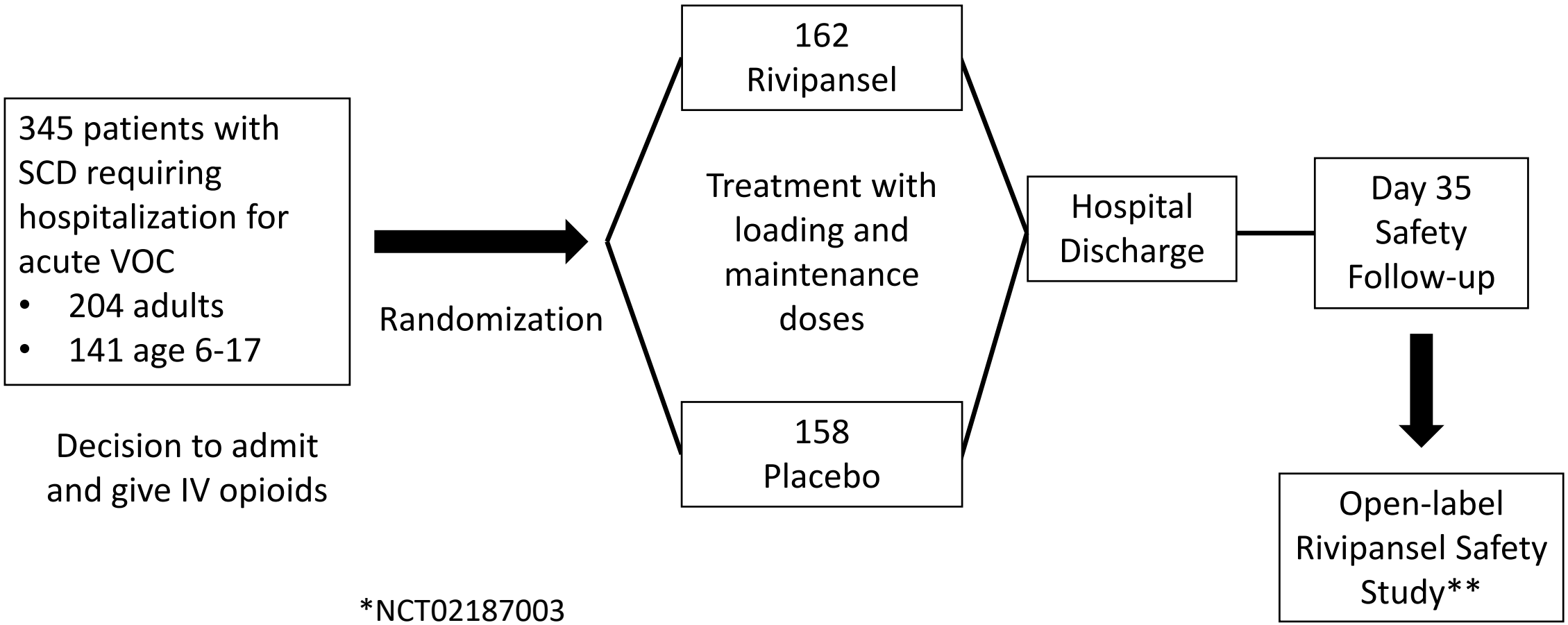
Rivipansel is a carbohydrate-based, pan-selectin inhibitor, with high potency against E-selectin.



Rivipansel demonstrated shorter hospital stays and significantly reduced opioid use in a randomized phase 2 study in acute VOC.

