FULL PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

ADAKVEO® 10 mg/mL concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 10 mg crizanlizumab.

One vial of 10 ml contains 100 mg crizanlizumab.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion, I.V

4 INDICATIONS AND USAGE

ADAKVEO® is indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

5 DOSAGE AND ADMINISTRATION

5.1 Recommended Dosage

Administer ADAKVEO 5 mg/kg by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter.

If a dose is missed, administer ADAKVEO as soon as possible.

If ADAKVEO is administered within 2 weeks after the missed dose, continue dosing according to the patient's original schedule.

If ADAKVEO is administered more than 2 weeks after the missed dose, continue dosing every 4 weeks thereafter.

ADAKVEO may be given with or without hydroxyurea.

5.2 Preparation and Administration

ADAKVEO should be prepared and administered by a healthcare professional.

Preparation

- Use aseptic technique to prepare the solution for infusion.
- Calculate the dose (mg) and the total volume (mL) of ADAKVEO solution required, and the number of ADAKVEO vials needed based on the patient's actual body weight.
    - Prepare 5 mg of ADAKVEO per kg of actual body weight.
- Calculate the volume of ADAKVEO to be used according to the following equation:

$$\text{Volume (mL)} = \frac{\text{patient's body weight (kg) x prescribed dose } \left[\frac{5\text{ mg}}{\text{kg}}\right]}{\text{concentration of ADAKVEO } \left[\frac{10\text{ mg}}{\text{mL}}\right]}$$

Dilution

Dilute ADAKVEO in 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a total volume of 100 mL for intravenous infusion as follows:

1. Obtain the number of vials required. One vial is needed for every 10 mL of ADAKVEO.
2. Bring vials to room temperature for a maximum of 4 hours prior to the start of preparation (piercing the first vial).
3. Visually inspect the vials.
    - Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
    - ADAKVEO is clear to opalescent, colorless or may have a slightly brownish-yellow tint.
    - Do not use if particles are present in the solution.
4. Obtain a 100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection infusion bag/container.
    - Infusion bags/containers must be made of either polyvinyl chloride (PVC), polyethylene (PE), or polypropylene (PP).
5. Remove a volume of 0.9% Sodium Chloride Injection or 5% Dextrose Injection from the infusion bag/container that is equal to the required volume of ADAKVEO solution.
6. Withdraw the necessary amount of ADAKVEO solution and dilute by adding to the infusion bag/container containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
    - The volume of ADAKVEO added to the infusion bag/container should not exceed 96 mL
7. Gently invert the infusion bag to mix the diluted solution. DO NOT SHAKE.
8. Single-dose vials. Discard unused portion.

Storage Conditions of the Diluted Solution

Chemical and physical in-use stability, from the start of preparation of the diluted solution for infusion until end of infusion, has been demonstrated for up to 8 hours at room temperature (up to 25°C) and at 2°C to 8°C for up to 24 hours overall. From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, including 4.5 hours at room temperature (up to 25°C) from the start of preparation to completion of the infusion, unless dilution has taken place in controlled and validated aseptic conditions.

Administration

- Administer ADAKVEO diluted solution by intravenous infusion over a period of 30 minutes through an intravenous line, which must contain a sterile, nonpyrogenic 0.2-micron inline filter.
- No incompatibilities have been observed between ADAKVEO and infusion sets composed of PVC, polyethylene (PE- lined PVC), polyurethane (PU), and in-line filter membranes composed of polyethersulfone (PES, neutral and positively charged), positively charged polyamide (PA), and polysulphone (PSU).
- Do not mix or coadminister with other drugs through the same intravenous line.
- After administration of ADAKVEO, flush the line with at least 25 mL of 0.9% Sodium Chloride injection or 5% Dextrose Injection.
- Dispose of any unused product or waste material in accordance with local requirements.

5.3 Management of Infusion-Related Reactions

No dose reductions are recommended. Management for infusion-related reactions for ADAKVEO is described in Table 1.

