Supplementary materials

Pharmacokinetics, pharmacodynamics, safety, and efficacy of crizanlizumab in patients with sickle cell disease

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Supplementary methods

Vaso-occlusive crisis (VOC) definition

VOCs were defined as acute onset of pain for which, in the opinion of the investigator, there is no medically determined explanation other than vaso-occlusion, and which requires a visit to a medical facility and/or healthcare professional and therapy with oral or parenteral opioids or a parenteral non-steroidal anti-inflammatory, and other complicated crises, such as acute chest syndrome, priapism, and hepatic or splenic sequestration.

Key exclusion criteria

Key exclusion criteria were: a history of stem cell transplant; an acute VOC event within 7 days of the first dose of crizanlizumab; receipt of blood products within 30 days of the first dose of crizanlizumab; and participation in a chronic transfusion program during the course of the trial (episodic transfusion in response to worsening anemia or VOC was permitted).

Patient enrollment and dosing schedule

The first 45 patients enrolled in SOLACE-adults received crizanlizumab via intravenous infusion over 30 minutes at a dose of 5.0 mg/kg on week 1 day 1, week 3 day 1 and then on day 1 of every 4-week cycle. No dose change or modification was allowed for patients assigned to crizanlizumab 5.0 mg/kg. Once a total of up to 45 patients had been enrolled at 5.0 mg/kg, an exploratory cohort enrolled 12 patients at a dose of 7.5 mg/kg, administered per the same schedule as the 5.0 mg/kg dose;

reduction in the dose of crizanlizumab from 7.5 to 5.0 mg/kg was permitted. The 5.0 and 7.5 mg/kg dose groups were non-randomized, non-comparable, independent cohorts. In both cohorts, patients were to receive crizanlizumab until unacceptable toxicity, loss to follow-up or discontinuation from the study. All patients were followed for safety up to 105 days after receiving the last dose of study treatment.

PK and PD parameters

- Area under the curve (AUC) from time zero to the last measurable concentration sampling time at starting dose (AUC_{d15}) and at steady state (AUC_{tau})
- Maximum observed serum drug concentration after dose administration (C_{max})
- Time to reach maximum observed serum drug concentration after dose administration (T_{max})
- Elimination half-life associated with the terminal slope of a semi logarithmic scale ($T_{½}$)
- PD-AUC at starting dose (AUC_{d15}) and at steady state (AUC_{d29})
- The coefficient of variation (CV%) for the primary PK (AUC_{d15}, AUC_{tau} or C_{max}) and PD variables (AUC_{d15}, AUC_{d29})

Criteria for an evaluable pharmacokinetic (PK)/pharmacodynamic (PD) profile

- The patient received the planned dose of 5.0 or 7.5 mg/kg of crizanlizumab prior to the starting dose PK/PD profile, or received three consecutive doses of the planned treatment before the multiple dose (steady state) PK/PD profile
- The patient provided at least one primary PK variable (AUC_{d15}, AUC_{tau}, or C_{max})/PD-AUC (starting dose or steady state) parameter
- The patient did not have any transfusion of blood products in the 4 weeks prior to the first sample of the PK/PD profile or during the full PK/PD profile

Definitions for potential infusion-related reaction (IRR) search strategies

- **Standard search:** Intended to identify the most common, non-specific potential signs and symptoms indicative of IRRs (including ~280 preferred terms [PTs] and excluding infusion-site reaction) occurring on the day of infusion.

- **Severe reactions search:** Intended to identify potentially more severe reactions (10 PTs focused on anaphylaxis and cytokine release syndrome, as well as the PT IRR) occurring any time after infusion.
- **Pain events search:** Included ~110 PTs related to pain occurring on the calendar day of infusion.
- **Complement-mediated search:** Intended to identify adverse events (AEs) of potential complement activation-related pseudoallergy (CARPA) occurring on the day of infusion.