Telen et al., Blood 2015

RESET: Phase 3 Randomized Controlled Trial*



*NCT02187003
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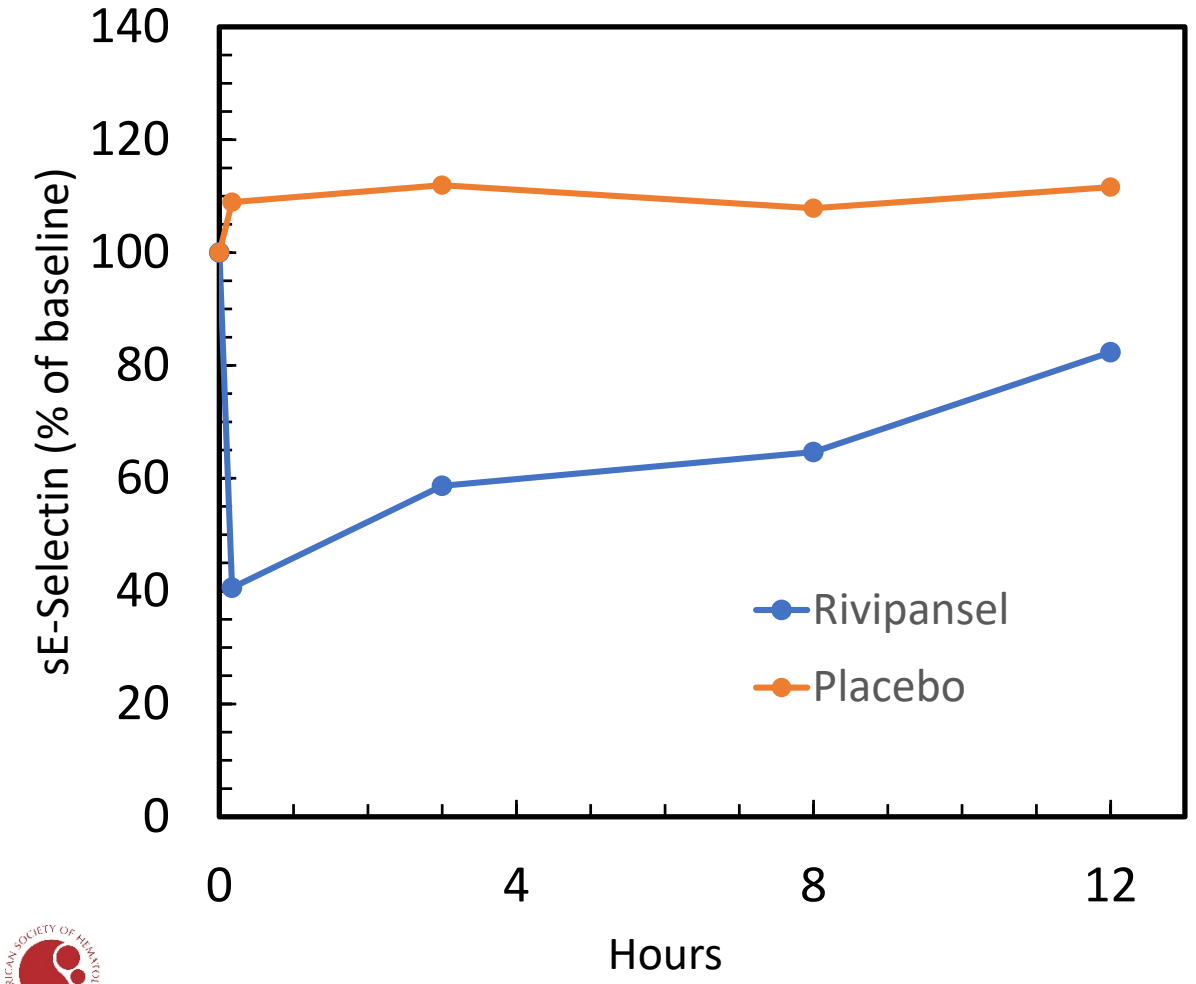
RESET Clinical Trial of Rivipansel in SCD

Primary endpoint: time to readiness for discharge (**TTRFD**), a composite endpoint with a standardized checklist of discharge criteria to be met and agreed upon by Subject and Investigator.

Key secondary endpoints:

- Time to Discharge (**TTD**)
- Time to Discontinuation of IV opioids (**TTDIVO**)
- Cumulative IV Opioid use (**CIVO**)

RESET: On-Target Effect of Rivipansel



In SCD, E-selectin on vascular endothelium is upregulated resulting in shedding of sE-selectin.