Table 1: Recommended Management for Infusion-Related Reactions

Severity of Adverse Reaction	Recommendation
Mild to moderate infusion-related reactions	• Temporarily interrupt the infusion or slow the rate of infusion • Initiate symptomatic treatment[a] (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antihistamines, intravenous fluids, and/or oxygen therapy) • For subsequent infusions, consider premedication and/or reduce the infusion rate
Severe infusion-related reactions	• Discontinue infusion • Institute appropriate medical care[a] • Consider permanent discontinuation of ADAKVEO
[a]Exercise caution with the use of corticosteroids in patients with sickle cell disease unless clinically indicated (e.g., treatment of anaphylaxis).	

6 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) as a clear to opalescent, colorless to slightly brownish-yellow solution in a single-dose vial.

7 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 12.

8 WARNINGS AND PRECAUTIONS

8.1 Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded.
It is recommended to record the batch number as well.

8.2 Infusion-Related Reactions

In the SUSTAIN clinical trial, infusion-related reactions (IRRs) (defined as occurring during/within 24 hours of infusion) were observed in 2 (3%) patients treated with ADAKVEO 5 mg/kg .

In the STAND clinical trial, IRRs were observed in 6 (7%) patients treated with ADAKVEO 5 mg/kg.

IRRs presented most frequently as pain, nausea, vomiting, fatigue, dizziness, pruritis, diarrhea, and pyrexia. Some IRRs have required hospitalizations. The majority of these IRRsoccurred during the first and second infusions.

Monitor for and advise patients to report signs and symptoms of IRRs.

Discontinue ADAKVEO infusion for severe IRRs and institute appropriate medical care *[see Dosage and Administration (5.3)]*.

For management recommendations of a mild or moderate infusion-related reaction *[see Dosage and Administration (5.3)]*.

Exercise caution with corticosteroids in patients with sickle cell disease unless clinically indicated (e.g., treatment of anaphylaxis). Use of corticosteroids may increase the risk of complications such as acute chest syndrome and fat embolism.

Infusion-Related Reactions and Vaso-occlusive Crises

Infusion-related reactions are sometimes indistinguishable from vaso-occlusive crisis (VOC) events. IRRs and VOCs may occur concomitantly and/or VOCs may occur as a consequence of an IRR.

8.3 Laboratory Test Interference

Interference with automated platelet counts (platelet clumping) has been observed following administration of ADAKVEO, in particular, when blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA). Mitigation strategies are recommended *[see Drug Interactions (10.1)]*.

9 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion-related reactions *[see Warnings and Precautions (8.1)]*

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Sickle Cell Disease

SUSTAIN Trial

The safety of ADAKVEO was evaluated in the SUSTAIN trial *[see Clinical Studies (15)]*. Eligible patients were diagnosed with sickle cell disease (any genotype, including HbSS, HbSC, HbS beta^0-thalassemia, HbS beta$^+$-thalassemia, and others). Patients received ADAKVEO 5 mg/kg (N = 66) or 2.5 mg/kg (N = 64) or placebo (N = 62) administered by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter. The safety evaluation below is limited to the patients who received the recommended dose of 5 mg/kg.

Among the 66 patients that received the recommended dose (5 mg/kg), 83% were exposed for 6 months or longer and 61% were exposed for approximately one year; forty-two (64%) patients were treated with ADAKVEO in combination with hydroxyurea.

Serious adverse reactions were reported in 2 patients (3%) treated with ADAKVEO 5 mg/kg; both reactions were pyrexia.

Two deaths (3%) occurred in the ADAKVEO 5 mg/kg treatment group. None of the deaths were considered to be related to ADAKVEO.

The most common adverse reactions (≥ 10%) were arthralgia, nausea, back pain, abdominal pain, pyrexiaand diarrhea.

Table 2 summarizes the adverse reactions in the SUSTAIN trial.

