Pharmacokinetics/Pharmacodynamics, Safety, and Efficacy of Crizanlizumab in Patients With Sickle Cell Disease Aged 12 to <18 Years: 2-Year Data From the Phase 2 SOLACE-Kids Study

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*Presenting author

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Oral presentation at European Hematology Association, held in person in Frankfurt, Germany and virtually from June 8 to 15, 2023.
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- **Matthew Heeney** reports consultancy for the Novartis steering committee, FORMA Therapeutics, Global Blood Therapeutics, Oric Pharma and Bluebird Bio and Pharmacosmos; research funding from Novartis; podcast speaker for Agios; and membership of a data and safety monitoring board for Vertex/CRISPR.

- **David Rees** reports lecture honoraria from Vertex and Novartis; consulting fees from Agios, Vertex, Vifor and and Forma Therapeutics for participation on advisory and steering committees; and participation on a data and safety monitoring committees for TauRx and Mitsubishi.

- **Mariane de Montalembert** reports lecture honoraria from Novartis and Addmedica; travel support for attending ASH congress from Addmedica; and participation on an entity’s Board of Directors or advisory committees for Novartis, Addmedica and Vertex.

Contd.
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- **Isaac Odame** reports receipt of consulting fees from Novartis (for steering committee) and from Novo Nordisk and AustinPx; research funding from Novartis; participation on a data and safety monitoring board for global blood therapeutics and advisory board for AustinPX and Novo Nordisk.

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Background

SCD is an inherited blood disorder1
- Characterized by hemolytic anemia, endothelial damage, and acutely painful VOCs
- Causes chronic and potentially life-threatening complications

Phase II SUSTAIN study2
- Crizanlizumab, a humanized monoclonal anti–P-selectin antibody, reduced the annualized rate of VOCs leading to a healthcare visit by 45.3% vs placebo (P=0.01) in patients with SCD

SOLACE-kids study – Initial 26-week analysis3
- Crizanlizumab 5 mg/kg was safe and well tolerated in patients (n=50) with SCD aged 12 to <18 years
- Results were consistent with the established profile in adults from the SUSTAIN study

Current analysis of SOLACE-kids study reports
- updated PK and PD (ex vivo P-selectin inhibition), safety, and efficacy results for patients with SCD aged 12 to <18 years who received crizanlizumab 5 mg/kg IV for 2 years (cutoff date: 05 May 2022)

IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

VOC is defined as pain crises and other complicated crises such as acute coronary syndrome, priapism, and hepatic or splenic sequestration.

SOLACE-kids is a Phase II, open-label, single-arm, multicenter study to assess appropriate dosing and evaluate the safety and efficacy of crizanlizumab in pediatric patients with SCD.

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

**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 (immunogenicity)

**Crizanlizumab 5 mg/kg IV is administered on Day 1, Day 15, then on Day 1 of every 4 weeks thereafter for up to 2 years**

**AE, adverse event; ER, emergency room; HU, hydroxyurea; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SCD, sickle cell disease; VOC, vaso-occlusive crisis.**

*Must be receiving HU for ≥6 months prior to screening and plan to continue taking it at the same dose and schedule during the study; **It is planned that at least 100 patients will be enrolled in total; †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† (Group 1) or by a population PK model (Groups 2 and 3), and ≥8 additional patients enrolled; §Each group separately or combined in close cutoff dates. Heeney MM et al. Oral JSCDH-D-22-1221467 presented at FSCDR 2022 https://bit.ly/Heeney1467
Patients in Group 1 (aged 12 to <18 years) were representative of the typical SCD population *(cutoff date: 5 May 2022)*

Baseline characteristics and duration of exposure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (N=50)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1, Q3)</td>
<td>14.9 (13.3, 16.9)</td>
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<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>29 (58.0)</td>
<td>44 (88.0)</td>
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<tr>
<td>Male</td>
<td>21 (42.0)</td>
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<td><strong>Race, n (%)</strong></td>
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<tr>
<td>Black or African American</td>
<td>32 (64.0)</td>
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<td>White</td>
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<td>White, Asian</td>
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<tr>
<td><strong>Concomitant medication, n (%)</strong></td>
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<tr>
<td>HU</td>
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HU, hydroxyurea; Q1, first quartile; Q3, third quartile; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Patients in Group 1 (aged 12 to <18 years) were representative of the typical SCD population

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All patients in Group 1 received crizanlizumab 5.0 mg/kg and 45 (90%) patients received treatment for ≥26 weeks and 43 (86%) patients received for ≥ 54 weeks.