Rivipansel: rapid 59% decrease in median sE-selectin levels from baseline with loading dose.

Placebo: median 9% increase in sE-selectin levels from baseline.

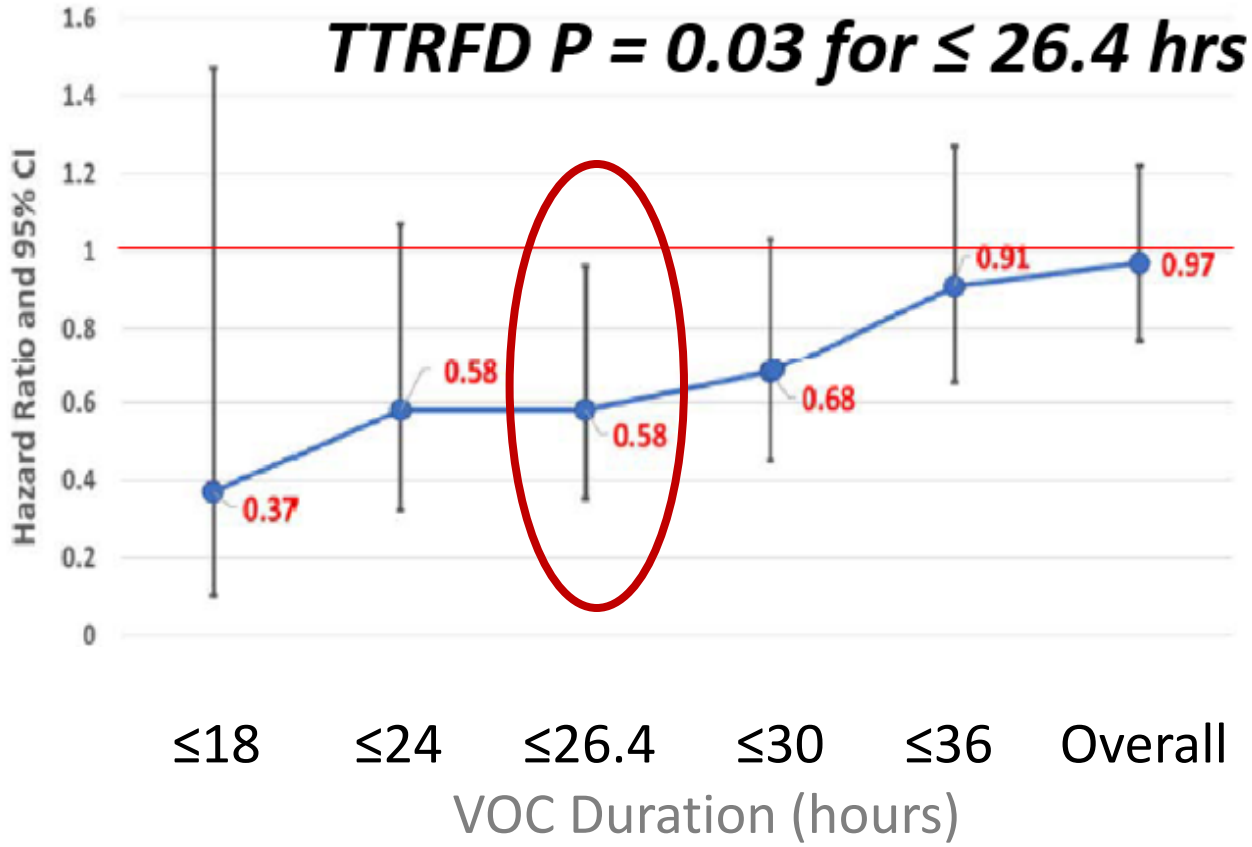
Analysis of RESET and Open Label Extension

Primary analysis of the RESET study did not show a benefit for rivipansel over placebo in the overall population for the primary or secondary outcomes.

