Initial Safety and Efficacy Results from the Phase II, Multicenter, Open-Label SOLACE-kids Trial of Crizanlizumab in Adolescents with Sickle Cell Disease (SCD)

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www.clinicaltrials.gov (NCT03474965) www.clinicaltrialsregister.eu (2017-001747-12)
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- **Matthew M Heeney** reports consultancy for Novartis, FORMA, AstraZeneca, Vertex/Crispr Therapeutics, bluebird bio, Keros and Cyclerion; research funding from Novartis, AstraZeneca and Cyclerion; honoraria from Keros; and membership of a Data and Safety Monitoring Board for Vertex/CRISPR Therapeutics.

- **Mariane de Montalembert** reports membership on an entity’s Board of Directors or advisory committees for Novartis, Addmedica, bluebird bio and Vertex; and honoraria from Novartis and Addmedica.

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- **Clark Brown** reports consultancy for Global Blood Therapeutics, Imara, Novartis and Novo Nordisk; and research funding from Global Blood Therapeutics, Imara, Novartis, Forma Therapeutics and Pfizer.

- **Yasser Wali** reports research funding from Novartis.

- **Thu Thuy Nguyen** is an employee of Novartis.

- **Du Lam** and **Nadege Pfender** are employees of Novartis and current equity holders in a publicly traded company.

- **Julie Kanter** reports consultancy for Fulcrum Therapeutics.
SCD is an inherited blood disorder with a complex pathophysiology, which is largely driven by vaso-occlusion and hemolytic anemia\(^1\)

Common complications of SCD in pediatric patients can include VOCs (the hallmark of SCD), dactylitis, stroke and acute splenic sequestration\(^1\)–\(^3\)

Dependent on the indication, management options for pediatric patients include analgesics, HU and chronic or acute blood transfusions\(^4,5\)

- These treatments are associated with various possible issues and may only partly reduce the potential for recurrent VOCs\(^6\)

There is an unmet need in pediatric patients with SCD to reduce both the frequency of VOCs and the associated complications patients can experience

HU, hydroxyurea; VOC, vaso-occlusive crisis
Crizanlizumab is a first-in-class humanized mAb that binds to P-selectin and blocks interactions between P-selectin and its ligands

P-selectin is a cell adhesion protein that acts as one of the drivers of multicellular adhesion in SCD pathophysiology\(^1,2\)

In the pivotal Phase II SUSTAIN study of patients with SCD aged \(\geq 16\) years, crizanlizumab 5.0 mg/kg significantly reduced the median annualized rate of VOCs vs placebo\(^4\)

**Pediatric patients with SCD have significantly higher levels of soluble P-selectin (a surrogate marker of P-selectin expression) than healthy controls\(^3\)**

*Stratified Wilcoxon Rank Sum test
AE, adverse event; mAb, monoclonal antibody; IQR, interquartile range; PSGL-1, P-selectin glycoprotein ligand 1
**Crizanlizumab** is a first-in-class humanized mAb that binds to P-selectin and blocks interactions between P-selectin and its ligands.

P-selectin is a cell adhesion protein that acts as one of the drivers of multicellular adhesion in SCD pathophysiology. In the pivotal Phase II SUSTAIN study of patients with SCD aged ≥16 years, crizanlizumab 5.0 mg/kg significantly reduced the median annualized rate of VOCs vs placebo. The frequency of AEs was similar in both the crizanlizumab 5.0 mg/kg and placebo treatment arms. Pediatric patients with SCD have significantly higher levels of soluble P-selectin (a surrogate marker of P-selectin expression) than healthy controls.

- **Crizanlizumab is approved to reduce the frequency of, or prevent recurrent VOCs in, SCD patients aged 16 years or older**

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1. ADAKVEO (crizanlizumab) prescribing information. Available at: [https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761128s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761128s000lbl.pdf) (accessed November 2021);
SOLACE-kids is a Phase II, open-label, multicenter study to assess appropriate dosing and evaluate the safety and efficacy of crizanlizumab in pediatric patients with SCD.

