Abstract: S267

Title: 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

Abstract Type: Oral Presentation

Session Title: SCD, clinics and research

Background:

Vaso-occlusive crises (VOCs) are a key characteristic of sickle cell disease (SCD). Safety and efficacy of crizanlizumab from 26-week analysis of SOLACE-kids study in 50 children with SCD aged 12 to <18 years were reported at ASH 2021. Safety and tolerability of the confirmed dose (5 mg/kg) of crizanlizumab in these children were consistent with the established profile in adults from the SUSTAIN study. Crizanlizumab also showed a reduction in the median annualized rate of VOCs compared to baseline.

Aims:

To confirm and establish appropriate dosing for different pediatric age groups (Part A), and to evaluate the safety and efficacy of the confirmed dose of crizanlizumab (Part B), in additional pediatric patients with SCD (ClinicalTrials.gov: NCT03474965; EudraCT: 2017-001747-12).

Methods:

SOLACE-kids is an ongoing Phase 2 study conducted in children with SCD (any genotype) and a history of ≥1 VOC leading to a healthcare visit within 12 months prior to screening. Eligible patients are grouped by age: Group 1 (12 to <18 years), Group 2 (6 to <12 years), and Group 3 (6 months to <6 years). Patients received crizanlizumab on Day 1, Day 15, then every 4 weeks (up to 2 years), with or without hydroxyurea (HU)/Hydroxycarbamide (HC). This analysis reports updated pharmacokinetics (PK) /pharmacodynamics (PD; ex vivo P-selectin inhibition), safety, and efficacy results for patients in Group 1 who received crizanlizumab 5 mg/kg IV for 2 years.

Results:

As of 05 May 2022, of 50 patients enrolled in Group 1 (median [range] age 14.9 [12.0–17.9] years; 58% female; 88% HbSS genotype; 64% Black/African American; 84% receiving HU), 33 (66%) completed treatment with crizanlizumab. Median (Q1-Q3) duration of crizanlizumab exposure was 106.1 (94.9–107) weeks; 86% and 56% of patients received treatment for ≥54 and ≥106 weeks, respectively.

Eleven patients' data were evaluated for PK/PD analysis. The mean area under the curve from time zero to the last measurable concentration after the first infusion (AUC_{d15}) and after multiple doses at steady state (AUC_{tau}) was 10500 and 15800 hr*µg/mL, respectively. The mean maximum serum concentrations (C_{max}) after the first infusion (80.5 µg/ml) and at steady state (95.6 µg/mL), indicated no significant accumulation of crizanlizumab. At steady state, the mean apparent elimination half-life ($T_{1/2}$) was 10.3 days. The mean P-selectin inhibition ranged from 98.7% to 100% at a first dose and from 88.6% to 97.6% at the steady-state dose.

Overall, 47 (94%) patients reported ≥1 adverse event (AEs), most commonly with headache (38%). Treatment-related AEs occurred in 15 (30%) patients, of which infusion-related reaction (10%) and nausea (6%) were most common. Grade ≥3 AEs occurred in 24 (48%), of which back pain and pain in extremity in 1 patient and increased bilirubin in 1 patient were related to crizanlizumab. None of the serious AEs or AEs leading to discontinuation (including one death due to bacterial meningitis), dose change, and/or interruption were deemed related to crizanlizumab per the investigator. None of these patients developed antibodies against crizanlizumab.

The impact of crizanlizumab on annualized rate of VOCs is summarized in **Table**.

Summary/Conclusion:

In this 2-year analysis, crizanlizumab 5 mg/kg with or without concomitant HU/HC has shown a reduction in VOCs resulting in decreased healthcare visits per year, consistent with the established profile of crizanlizumab in adults. Crizanlizumab was safe and well tolerated with no new/unexpected safety concerns. These results confirm 5 mg/kg as an adequate dose in pediatrics with SCD aged 12 to <18 years.

Table. Efficacy endpoint – Annualized rates of on-treatment VOCs in patients with SCD

	Annualized rate of VOCs[a]	Absolute change from baseline
Annualized rate of VOCs leading to healthcare visit, median (Q1, Q3)		
Baseline (n=50)	3 (1, 5)	NA
On-treatment (n=50)[b]	2.21 (0.55, 4.39)	−1 (−3, 0.52)
Year 1 (n=42)	2 (0, 3)	−1.5 (−3, 0)
Year 2 (n=32)	2.5 (1, 4)	−1 (−2, 0.5)
No HU/HC use at study entry, median (Q1, Q3)		
Baseline (n=6)	2 (1, 3)	NA
On-treatment (n=6)[b]	0.73 (0, 1.27)	−0.62 (−3, −0.02)
HU/HC use at study entry, median (Q1, Q3)		
Baseline (n=44)	3 (1.5, 5)	NA
On-treatment (n=44)[b]	2.89 (0.97, 4.4)	−1 (−2.77, 0.67)
<5 VOCs at study entry, median (Q1, Q3)		
Baseline (n=34)	2 (1, 3)	NA
On-treatment (n=34)[b]	0.98 (0.49, 2.95)	−0.52 (−2, 0.82)
≥5 VOCs at study entry, median (Q1, Q3)		
Baseline (n=16)	8 (5, 9.5)	NA
On-treatment (n=16)	4.28 (3.42, 7.4)	−2.8 (−5.31, −0.71)
Annualized rate of VOC-related hospitalizations and emergency room visits, median (Q1, Q3)		
Baseline (n=50)	4 (2, 6)	NA
On-treatment (n=50)	0.98 (0, 3.4)	−1.59 (−3.85, −0.51)
Year 1 (n=42)	1 (0, 2)	−2 (−4, −1)
Year 2 (n=32)	1 (0, 3)	−2 (−4, 0)

HC, hydroxycarbamide; HU, hydroxyurea; NA, not applicable; SCD, sickle cell disease; VOC, vaso-occlusive crises

[a]Annualized rate of VOC = (Number of VOC reported until end date × 365.25)/ (End date – Date of first dose of study treatment+1), where VOC is defined as pain crises and other complicated crises such as acute coronary syndrome, priapism and hepatic or splenic sequestration; [b]During crizanlizumab treatment, overall 8 patients did not encounter a VOC that required a healthcare visit; of these 2 patients reported no HU/HC use and 6 patients reported HU/HC use at study entry, and all these 8 patients had <5 VOCs at study entry.

Keywords: Sickle cell disease, Vasoocclusive crisis, P-selectin, Pediatric