BUT…Could E-selectin inhibition with rivipansel earlier in VOC improve outcomes?

- Additional analysis: Determine outcomes by time interval between onset of VOC and treatment initiation with rivipansel or placebo.
- Study Populations Analyzed
  - RESET study (post-hoc): RESET (rivipansel) vs RESET (placebo)
  - Open-Label Extension (OLE): OLE (rivipansel) vs RESET (placebo and rivipansel), using pre-defined outcomes based on RESET analysis.

TTRFD by VOC Duration Before Treatment



Progressive reduction in TTRFD with earlier rivipansel treatment.

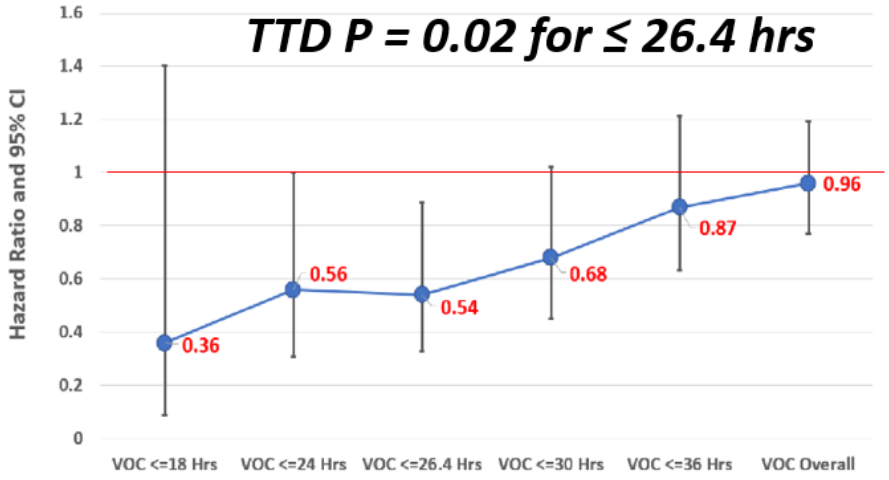
The earliest quartile for treatment in the overall population was **26.4** hrs.

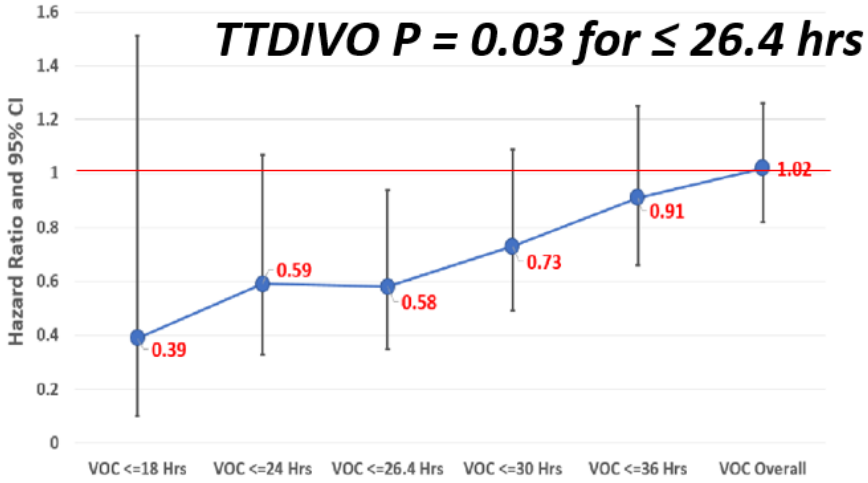
Treatment within 26.4 hrs led to a **56.3** hr decrease in median TTRFD (from 122 to 65.7 hrs).