**Primary endpoints**
- PK and PD (P-selectin inhibition) parameters
- Frequency of AEs

**Secondary endpoints**
- Annualized rate of
  - VOCs leading to a healthcare visit
  - VOCs treated at home
  - Hospitalizations and ER visits (both overall and VOC related)
- Other safety measures

**Patients (Target enrollment N≥100)**
- Patients aged 6 months to <18 years
- ≥1 VOC within the preceding 12 months
- Confirmed diagnosis of SCD (any genotype)
- Concomitant HU allowed*

**Part A**
- Part A: confirm and establish dosing‡

**Part B**
- Part B: expand recruitment and evaluate the long-term safety and efficacy of the confirmed dose§

*Must be receiving HU for ≥6 months prior to screening and plan to continue taking it at the same dose and schedule during the trial; †Once the appropriate dose is confirmed in patients aged ≥2 years, patients aged 6 months to <2 years can be included; ‡If unconfirmed, dose will be adjusted based on exposure levels observed in adult patients enrolled in the SOLACE-adults study; §Each group separately or combined in close cut-off dates; **It is planned that at least 100 patients will be enrolled in total

**IV crizanlizumab is administered on Day 1 of Week 1, Day 1 of Week 3, then every 4 weeks thereafter for up to 2 years**
SOLACE-kids is a Phase II, open-label, multicenter study to assess appropriate dosing and evaluate the safety and efficacy of crizanlizumab in pediatric patients with SCD.

The aim of this analysis is to describe the initial safety and efficacy results for patients aged 12 to <18 years enrolled in Group 1 of the SOLACE-kids trial who completed ≥26 weeks of treatment or who discontinued prematurely (n=50)*

*Must be receiving HU for ≥6 months prior to screening and plan to continue taking it at the same dose and schedule during the trial; †Once the appropriate dose is confirmed in patients aged ≥2 years, patients aged 6 months to <2 years can be included; ‡If unconfirmed, dose will be adjusted based on exposure levels observed in adult patients enrolled in the SOLACE-adults study1 (Group 1) or by a population PK model (Groups 2 and 3), and ≥8 additional patients enrolled; §Each group separately or combined in close cut-off dates; **It is planned that at least 100 patients will be enrolled in total.

Group 1
12 to <18 years
Part A
At least 8 enrolled patients
Part B
At least 18 enrolled patients**
15-week post-treatment follow-up

Group 2
6 to <12 years
Part A
At least 8 enrolled patients
Part B
At least 18 enrolled patients**
15-week post-treatment follow-up

Group 3
6 months to <6 years
Part A
At least 8 enrolled patients
Part B
At least 6 enrolled patients**

Primary endpoints
- PK and PD (P-selectin inhibition) parameters
- Frequency of AEs

Patients (Target enrollment N ≥ 100)
- Patients aged 6 months to <18 years
- ≥1 VOC within the preceding 12 months
- Confirmed diagnosis of SCD (any genotype)
- Concomitant HU allowed*
- IV crizanlizumab is administered on Day 1 of Week 1, Day 1 of Week 3, then every 4 weeks thereafter for up to 2 years

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*Data cut-off: 28 August 2020
Patients in Group 1 were representative of the typical SCD population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median (min–max) 14.9 (12.0–17.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 (58.0)</td>
</tr>
<tr>
<td>Male</td>
<td>21 (42.0)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>32 (64.0)</td>
</tr>
<tr>
<td>White</td>
<td>9 (18.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (14.0)</td>
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<tr>
<td>Multiple</td>
<td>2 (4.0)</td>
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<tr>
<td>White, Asian</td>
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Baseline characteristics and duration of exposure

