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

345 patients with SCD requiring hospitalization for acute VOC
- 204 adults
- 141 age 6-17

Decision to admit and give IV opioids

Randomization

162 Rivipansel
Treatment with loading and maintenance doses

158 Placebo

Hospital Discharge

Day 35 Safety Follow-up

Open-label Rivipansel Safety Study**

*NCT02187003
**NCT02433158
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)
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.

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

TTD & TTDIVO endpoints were significant at 26.4 hours.

**TTD P = 0.02 for ≤ 26.4 hrs**

**TTDIVO P = 0.03 for ≤ 26.4 hrs**

**CIVO NS for ≤ 26.4 hrs**
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

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Rivipansel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>3/24 (13%)</td>
<td>2/23 (9%)</td>
</tr>
<tr>
<td>48 hours</td>
<td>8/24 (33%)</td>
<td>5/23 (22%)</td>
</tr>
<tr>
<td>72 hours</td>
<td>14/24 (58%)</td>
<td>9/23 (39%)</td>
</tr>
</tbody>
</table>

TTRFD P = 0.02 for ≤30 hrs
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

<table>
<thead>
<tr>
<th></th>
<th>Rivipansel (OLE)</th>
<th>Placebo (RESET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Early Treatment</td>
<td>38</td>
<td>46</td>
</tr>
<tr>
<td>Median TTD (90% CI), hrs</td>
<td>80.89 (67.07, 90.33)</td>
<td>103.97 (91.03, 132.85)</td>
</tr>
<tr>
<td>Difference in Median TTD</td>
<td>-23.08 hours</td>
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</tr>
<tr>
<td>Hazard Ratio (CI), Log-Rank Test P-value</td>
<td><strong>0.80 (0.55, 1.16)</strong>, P = 0.0617</td>
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</tr>
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</table>

## TTD Superiority Analysis Pediatric Population

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<tr>
<td>Subjects with Early Treatment</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>Median TTD (90% CI), hrs</td>
<td>71.90 (62.48, 89.32)</td>
<td>92.82 (71.22, 121.17)</td>
</tr>
<tr>
<td>Difference in Median TTD</td>
<td>-20.92 hours</td>
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<tr>
<td>Hazard Ratio (CI), Log-Rank Test P-value</td>
<td><strong>0.58 (0.34, 0.97)</strong>, P = 0.0797</td>
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</tbody>
</table>
# OLE Non-Inferiority Analysis: TTD

## TTD Non-Inferiority Analysis Overall Population

<table>
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<th>Rivipansel (OLE)</th>
<th>Rivipansel (RESET)</th>
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<tbody>
<tr>
<td>Subjects with Early Treatment</td>
<td>38</td>
<td>50</td>
</tr>
<tr>
<td>Median TTD (90% CI), hrs</td>
<td>80.89 (67.07, 90.33)</td>
<td>71.34 (59.03, 97.10)</td>
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<tr>
<td>Difference in Median TTD</td>
<td><strong>9.55 hours (non-inferior)</strong></td>
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## TTD Non-Inferiority Analysis Pediatric Population

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<td>Subjects with Early Treatment</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Median TTD (90% CI), hrs</td>
<td>71.90 (62.48, 89.32)</td>
<td>69.63 (47.72, 97.10)</td>
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<tr>
<td>Difference in Median TTD</td>
<td><strong>2.27 hours (non-inferior)</strong></td>
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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