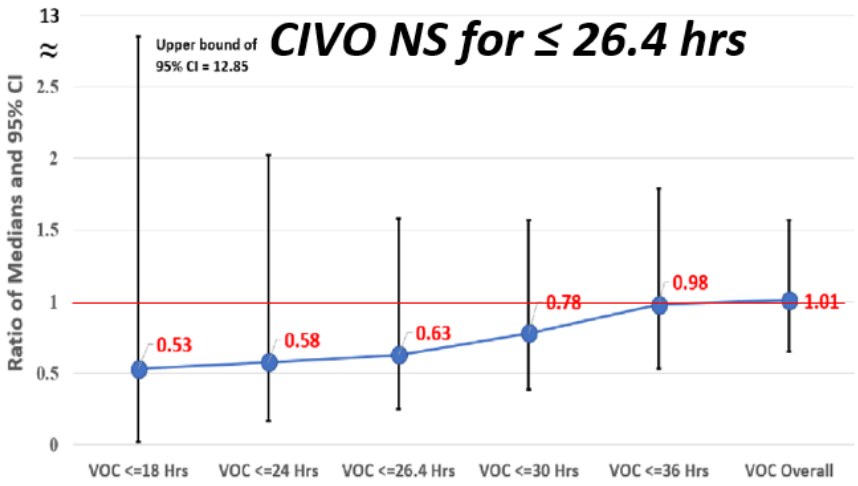
TTD, TTDIVO, CIVO by VOC Duration

Consistent with TTRFD, the key secondary endpoints favor early rivipansel treatment.

TTD & TTDIVO endpoints were significant at 26.4 hours.