SCD, sickle cell disease.
No new safety signals were identified in patients aged 12 to <18 years

- **47 (94%)** patients had ≥1 AE
- **15 (30%)** patients reported treatment-related AEs.
  - Most frequent treatment-related AEs:
    - Headache: n=19 (38%)
    - COVID-19 and vomiting: n=14 (28%) each
    - Pyrexia: n=13 (26%)
  - Grade ≥3 treatment-related AEs: n=2 (4%)
  - Treatment-related serious AEs: n=0

- **16 (32%)** patients had ≥1 AE leading to dose interruption/change.
  - Most frequent AEs leading to dose interruption or change:
    - COVID-19: n=5 (10%)
    - IRR: n=2 (4%)
    - Back pain and dizziness: n=2 (4%) each
  - Grade ≥3 AEs leading to dose interruption or change: n=5 (10%)

- Of the 2 (4%) patients reporting AEs leading to discontinuation, none (including 1 death due to bacterial meningitis) was deemed related to crizanlizumab per the investigator.

AE, adverse event; IRR, infusion-related reaction.
*By preferred term; †Two Grade ≥3 treatment-related AEs (back pain and pain in extremity) were reported in the same patient.
AEs of special interest: Few patients had possible IRRs presenting as pain events and all had resolved or were resolving at data cutoff

**Effect on hemostasis**

- All grades: n=12 (24%)
- Grade ≥3: n=1 (2%)

No AEs were related to crizanlizumab treatment, and all had resolved by data cutoff.

11 (22%) patients had hemorrhage events* and 1 (2%) patient had thrombosis.

**Infections**

- All grades: n=37 (74%)
- Grade ≥3: n=6 (12%)**

Conjunctivitis reported in 1 (2%) patient was related to crizanlizumab treatment.

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

**Potential severe IRRs‡**

- All grades: n=7 (14%)
- Grade ≥3: n=1 (2%)

No AEs were related to crizanlizumab treatment, and all had resolved or were resolving at data cutoff.

**Potential IRRs presenting as pain events§**

- All grades: n=11 (22%)
- Grade ≥3: n=1 (2%)

No AEs were serious and n=1 (2%) was related to crizanlizumab treatment.

All had resolved or were resolving at data cutoff.

---

AE, adverse event; IRR, infusion-related reaction.

*Hemorrhage events included epistaxis and hematuria (3 [6%], contusion (2 [4%]), and haematochezia, intermenstrual bleeding, increased international normalized ratio, post procedural haemorrhage, rectal haemorrhage, retinal haemorrhage (1 [2%] patient each); **1 patient was reported with serious and grade 5 infection of encephalitis, bacterial meningitis, and septic shock;

‡Severe reaction, intended to identify potentially more severe reactions, and occurring any time after infusion (regardless of grade and causality); §'Pain events' on the day of infusion.
Conjunctivitis reported in 1 (2%) patient was related to crizanlizumab treatment.

AEs of special interest: Few patients had possible IRRs presenting as pain events and all had resolved or were resolving at data cutoff.

**Effect on hemostasis**

- All grades: n=12 (24%)

**Infections**

- All grades: n=37 (74%)

**Potential severe IRRs‡**

- All grades: n=7 (14%)

**Potential IRRs presenting as pain events$**

- All grades: n=11 (22%)

No patients developed anti-drug antibodies against crizanlizumab.

AEs were related to crizanlizumab treatment, and all had resolved by data cutoff.

- 11 (22%) patients had hemorrhage events* and 1 (2%) patient had thrombosis

Conjunctivitis reported in 1 (2%) patient was related to crizanlizumab treatment.

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

No AEs were serious and n=5 (10%) were related to crizanlizumab treatment.

- Anaphylactic reaction of grade 3 and drug hypersensitivity of grade 1 (not related to crizanlizumab) were reported in 1 patient each

No AEs were related to crizanlizumab treatment, and all had resolved by data cutoff.