Table 2: Adverse Reactions (≥ 10%) in Patients Receiving ADAKVEO With a Difference Between Arms of > 3% Compared to Placebo in SUSTAIN

	ADAKVEO 5 mg/kg N = 66 %	**Placebo N = 62 %**

Adverse Reactions	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Arthralgia	18	2	8	2
Nausea	18	0	11	2
Back pain	15	0	11	0
Abdominal pain[a]	12	0	5	0
Pyrexia	11	12	7	0
Diarrhea	11	0	3	2
[a]Abdominal pain: abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal tenderness.				

Clinically relevant adverse reactions (all Grades) that were reported in less than 10% of patients treated with ADAKVEO included: oropharyngeal pain, vomiting, pruritus (pruritus and vulvovaginal pruritus), musculoskeletal chest pain, myalgia, infusion-site reaction (infusion-site extravasation, infusion-site pain, and infusion-site swelling), and infusion-related reaction.

STAND Trial

The safety of ADAKVEO was also evaluated in the STAND trial *[see Clinical Studies (14.1)]*. Eligible patients were diagnosed with sickle cell disease (any genotype, including HbSS, HbSC, HbS beta^0-thalassemia, HbS beta$^+$-thalassemia, and others). Patients received ADAKVEO 5 mg/kg (N = 84) or 7.5 mg/kg (N = 83) or placebo (N = 85) administered by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter. The safety evaluation below is limited to the patients who received the recommended dose of 5 mg/kg.

Among the 84 patients that received the recommended dose (5 mg/kg), 93% were exposed for approximately 6 months or longer and 88% were exposed for approximately one year; sixty-two (74%) patients were treated with ADAKVEO in combination with hydroxyurea.

Serious adverse reactions were reported in 2 patients (2%) treated with ADAKVEO 5 mg/kg and this reaction was pain. The most common adverse reactions (≥ 10%) were headache, nausea, fatigue, vomiting, and oropharyngeal pain.

Table 3: Adverse Reactions (≥ 10%) in Patients Receiving ADAKVEO With a Difference Between Arms of > 3% Compared to Placebo in STAND

	ADAKVEO 5 mg/kg N = 84 %		Placebo N = 85 %	
Adverse Reactions	All Grades %	Grade ≥ 3 %	All Grades %	Grade ≥ 3 %
Headache	25	1	19	0
Nausea	17	0	9	0
Fatigue[a]	13	0	8	0
Vomiting	10	0	5	0
Oropharyngeal pain	10	0	4	0
[a]Fatigue includes asthenia and malaise.				

Clinically relevant adverse reactions (all Grades) that were reported in less than 10% of patients treated with ADAKVEO or events having a difference of less than 3% between ADAKVEO treatment arms and placebo included: diarrhea, pruritus, dizziness, infusion-related reaction, infusion-site reaction.

9.2 Effects on ability to drive and use machines

Adakveo may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of crizanlizumab.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/
And to Novartis using the following email address: Safetydest.israel@novaris.com

10 DRUG INTERACTIONS

10.1 Laboratory Test Interference

Platelet Tests

ADAKVEO interferes with automated platelet counts (platelet clumping) in particular when blood samples are collected in tubes containing EDTA, which may lead to unevaluable or falsely decreased platelet counts. Run blood samples within 4 hours of blood collection or collect blood samples in tubes containing citrate. When needed, estimate platelet count via peripheral blood smear.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

Based on data from animal studies, ADAKVEO has the potential to cause fetal harm when administered to a pregnant woman. In an animal reproduction study, intravenous administration of crizanlizumab to pregnant cynomolgus monkeys from the onset of organogenesis through delivery resulted in a non-dose related increased fetal loss (abortions/stillbirths) at doses approximately 2.8 times the exposure at the recommended clinical dose at 5 mg/kg/dose once every 4 weeks *(see Data)*.

There are insufficient human data on ADAKVEO use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to a fetus. ADAKVEO should only be used during pregnancy if the expected benefit to the patient justifies the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is approximately 14% and up to 43%, respectively. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Women with sickle cell disease have an increased risk of adverse pregnancy outcomes for the mother and the fetus. Pregnant women are at greater risk for VOCs, pre-eclampsia, eclampsia, and maternal mortality. For the fetus, there is an increased risk for intrauterine growth restriction, preterm delivery, low birth weight, and perinatal mortality.