Preferred terms used in IRR searches

Standard search (excludes infusion-site reactions and intended to investigate the most common, nonspecific, potential signs and symptoms indicative of IRRs occurring on the day of infusion):

Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, acquired c1 inhibitor deficiency, acute kidney injury, acute myocardial infarction, acute phase reaction, acute pulmonary edema, acute respiratory distress syndrome, acute respiratory failure, allergic cough, allergic edema, allergic pharyngitis, allergic reaction to excipient, allergic respiratory symptom, allergy to immunoglobulin therapy, altered state of consciousness, anamnestic reaction, anaphylactic reaction, anaphylactic shock, anaphylactic transfusion reaction, anaphylactoid reaction, anaphylactoid shock, anaphylaxis treatment, angina pectoris, angioedema, antiallergic therapy, anuria, anxiety, arrhythmia, arthralgia, asthenia, asthma, atopic cough, atrial fibrillation, atrial flutter, atrial tachycardia, auricular swelling, back pain, blood pressure decreased, blood pressure diastolic decreased, blood pressure diastolic increased, blood pressure immeasurable, blood pressure increased, blood pressure systolic decreased, blood pressure systolic increased, bradycardia, bradypnoea, breast edema, breast swelling, bronchial edema, bronchospasm, burning sensation, cardiac arrest, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, cardio-respiratory distress, cardiogenic shock, cardiovascular insufficiency, cerebral hypoperfusion, chest discomfort, chest pain, chills, choking, choking sensation, circulatory collapse, circumoral edema, circumoral swelling, clonic convulsion, clonus, cold sweat, confusional state, congestive hepatopathy, conjunctival edema, corneal

edema, cough, cyanosis, cytokine release syndrome, cytokine storm, depressed level of consciousness, dermatitis, dermatitis allergic, diarrhea, diastolic hypotension, distributive shock, dizziness, drug eruption, drug hypersensitivity, dry throat, dysgeusia, dyspepsia, dysphonia, dyspnea, ear swelling, epigastric discomfort, epiglottic edema, erythema, eye allergy, eye edema, eye pruritus, eye swelling, eyelid edema, face edema, facial discomfort, fatigue, feeling cold, feeling hot, feeling of body temperature change, fixed eruption, flushing, gastrointestinal edema, generalized edema, generalized tonic-clonic seizure, genital swelling, gingival edema, gingival swelling, head discomfort, headache, heart rate abnormal, heart rate decreased, heart rate increased, hepatojugular reflux, hepatorenal failure, hot flush, hyperhidrosis, hyperpyrexia, hypersensitivity, hypertension, hyperventilation, hypoperfusion, hypotension, hypotensive crisis, hypoxia, idiopathic angioedema, idiopathic urticaria, illness, IRR, intestinal angioedema, irregular breathing, joint stiffness, jugular vein distension, kounis syndrome, laryngeal dyspnea, laryngeal obstruction, laryngeal edema, laryngospasm, laryngotracheal edema, limbal swelling, lip edema, lip swelling, localized edema, loss of consciousness, lung infiltration, malaise, mouth swelling, mucocutaneous rash, multiple organ dysfunction syndrome, muscle spasms, myalgia, myocardial depression, myocardial infarction, nasal congestion, nasal obstruction, nasal edema, nausea, nodular rash, non-pitting edema, obstructive airways disorder, ocular hyperemia, oculorespiratory syndrome, edema, edema blister, edema genital, edema mouth, edema mucosal, edema peripheral, oral mucosal eruption, oral pruritus, orbital edema, organ failure, oropharyngeal edema, oropharyngeal spasm, oropharyngeal swelling, pain, palatal edema, palatal swelling, palpitations, penile edema, penile swelling, periarticular thenar erythema with onycholysis, periorbital edema, periorbital swelling, peripheral swelling, pharyngeal edema, pharyngeal swelling, physical deconditioning, platelet count decreased, post procedural complication, post procedural discomfort, post procedural hypotension, prerenal failure, presyncope, procedural shock, product intolerance, pruritus, pruritus allergic, pseudoallergic reaction, pulmonary edema, pyrexia, rash, rash erythematous, rash macular, rash pruritic, red man syndrome, renal failure, respiratory arrest, respiratory distress, respiratory failure, respiratory rate decreased, respiratory rate increased, reversible airways obstruction, rhinitis, rhinitis allergic, scleral edema, scrotal edema, scrotal swelling, seizure, seizure like phenomena, sensation of foreign body, serum

sickness, serum sickness-like reaction, shock, shock symptom, skin exfoliation, skin edema, skin reaction, skin swelling, sneezing, soft tissue swelling, somnolence, stridor, suffocation feeling, swelling, swelling face, swelling of eyelid, swollen tongue, symmetrical drug-related intertriginous and flexural exanthema, syncope, tachycardia, tachypnea, throat irritation, throat tightness, thrombocytopenia, tongue edema, tongue pruritus, tonic-clonic movements, tonic convulsion, tracheal obstruction, tracheal edema, tracheostomy, tremor, type I hypersensitivity, upper airway obstruction, urticaria, urticaria cholinergic, urticaria chronic, urticaria papular, urticarial dermatitis, vaginal edema, ventricular fibrillation, visceral edema, vision blurred, vomiting, vulval edema, vulvovaginal swelling, wheezing