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<thead>
<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Genotype, n (%)</td>
<td></td>
</tr>
<tr>
<td>HbSS</td>
<td>44 (88.0)</td>
</tr>
<tr>
<td>HbSC</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>HbSβ&lt;sup&gt;0&lt;/sup&gt;</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>HbSβ&lt;sup&gt;+&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Concomitant medication, n (%)</td>
<td></td>
</tr>
<tr>
<td>HU</td>
<td>42 (84.0)</td>
</tr>
<tr>
<td>L-glutamine + HU</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>None</td>
<td>6 (12.0)</td>
</tr>
<tr>
<td>Duration of treatment (weeks)</td>
<td>Median (min–max) 36.6 (6–98)</td>
</tr>
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max, maximum; min, minimum
Patients in Group 1 were representative of the typical SCD population

Baseline characteristics and duration of exposure

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All patients in Group 1 received crizanlizumab 5.0 mg/kg and 44 (88%) patients received treatment for ≥26 weeks
No new safety signals were identified in patients aged 12 to <18 years

43 (86%) patients had ≥1 AE

Most commonly reported AEs (all grades)*
- Headache: n=14 (28%)
- Vomiting: n=12 (24%)
- Back pain: n=9 (18%)

Grade ≥3 AEs
- n=13 (26%)

Serious AEs
- n=11 (22%)

Most frequent treatment-related AEs*
- IRR: n=4 (8%)
- Back pain: n=3 (6%)
- Vomiting, dizziness and nausea: n=2 (4%) each

Grade ≥3 treatment-related AEs
- n=1 (2%)†

Treatment-related serious AEs
- n=0

*By preferred term; †Two Grade ≥3 treatment-related AEs (back pain and pain in extremity) were reported in the same patient
No new safety signals were identified in patients aged 12 to <18 years

43 (86%) patients had ≥1 AE

<table>
<thead>
<tr>
<th>AEs leading to dose interruption were reported in 8 (16%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• One AE (infusional headache) was related to crizanlizumab and led to partial dose administration; this resolved on day of onset</td>
</tr>
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| Grade ≥3 AEs n=13 (26%)                |
| Serious AEs n=11 (22%)                |

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<th>Treatment-related AEs were reported in 12 (24%) patients</th>
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| Grade ≥3 treatment-related AEs n=1 (2%)†               |
| Treatment-related serious AEs n=0                      |

All reported changes in liver function parameters during the study were transient and may be attributed to fluctuating degrees of hemolysis expected in patients with SCD

*By preferred term; †Two Grade ≥3 treatment-related AEs (back pain and pain in extremity) were reported in the same patient

See supplementary slides for further information on changes in liver function parameters
No effects on hemostasis or infections were related to treatment*

<table>
<thead>
<tr>
<th>Effect on hemostasis</th>
<th>Infections</th>
</tr>
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<tbody>
<tr>
<td>All grades n=5 (10%)</td>
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<td>No Grade ≥3 AEs</td>
<td>Grade ≥3 n=2 (4%)</td>
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<td>n=1 (2%) were related to treatment</td>
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</tbody>
</table>

One patient died of presumed bacterial meningitis (not considered treatment related)

*AEs of special interest chosen based on the crizanlizumab mechanism of action and those potentially related to treatment with monoclonal antibodies
Potential IRRs were assessed using three different search strategies*

**Effect on hemostasis**
- All grades, n=5 (10%)
- No Grade ≥3 AEs

No AEs were related to treatment, and all had resolved by data cut-off

**Infections**
- All grades, n=23 (46%)
- Grade ≥3, n=2 (4%)

n=1 (2%) were related to treatment

One patient died of presumed bacterial meningitis (not considered treatment related)

**Potential severe IRRs**

**Definition**

Events more likely to be caused by the infusion and to have a potentially more severe clinical course occurring any time after infusion (regardless of grade and causality)

*AEs of special interest chosen based on the crizanlizumab mechanism of action and those potentially related to treatment with monoclonal antibodies; †Not including VOCs
Potential severe IRRs considered treatment-related occurred in <10% of patients and none were serious