Data

Animal Data

In an enhanced pre- and postnatal development study in cynomolgus monkeys, pregnant animals received intravenous doses of crizanlizumab at 10 and 50 mg/kg once every 2 weeks during the period of onset of organogenesis through delivery. No maternal toxicity was observed. Maternal exposures at doses of 10 and 50 mg/kg were between 2.8 and 16 times, respectively, the human clinical exposure based on area under the curve (AUC) in patients with sickle cell disease at 5 mg/kg/dose once every 4 weeks. There was an increase in fetal loss (abortions or still births) at both crizanlizumab doses which was higher in the third trimester.

There were no effects on infant growth and development through 6-months postpartum that were attributable to crizanlizumab.

Measurable crizanlizumab serum concentrations were observed in the infant monkeys at postnatal Day 28, confirming that crizanlizumab crosses the placental barrier.

11.2 Lactation

Risk Summary

There is no data on the presence of crizanlizumab in human or animal milk, the effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to crizanlizumab are unknown.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for ADAKVEO and any potential adverse effects on the breastfed child from ADAKVEO or from the underlying maternal condition.

11.3 Pediatric Use

The safety and effectiveness of ADAKVEO for sickle cell disease have been established in pediatric patients aged 16 years and older. Use of ADAKVEO for sickle cell disease is supported by evidence from adequate and well-controlled studies in adults and pediatric patients (SUSTAIN trial). The SUSTAIN trial enrolled one pediatric patient treated with ADAKVEO 5 mg/kg aged 16 years old *[see Adverse Reactions (9.1), Clinical Pharmacology (13), Clinical Studies (15)]*.

The safety and efficacy of ADAKVEO in pediatric patients below the age of 16 years have not been established.

11.4 Geriatric Use

There were no ADAKVEO-treated patients 65 years of age and older in the clinical studies for sickle cell disease *[see Clinical Studies (15)]*. Clinical studies of ADAKVEO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

12 DESCRIPTION

Crizanlizumab is a P-selectin blocker humanized IgG2 kappa monoclonal antibody that binds to P-selectin. Crizanlizumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is composed of 2 heavy chains, each containing 448 amino acids, and 2 light chains each containing 218 amino acids, with a theoretical molecular weight of approximately 146 kDa.

ADAKVEO (crizanlizumab) injection is supplied as a sterile, preservative-free, clear to opalescent, colorless to slightly brownish-yellow solution for dilution and subsequent administration by intravenous infusion. Each 10 mL vial contains 100 mg crizanlizumab, sucrose (753.3 mg), sodium citrate (50.5 mg), citric acid (5.4 mg), polysorbate 80 (2 mg), and water for injection with a pH of 6.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Crizanlizumab is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1). Crizanlizumab can also dissociate preformed P-

selectin/PSGL-1 complex.

Binding P-selectin on the surface of the activated endothelium and platelets blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes.

13.2 Pharmacodynamics

ADAKVEO resulted in a dose-dependent P-selectin inhibition (measured *ex vivo*) in patients with sickle cell disease and healthy volunteers.

13.3 Pharmacokinetics

The pharmacokinetics of crizanlizumab were evaluated in healthy volunteers and patients with sickle cell disease. The mean crizanlizumab C_{max}, AUC_{last}, or AUC_{inf} increased disproportionally over the dose range of 0.2 to 8 mg/kg (0.04 to 1.6 times the approved recommended dosage) in healthy volunteers. In healthy volunteers administered the 5 mg/kg dose, the mean [coefficient of variation (CV%)] crizanlizumab C_{max}, AUC_{last}, or AUC_{inf} were 0.16 (15.3%) mg/mL, 33.6 (12.6%) mg*hr/mL and 34.6 (13.1%) mg*hr/mL, respectively.