Severe reactions search (intended to identify potentially more serious reactions relating to anaphylaxis and cytokine release syndrome occurring any time after infusion and regardless of grade and causality):

Anaphylactic reaction, anaphylactic shock, bronchospasm, capillary leak syndrome, cytokine release syndrome, drug hypersensitivity, hypersensitivity, IRR, shock, systemic inflammatory response syndrome

Pain events search (events linked to pain on the day of infusion):

Abdominal pain, abdominal pain lower, abdominal pain upper, adnexa uteri pain, amplified musculoskeletal pain syndrome, anal spasm, angina pectoris, arthralgia, axillary pain, back pain, bladder pain, bone pain, breast pain, bronchospasm, central pain syndrome, cervicogenic headache, chest discomfort, chest pain, chronic idiopathic pain syndrome, cluster headache, complex regional pain syndrome, diaphragmalgia, discomfort, drug withdrawal headache, dysesthesia, dysphonia, ear pain, eosinophilia myalgia syndrome, erythromelalgia, external ear pain, eye pain, eyelid pain, facial neuralgia, facial pain, flank pain, gastrointestinal pain, genital pain, gingival pain, glossopharyngeal neuralgia, groin pain, growing pains, headache, hepatic pain, inflammatory pain, intercostal neuralgia, ischemic limb pain, laryngeal pain, laryngospasm, ligament pain, lip pain, masticatory pain, medical device site pain, metatarsalgia, mucosal pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myalgia intercostal, myofascial pain syndrome, myofascial spasm, neck pain,

neuralgia, neuromuscular pain, new daily persistent headache, nipple pain, non-cardiac chest pain, nyctalgia, occipital neuralgia, esophageal pain, esophageal spasm, onychalgia, oral pain, oropharyngeal pain, oropharyngeal spasm, pain, pain in extremity, pain in jaw, pain of skin, pain threshold decreased, painful respiration, paresthesia, pelvic pain, perineal pain, periorbital pain, pleuritic pain, polymyalgia rheumatica, procedural pain, proctalgia, pseudoangina, pubic pain, pulmonary pain, radicular pain, rectal spasm, rhinalgia, scar pain, scrotal pain, sickle cell anemia with crisis, sphenopalatine neuralgia, spinal pain, suprapubic pain, tenderness, tendon pain, tracheal pain, trigeminal neuralgia, uterine cervical pain, uterine pain, vascular headache, vascular pain, visceral pain, vulvovaginal pain

Complement-mediated search (intended to identify AEs of potential CARPA occurring on the day of infusion):

Complement factor C3 increased, complement factor abnormal, complement factor increased, complement fixation abnormal, complement fixation test positive, complement split products increased, total complement activity increase

Supplementary results

Dose compliance

Most patients received the planned dose schedule in SOLACE-adults. The median (interquartile range) relative dose compliance (ratio of doses received and planned doses) was 100% (96.7–100.1%) in the 5.0 mg/kg group and 100% (100.0–100.1%) in the 7.5 mg/kg group. In the 5.0 and 7.5 mg/kg groups, respectively, 6.8% and 3.3% of infusions were delayed or interrupted. The most common reasons overall for dose delay/interruption were VOCs (imposed as per initial study protocol), patient decision and technical problems with dosing; only 11 patients (19%) required dose delay/interruption because of AEs.

Other AEs of potential interest

There were no AEs of potential drug-induced liver injury. Two (4.4%) AEs of potentially prolonged QT interval were reported in the 5.0 mg/kg group, both of which resolved spontaneously after 2 and 4 days. The AE that resolved after 2 days was an isolated event and treatment with crizanlizumab continued without reoccurrence of QT interval prolongation. The second event occurred in conjunction with a potentially related AE of hypokalemia that was not considered treatment related. Neither AE was deemed to be clinically significant.