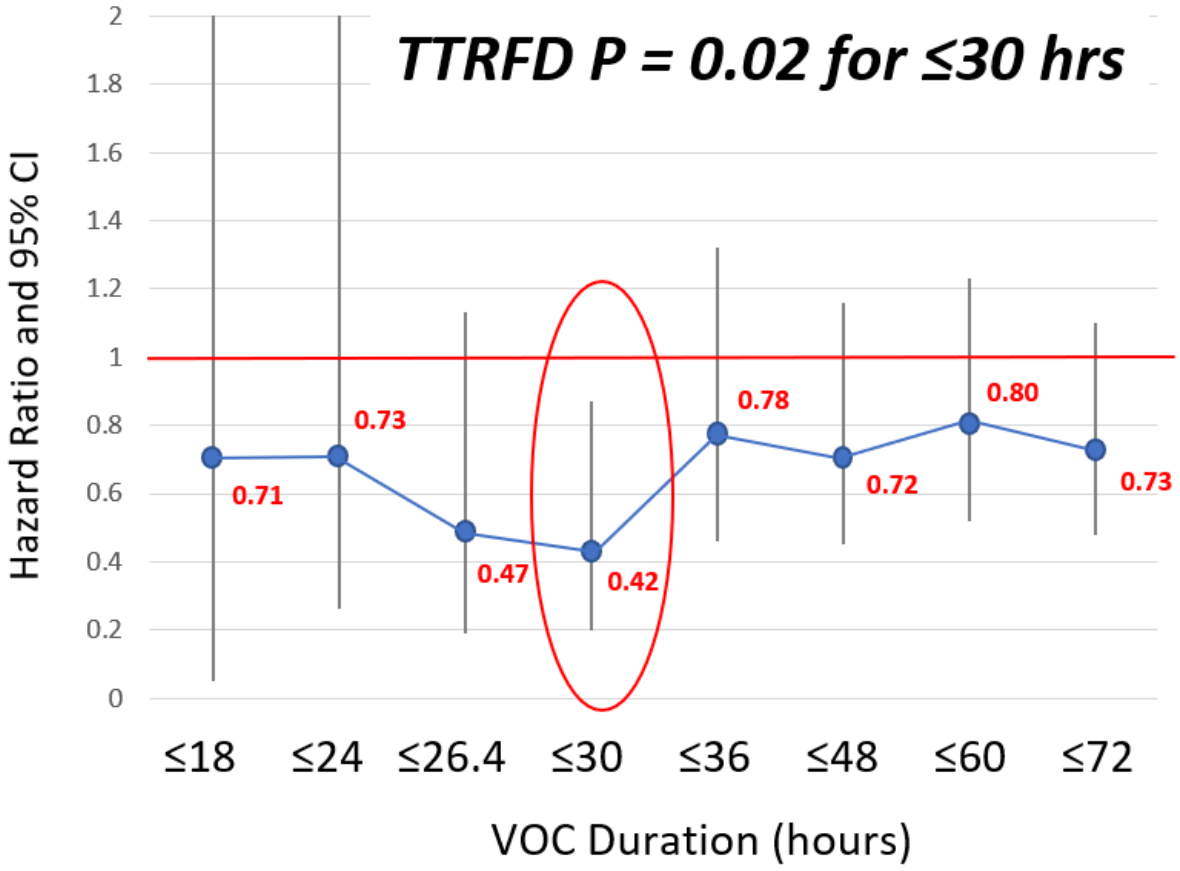
RESET Study: Pediatric Results

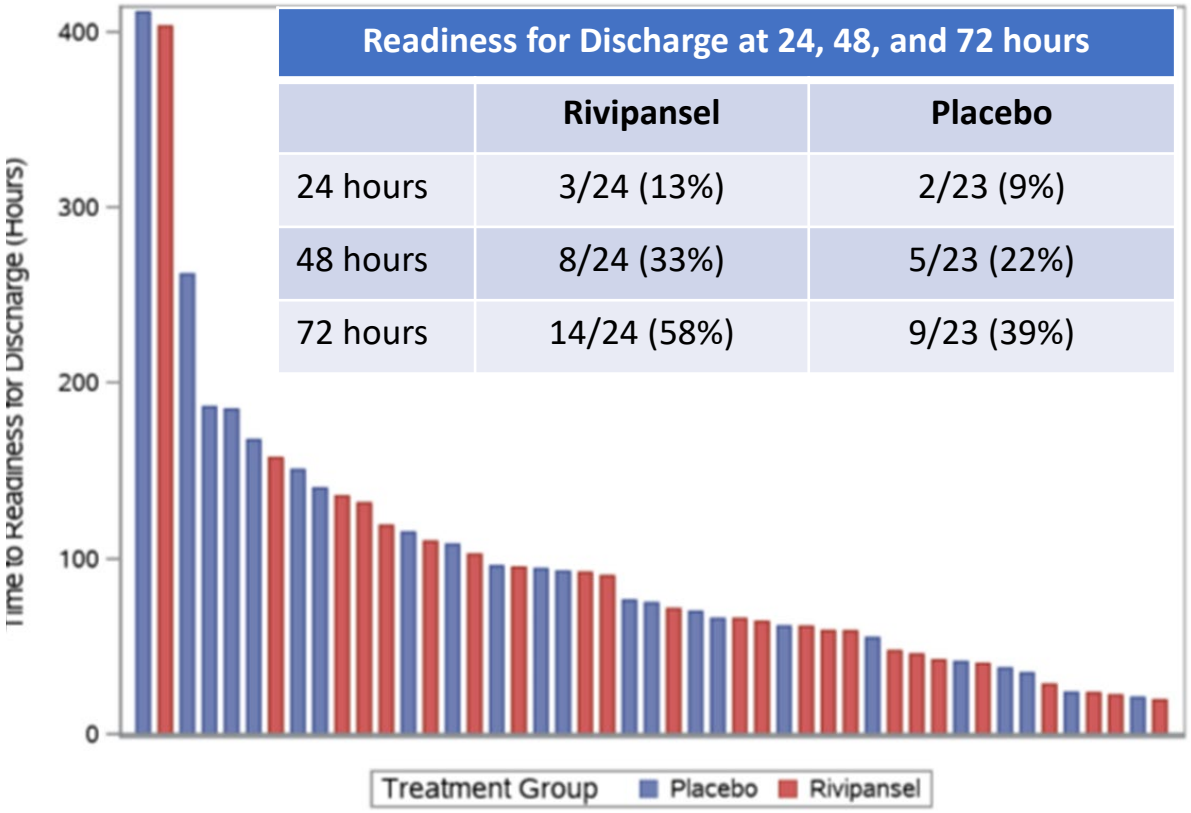
- Children with sickle cell disease contributed almost 10% of hospitalizations for acute VOC in the United States in 2016.*

- Pediatric subjects were well represented in the RESET study.
  - Children from 6-17 yrs (n = 141) constituted 41% of RESET subjects.
  - (71 rivipansel arm/70 placebo arm).