Distribution

The mean (% CV) volume of distribution was 4.26 (25.1%) L after a single crizanlizumab 5 mg/kg intravenous infusion in healthy volunteers.

Elimination

The mean (% CV) terminal elimination half-life ($t_{1/2}$) of crizanlizumab was 10.6 (20.5%) days and the mean clearance was 11.7 (16.2%) mL/hr at 5 mg/kg doses in healthy volunteers. The mean (% CV) elimination $t_{1/2}$ of crizanlizumab was 11.4 (31.5%) days during dosing interval in patients with sickle cell disease.

Metabolism

Crizanlizumab is expected to be metabolized into small peptides by catabolic pathways. Specific

Populations

The effect of renal or hepatic impairment on the pharmacokinetics of crizanlizumab is unknown.

Drug Interaction Studies

Hydroxyurea had no clinically meaningful effect on crizanlizumab pharmacokinetics in patients in clinical studies.

13.4 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ADAKVEO or of other crizanlizumab products.

The immunogenicity of ADAKVEO was evaluated using a validated bridging immunoassay for the detection of binding anti-crizanlizumab antibodies. In a single arm, open label multiple dose study, 0 of the 45 patients with sickle cell disease treated with ADAKVEO 5 mg/kg tested positive for treatment-induced anti-crizanlizumab antibodies.

In a single-dose study of healthy subjects, 1 of the 61 (1.6%) evaluable subjects tested positive for a treatment-induced anti- crizanlizumab antibodies. No treatment induced anti-crizanlizumab antibodies were detected (0 of 84 patients) in a Phase 3 study at 5 mg/kg over the 52 week time period (samples collected at baseline, Weeks 3, 15, 19, 27, and 51). Therefore, no significant effect on pharmacokinetics or pharmacodynamics has been observed or is expected.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with crizanlizumab.

In the 26-week repeat-dose toxicity study, cynomolgus monkeys were administered crizanlizumab once every 4 weeks at

doses up to 50 mg/kg (at least 13.1 times the human clinical exposure based on AUC in patients with sickle cell disease at 5 mg/kg once every 4 weeks). There were no adverse effects of crizanlizumab on male or female reproductive organs.

14.2 Animal Toxicology and/or Pharmacology

In the 26-week repeat-dose toxicity study, administration of crizanlizumab in cynomolgus monkeys at dose levels up to 50 mg/kg/dose once every 4 weeks resulted in inflammation of the vessels in multiple tissues in 2 out of 10 animals.

15 CLINICAL STUDIES

SUSTAIN

The efficacy of ADAKVEO was evaluated in patients with sickle cell disease in SUSTAIN [NCT01895361], a 52-week, randomized, multicenter, placebo-controlled, double-blind study. A total of 198 patients with sickle cell disease, any genotype (HbSS, HbSC, HbS/beta^0-thalassemia, HbS/beta$^+$-thalassemia, and others), and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. Patients were randomized 1:1:1 to ADAKVEO 5 mg/kg (N = 67), ADAKVEO 2.5 mg/kg (N = 66), or placebo (N = 65) administered over a period of 30 minutes by intravenous infusion on Week 0, Week 2, and every 4 weeks thereafter for a treatment duration of 52 weeks. Randomization was stratified by patients already receiving hydroxyurea (Y/N) and by the number of VOCs in the previous 12 months (2 to 4, 5 to 10).

Patients received ADAKVEO (with or without hydroxyurea) and were allowed to receive occasional transfusions and pain medications [i.e., acetaminophen ,NSAIDs, and opioids] on an as needed basis.

Patients recruited in the study had complications associated with sickle cell disease and other comorbidities, including a history of acute chest syndrome (18%); pulmonary hypertension (8%); priapism (7%); psychiatric manifestations (25%), including depression and anxiety; hypertension (17%); cholelithiasis (17%). Demographic and other baseline characteristics were similar among the treatment groups (see Table 4).