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No AEs were related to treatment, and all had resolved by data cut-off

n=1 (2%) were related to treatment
One patient died of presumed bacterial meningitis (not considered treatment related)

No AEs were serious and n=4 (8%) were related to treatment

No case of anaphylaxis to crizanlizumab was reported
Potential IRRs were assessed using three different search strategies*

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| **All grades**  
  n=5 (10%)  
  No Grade ≥3 AEs | All grades  
  n=23 (46%)  
  Grade ≥3  
  n=2 (4%)  
  n=1 (2%) were related to treatment  
  One patient died of presumed bacterial meningitis (not considered treatment related) | All grades  
  n=6 (12%)  
  No Grade ≥3 AEs  
  No AEs were related to treatment  
  No case of anaphylaxis to crizanlizumab was reported |

No AEs were related to treatment, and all had resolved by data cut-off

<table>
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<tr>
<th>Signs/symptoms indicative of possible IRR</th>
</tr>
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<tbody>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Excluded infusion site-reaction and intended to identify the <strong>most common, non-specific, potential signs and symptoms</strong> indicative of IRRs occurring on the day of infusion</td>
</tr>
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*AEs of special interest chosen based on the crizanlizumab mechanism of action and those potentially related to treatment with monoclonal antibodies; †Not including VOCs
Most signs and symptoms of potential IRRs were mild and non-serious

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No AEs were related to treatment, and all had resolved by data cut-off

n=1 (2%) were related to treatment
One patient died of presumed bacterial meningitis (not considered treatment related)

No AEs were serious and n=4 (8%) were related to treatment
No case of anaphylaxis to crizanlizumab was reported

No AEs were serious and n=11 (22%) were related to treatment
All resolved on day of treatment except one case of Grade 1 dizziness

No AEs were related to treatment, and all had resolved by data cut-off.
Potential IRRs were assessed using three different search strategies*

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No AEs were related to treatment, and all had resolved by data cut-off.

- *AEs of special interest chosen based on the crizanlizumab mechanism of action and those potentially related to treatment with monoclonal antibodies; †Not including VOCs

- **Effect on hemostasis**
  - All grades n=5 (10%)
  - No Grade ≥3 AEs

- **Infections**
  - All grades n=23 (46%)
  - Grade ≥3 n=2 (4%)
  - n=1 (2%) were related to treatment

- **Potential severe IRRs**
  - All grades n=6 (12%)
  - No AEs were serious and n=4 (8%) were related to treatment

- **Signs/symptoms indicative of possible IRR**
  - All grades n=15 (30%)
  - No AEs were serious and n=11 (22%) were related to treatment


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**Potential IRRs presenting as pain events**

**Definition**

- Pain events† occurring **on the day of infusion**

- One patient died of presumed bacterial meningitis (not considered treatment related)

- No case of anaphylaxis to crizanlizumab was reported

- All resolved on day of treatment except one case of Grade 1 dizziness
Few patients had possible IRRs presenting as pain events and all had resolved or were resolving at data cut-off

<table>
<thead>
<tr>
<th>Effect on hemostasis</th>
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<th>Signs/symptoms indicative of possible IRR</th>
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<td>Grade ≥3 n=1 (2%)</td>
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- No AEs were related to treatment, and all had resolved by data cut-off

Potential IRRs presenting as pain events

- All grades n=8 (16%)
- Grade ≥3 n=1 (2%)

- No AEs were serious and n=3 (6%) were related to treatment
- All had resolved or were resolving by data cut-off

- One patient died of presumed bacterial meningitis (not considered treatment related)
- No case of anaphylaxis to crizanlizumab was reported
- All resolved on day of treatment except one case of Grade 1 dizziness
Immunogenicity was also an AE of special interest

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<td>All grades n=8 (16%)</td>
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</tbody>
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No AEs were related to treatment, and all had resolved by data cut-off

- n=1 (2%) were related to treatment
  - One patient died of presumed bacterial meningitis (not considered treatment related)
- No AEs were serious and n=4 (8%) were related to treatment
- No case of anaphylaxis to crizanlizumab was reported
- No AEs were serious and n=11 (22%) were related to treatment
  - All resolved on day of treatment except one case of Grade 1 dizziness
- No AEs were serious and n=3 (6%) were related to treatment
  - All had resolved or were resolving by data cut-off

No patients developed anti-drug antibodies against crizanlizumab
The incidence of AEs of special interest in Group 1 is comparable with that observed in adults who received crizanlizumab 5.0 mg/kg in the SUSTAIN study.