**AHRQ HCUP Statistical Brief #251. September 2019.*

Readiness for Discharge in Pediatric Subjects





Readiness for Discharge at 24, 48, and 72 hours		
	Rivipansel	**Placebo**
24 hours	3/24 (13%)	2/23 (9%)
48 hours	8/24 (33%)	5/23 (22%)
72 hours	14/24 (58%)	9/23 (39%)

Early treatment with rivipansel correlates with more subjects ready for discharge by 72h

Open Label Extension (OLE) Study

Comparison of efficacy data in OLE to RESET.

- **Eligibility**:
  - Enrollment in OLE after RESET participation
- **Demographics (81 subjects):**
  - 43 adult, 38 pediatric subjects.
  - 17 adult, 21 pediatric early treatments
- **Endpoints**:
  - TTD (primary)
  - TTDIVO, CIVO (secondary)

- **Methods of Analysis**

- Superiority analysis compared early rivipansel treatment on OLE to early placebo treatment on RESET
  - 90% CI specified *(p <0.10)*
- Non-Inferiority analysis compared early rivipansel treatment on OLE to early rivipansel on RESET.
  - 20% margin of inferiority specified

OLE Superiority Analysis: TTD

TTD Superiority Analysis Overall Population		
	Rivipansel (OLE)	Placebo (RESET)
Subjects with Early Treatment	38	46
Median TTD (90% CI), hrs	80.89 (67.07, 90.33)	103.97 (91.03, 132.85)
Difference in Median TTD	-23.08 hours	
Hazard Ratio (CI), Log-Rank Test P-value	**0.80 (0.55, 1.16), P = 0.0617**	

TTD Superiority Analysis Pediatric Population		
	Rivipansel (OLE)	Placebo (RESET)
Subjects with Early Treatment	21	23
Median TTD (90% CI), hrs	71.90 (62.48, 89.32)	92.82 (71.22, 121.17)
Difference in Median TTD	-20.92 hours	
Hazard Ratio (CI), Log-Rank Test P-value	**0.58 (0.34, 0.97), P = 0.0797**	

OLE Non-Inferiority Analysis: TTD

TTD Non-Inferiority Analysis Overall Population		
	Rivipansel (OLE)	Rivipansel (RESET)
Subjects with Early Treatment	38	50
Median TTD (90% CI), hrs	80.89 (67.07, 90.33)	71.34 (59.03, 97.10)
Difference in Median TTD	**9.55 hours (non-inferior)**	

TTD Non-Inferiority Analysis Pediatric Population		
	Rivipansel (OLE)	Rivipansel (RESET)
Subjects with Early Treatment	21	24
Median TTD (90% CI), hrs	71.90 (62.48, 89.32)	69.63 (47.72, 97.10)
Difference in Median TTD	**2.27 hours (non-inferior)**	

Conclusions

Initiation of treatment with rivipansel earlier in VOC is associated with potentially meaningful benefit, shortening IV opioid use and hospital stay.

- Benefit may be greater for pediatric patients, for which rivipansel was granted Rare Pediatric Disease Designation (October 5, 2020)

Biomarker data confirm on-target effect, suggesting that the diminishing benefit of later treatment results from downstream pathophysiology independent of E-selectin inhibition.

The benefit of early initiation of treatment found in post-hoc analysis of the RESET study was similar in the subjects treated early with rivipansel in the OLE.

Rivipansel could change the treatment paradigm from one of delay in seeking care to more rapid intervention early in the course of VOC.

- END OF PRESENTATION