Supplementary Table 1. AEs, regardless of relationship to study drug, occurring in >5% of patients overall by preferred term in SOLACE-adults

Preferred term	Crizanlizumab 5.0 mg/kg N = 45		Crizanlizumab 7.5 mg/kg N = 12	
	All grades, n (%)	Grade ≥3, n (%)	All grades, n (%)	Grade ≥3, n (%)
Any AE	44 (97.8)	22 (48.9)	12 (100)	4 (33.3)
Pyrexia	13 (28.9)	0	3 (25.0)	1 (8.3)
Headache	11 (24.4)	0	2 (16.7)	0
Hypokalemia	9 (20.0)	7 (15.6)	2 (16.7)	0
URTI	9 (20.0)	0	2 (16.7)	0
Arthralgia	8 (17.8)	0	0	0
Nausea	6 (13.3)	0	1 (8.3)	0
Back pain	6 (13.3)	0	1 (8.3)	0
Chest pain	5 (11.1)	0	1 (8.3)	0
Vomiting	4 (8.9)	0	2 (16.7)	0
Peripheral edema	5 (11.1)	0	0	0
Pain in extremity	5 (11.1)	0	0	0
Pharyngitis	4 (8.9)	0	1 (8.3)	0
Pruritis	4 (8.9)	1 (2.2)	1 (8.3)	0
Road traffic accident	4 (8.9)	0	1 (8.3)	0
Constipation	2 (4.4)	0	2 (16.7)	0
Dehydration	3 (6.7)	0	1 (8.3)	0
Diarrhea	3 (6.7)	0	1 (8.3)	0
Gastroenteritis	3 (6.7)	0	1 (8.3)	0
Hypertension	4 (8.9)	0	0	0
Hypoxia	3 (6.7)	2 (4.4)	1 (8.3)	0

Insomnia	4 (8.9)	1 (2.2)	0	0
Osteonecrosis	3 (6.7)	1 (2.2)	1 (8.3)	0
Rash	3 (6.7)	0	1 (8.3)	0
Upper abdominal pain	3 (6.7)	0	0	0
Anxiety	2 (4.4)	0	1 (8.3)	0
Cough	3 (6.7)	0	0	0
Cystitis	2 (4.4)	0	1 (8.3)	0
Deafness neurosensory	2 (4.4)	1 (2.2)	1 (8.3)	0
Decreased appetite	3 (6.7)	0	0	0
Fatigue	3 (6.7)	0	0	0
Gastritis	3 (6.7)	0	0	0
Joint swelling	3 (6.7)	0	0	0
Oropharyngeal pain	3 (6.7)	0	0	0
Pneumonia	3 (6.7)	1 (2.2)	0	0
Post-traumatic pain	3 (6.7)	1 (2.2)	0	0
Urinary tract infection	3 (6.7)	1 (2.2)	0	0
AEs leading to treatment discontinuation	1 (2.2)	1 (2.2)	1 (8.3)	1 (8.3)

URTI, upper respiratory tract infection.

Supplementary Table 2. Overview of AESI in SUSTAIN

Safety topic	Placebo N = 62 n (%)		Crizanlizumab 2.5 mg/kg N = 64 n (%)		Crizanlizumab 5.0 mg/kg N = 66 n (%)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Infections (all)	33 (53.2)	3 (4.8)	29 (45.3)	3 (4.7)	35 (53.0)	5 (7.6)
Potential signs and symptoms of IRRs (standard search)*	14 (22.6)	0	20 (31.3)	0	23 (34.8)	0
IRR (severe reactions search)*	0	0	4 (6.3)	0	2 (3.0)	0
Pain events*	13 (21.0)	0	12 (18.8)	0	14 (21.2)	0
CARPA (complement-mediated search)*	0	0	0	0	0	0
Effect on hemostasis – hemorrhage	8 (12.9)	0	7 (10.9)	1 (1.6)	11 (16.7)	1 (1.5)
ADAs	0	0	0	0	1 (1.5)†	0

AEs were evaluated based on MedDRA version 23.1.

*As the different searches are not mutually exclusive (ie some events are captured in multiple searches), the total number of patients in the combined search is less than the sum of the individual search categories.

†Transiently detected and spontaneously resolved.

ADA, anti-drug antibodies; AESI, adverse events of special interest.

Supplementary Table 3. VOCs occurring within 24 hours of infusion (the same day or the day after infusion) in SUSTAIN

	Placebo N = 62	**Crizanlizumab 2.5 mg/kg N = 64**	**Crizanlizumab 5.0 mg/kg N = 66**
Patients with a VOC on the same day or the day after infusion, n (%)	19 (30.6)	10 (15.6)	14 (21.2)
Total number of VOCs on the same day or the day after infusion, n	32	15	20
Proportion of infusions associated with a VOC on the same day or the day after infusion, %	4.7	2.0	2.8