The incidence of infections, potential signs and symptoms of IRRs or pain events, and effects on hemostasis in patients who received crizanlizumab 5.0 mg/kg in Group 1 was comparable with that observed with crizanlizumab in SUSTAIN, with many patients in the placebo group of SUSTAIN also experiencing these AEs of special interest.

### Table: Incidence of AEs of Special Interest

<table>
<thead>
<tr>
<th></th>
<th>SOLACE-kids Crizanlizumab 5.0 mg/kg N=50</th>
<th>SUSTAIN Placebo N=62</th>
<th>SUSTAIN Crizanlizumab 5.0 mg/kg N=66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect on hemostasis</strong></td>
<td>5 (10.0) n (%)</td>
<td>8 (12.9) n (%)</td>
<td>11 (16.7) n (%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>23 (46.0) n (%)</td>
<td>11 (22.0) n (%)</td>
<td>35 (53.0) n (%)</td>
</tr>
<tr>
<td><strong>Potential severe IRRs</strong></td>
<td>6 (12.0) n (%)</td>
<td>0</td>
<td>2 (3.0) n (%)</td>
</tr>
<tr>
<td><strong>Signs/symptoms indicative of</strong></td>
<td></td>
<td></td>
<td>23 (34.8) n (%)</td>
</tr>
<tr>
<td><strong>Potential IRRs presenting as</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>pain events</strong></td>
<td>15 (30.0) n (%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-drug antibodies</strong></td>
<td>8 (16.0) n (%)</td>
<td>0</td>
<td>1 (1.5)* n (%)</td>
</tr>
</tbody>
</table>

*Transiently detected and spontaneously resolved
Crizanlizumab treatment led to a reduction in VOCs and hospital/ER visits

VOCs leading to healthcare visit

Baseline
On crizanlizumab treatment

Median annualized rate of VOCs:

- Baseline: 3.00 (Q1–Q3: 1.0–5.0)
- On crizanlizumab treatment: 1.61 (Q1–Q3: 0–3.7)

Median absolute reduction from baseline:

- VOCs: −1.0 (Q1–Q3: −3.0 to 0.5)

Hospitalizations and ER visits

Baseline
On crizanlizumab treatment

Median annualized rate of hospitalizations/ER visits:

- Baseline: 4.00 (Q1–Q3: 2.0–8.0)
- On crizanlizumab treatment: 1.54 (Q1–Q3: 0–2.7)

Median absolute reduction from baseline:

- Hospitalizations and ER visits: −2.4 (Q1–Q3: −5.0 to 1.0)

18 (36%) patients did not experience a VOC leading to a healthcare visit during the median 36.6 weeks of crizanlizumab treatment.
The SOLACE-kids trial aims to address an unmet medical need in pediatric patients with SCD.

This initial analysis of SOLACE-kids Group 1 shows that crizanlizumab 5.0 mg/kg is safe and well tolerated in patients aged 12 to <18 years, with a safety profile consistent with the established safety profile in adult patients. No new safety signals were identified.

Crizanlizumab 5.0 mg/kg treatment led to a clinically relevant reduction in the median annualized rate of VOCs leading to a healthcare visit compared with baseline.

The SOLACE-kids trial is ongoing, with dose confirmation currently being performed for Group 2 (patients aged 6 to <12 years). Group 1 of SOLACE-kids has completed recruitment.

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