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

No AEs were serious and n=1 (2%) was related to crizanlizumab treatment.

- All had resolved or were resolving by data cutoff

AE, adverse event; IRR, infusion-related reaction.

*Hemorrhage events included epistaxis and hematuria (3 [6%], contusion (2 [4%]), and haematochezia, intermenstrual bleeding, increased international normalized ratio, post procedural haemorrhage, rectal haemorrhage, retinal haemorrhage (1 [2%] patient each). **1 patient was reported with serious and grade 5 infection of encephalitis, bacterial meningitis, and septic shock; ‡Severe reaction, intended to identify potentially more severe reactions, and occurring any time after infusion (regardless of grade and causality); §Pain events on the day of infusion.
The incidence of grade ≥3 AEs of special interest in patients who received crizanlizumab 5.0 mg/kg in Group 1 of SOLACE-kids was comparable with that observed with crizanlizumab in SUSTAIN.

<table>
<thead>
<tr>
<th>Effect on hemostasis</th>
<th>SOLACE-kids</th>
<th>SUSTAIN¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crizanlizumab 5.0 mg/kg</td>
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</tr>
<tr>
<td></td>
<td>N=50</td>
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</tr>
<tr>
<td>All grades</td>
<td>12 (24%)</td>
<td>11 (16.7%)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>1 (2.0%)</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>Infections</td>
<td>37 (74.0%)</td>
<td>35 (53.0%)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>6 (12.0%)</td>
<td>5 (7.6%)</td>
</tr>
<tr>
<td>Potential severe IRRs</td>
<td>7 (14.0%)</td>
<td>2 (3.0%)</td>
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<tr>
<td>Grade ≥3</td>
<td>1 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Potential IRRs present as pain events</td>
<td>11 (22.0%)</td>
<td>14 (21.2%)</td>
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<td>Grade ≥3</td>
<td>1 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Anti-drug antibodies</td>
<td>0</td>
<td>1 (1.5)*</td>
</tr>
</tbody>
</table>

¹Hemorrhage events included epistaxis and hematuria (3 [6%], contusion (2 [4%]), and haematochezia, intermenstrual bleeding, increased international normalized ratio, post procedural haemorrhage, rectal haemorrhage, retinal haemorrhage (1 [2%] patient each); ²1 patient was reported with serious and grade 5 infection of encephalitis, bacterial meningitis, and septic shock; ³Severe reaction, intended to identify potentially more severe reactions, and occurring any time after infusion (regardless of grade and causality); §'Pain events' on the day of infusion.

Serum crizanlizumab concentrations achieved maximum levels (Cmax) at the end of the 30-minute infusion, remaining steady for 4 hours post-infusion, for 5.0 mg/kg dose.

At steady state

Post-dose PK parameters (n=11)

After first dose (Single infusion)

- **AUCd15**: 10,500 (2290) \(\mu g \times h/mL^*\)
- **Cmax**: 80.5 (17.7) \(\mu g/mL^*\)
- **Tmax**: 0.633 h

After multiple doses (Steady state)

- **AUCtau**: 15,800 (2080) \(\mu g \times h/mL^*\)
- **Cmax**: 95.6 (26.6) \(\mu g/mL^*\)
- **Tmax**: 1.72 h
- **T1/2**: 10.3 days

Mean pre-dose** concentrations obtained every 4 weeks from Week 7 to Week 51 ranged from 7.1 \(\mu g/mL\) to 10.3 \(\mu g/mL\).

AUCd15, area under the curve from time zero to the end of doing interval after the first infusion; AUCtau, area under the curve from time zero to the last measurable concentration after multiple doses at steady state; Cmax, maximum serum concentration; PK, pharmacokinetics; PD, pharmacodynamics; SD, standard deviation; Tmax, median time to reach maximum concentration; T1/2, mean apparent elimination half-life. *Mean (SD); **Pre-dose crizanlizumab concentrations were collected in participants of Parts A and B in Group 1 (n=50) while all other PK/PD analysis were performed in participants of Part A in Group 1 (n=11).
Crizanlizumab treatment achieved complete and sustained inhibition of P-selectin sustained throughout the 4-week dosing interval.

At steady state

Linear view

Post-dose P-selectin inhibition (n=11)

After first dose (Single infusion)
- AUCd15: 33,700 (2440) h × %*
- P-selectin inhibition‡: 98.7% to 100%

After multiple doses (Steady state)
- AUCtau: 66,700 (9560) h × %*
- P-selectin inhibition‡: 88.6% to 97.6%

Mean pre-dose§ P-selectin inhibition ranged from 85.4% to 99.3% from Week 3 up to Week 51

AUCd15, area under the curve from time zero to the last measurable concentration after the first infusion; AUCtau, area under the curve from time zero to the last measurable concentration after multiple doses at steady state; PK, pharmacokinetics, PD, pharmacodynamics; SD, standard deviation.

*Mean (SD); ‡Mean; §Pre-dose P-selectin inhibition data were collected in participants of Parts A and B in Group 1 (n=47) while all other PK/PD analysis were performed in participants of Part A in Group 1 (n=11).
Crizanlizumab treatment led to a reduction in VOCs and hospital/ER visits

8 (16%) patients did not experience a VOC leading to a healthcare visit during the median 106 weeks of crizanlizumab treatment

**VOCs leading to healthcare visit**

- Baseline Median annualized rate of VOCs: 3.00 (Q1, Q3: 1.0, 5.0)
- On crizanlizumab treatment Median annualized rate of VOCs: 2.21 (Q1, Q3: 0.55, 4.39)

**VOC-related hospitalizations and ER visits**

- Baseline Median annualized rate of hospitalizations/ER visits: 4.00 (Q1, Q3: 2.0, 6.0)
- On crizanlizumab treatment Median annualized rate of hospitalizations/ER visits: 0.98 (Q1, Q3: 0, 3.4)

ER, emergency room; Q1, first quartile, Q3, third quartile; VOC, vaso-occlusive crisis.
Crizanlizumab treatment led to a notable reduction in VOCs in patients with no HU use and ≥5 VOCs

### VOCs leading to healthcare visit by HU use at study entry

- **No HU use (n=6)**
  - Baseline: 2.00 (Q1, Q3: 1.0, 3.0)
  - On crizanlizumab treatment: 0.73 (Q1, Q3: 0, 1.27)
  - Median absolute reduction from baseline: −0.62 (Q1, Q3: −3, −0.02)

- **HU use (n=44)**
  - Baseline: 3.00 (Q1, Q3: 1.5, 5.0)
  - On crizanlizumab treatment: 2.89 (Q1, Q3: 0.97, 4.4)
  - Median absolute reduction from baseline: −1 (Q1, Q3: −2.77, 0.67)

### VOCs leading to healthcare visit by VOC frequency at study entry

- **<5 VOCs (n=34)**
  - Baseline: 2.00 (Q1, Q3: 1.0, 3.0)
  - On crizanlizumab treatment: 0.98 (Q1, Q3: 0.49, 2.95)
  - Median absolute reduction from baseline: −2.8 (Q1, Q3: −5.31, −0.71)

- **≥5 VOCs (n=16)**
  - Baseline: 8.00 (Q1, Q3: 5, 9.5)
  - On crizanlizumab treatment: 4.28 (Q1, Q3: 3.42, 7.4)
  - Median absolute reduction from baseline: −3.8 (Q1, Q3: −5.31, −0.71)

Q1, first quartile, Q3, third quartile; VOC, vaso-occlusive crisis.
Conclusions

• Serum crizanlizumab concentrations rose to maximum levels shortly after infusion and achieved near complete and sustained ex vivo P-selectin inhibition.

• Stable pre-dose concentrations were observed throughout the study, with a lack of accumulation.

• This 2-year analysis of SOLACE-kids Group 1 shows that crizanlizumab 5.0 mg/kg with or without HU is safe and well tolerated in patients with SCD aged 12 to <18 years, consistent with the established safety profile in adult patients from the SUSTAIN study.¹ 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 study 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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EMA position on crizanlizumab

Response to unsolicited queries

• Currently, all ongoing studies are continuing as per protocol
• No new patients will be treated with crizanlizumab in the European Union
• For patients currently on crizanlizumab, healthcare professionals should discuss alternative treatment options with them

For additional queries, please contact a Novartis representative at the exhibition booth in Hall 3.1, Level 1