Table 4: Demographics and Baseline Characteristics in SUSTAIN Study

	ADAKVEO 5 mg/kg (N = 67)	**Placebo (N = 65)**
Age (years)		
Median	29	26
Range	16, 63	16, 56
Gender, n (%)		
Male	32 (48%)	27 (42%)
Female	35 (52%)	38 (59%)
Ethnicity, n (%)		
Hispanic or Latino	20 (30%)	11 (17%)
Not Hispanic or Latino	45 (67%)	53 (82%)
Unknown	2 (3%)	1 (2%)
Race		
Black or African American	60 (90%)	60 (92%)
White	4 (6%)	3 (5%)
Other	3 (5%)	2 (3%)
Sickle cell disease genotype, n (%)		
HbSS	47 (70%)	47 (72%)
HbSC	9 (13%)	8 (12%)
HbS/beta^0 - thalassemia	3 (5%)	7 (11%)
HbS/beta$^+$ - thalassemia	7 (10%)	1 (2%)
Other	1 (2%)	2 (3%)
Hydroxyurea use, n (%)		

Yes	42 (63%)	40 (62%)
No	25 (37%)	25 (39%)
Number of VOCs in previous 12 months, n (%)		
2 to 4	42 (63%)	41 (63%)
5 to 10	25 (37%)	24 (37%)

Abbreviation: VOCs, vasoocclusive crises.

Efficacy was evaluated in the SUSTAIN study by the annual rate of VOCs leading to a healthcare visit. A VOC leading to a healthcare visit was defined as an acute episode of pain with no cause other than a vasoocclusive event that required a medical facility visit and treatment with oral or parenteral opioids, or parenteral NSAIDs. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) were also considered VOCs.

Patients with sickle cell disease who received ADAKVEO 5 mg/kg had a lower median annual rate of VOC compared to patients who received placebo (1.63 vs. 2.98) which was statistically significant (p = 0.010). Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use.

Thirty-six percent (36%) of patients treated with ADAKVEO 5 mg/kg did not experience a VOC compared to 17% of placebo-treated patients. The median time to first VOC from randomization was 4.1 months in the ADAKVEO 5 mg/kg arm compared to 1.4 months in the placebo.

The main efficacy results of the pivotal study, SUSTAIN, are summarized in Table 5.

Table 5: Efficacy Results From SUSTAIN Trial in Sickle Cell Disease[a]

Event	**ADAKVEO, 5 mg/kg[b] (n=67)**	**Placebo[b] (n=65)**	**Treatment Difference Estimate[c]**
Annual rate of VOCs[a]	1.63	2.98	HL = -1.01, (-2.00, 0.00)
Annual rate of days hospitalized	4	6.87	

Abbreviations: HL, hodges-lehmann; VOCs, vasoocclusive crises.
[a]VOCs were as assessed by an independent review committee.
[b]Standard median.
[c]HL median difference [95% confidence interval (CI)].

STAND

The efficacy of two doses of ADAKVEO, with or without HU/HC, was evaluated, but not established, in the STAND trial [NCT03814746], a randomized, placebo-controlled, double-blind, multicenter clinical study in adolescent and adult sickle cell disease patients with a history of VOCs. The efficacy results of STAND study are summarized in Table 7 below.

In this study, VOC was defined as a pain crisis (acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion) which requires therapy with oral or parenteral opioids or parenteral NSAID. Acute chest syndrome (ACS), priapism and hepatic or splenic sequestration were considered VOCs in this study.

A total of 252 sickle cell disease patients were randomized to the study, 85 in placebo arm, 84 in ADAKVEO 5 mg/kg arm and 83 in ADAKVEO 7.5 mg/kg arm. The 7.5 mg/kg ADAKVEO dose is not approved and is not recommended for use. Demographic and other baseline characteristics were similar among the treatment groups (see Table 6).

Table 6: Demographics and Baseline Characteristics in STAND Study

	ADAKVEO 5 mg/kg (N = 84)	**Placebo (N = 85)**
Age (years)		
Median	24	25
Range	12, 64	12, 68

	ADAKVEO 5 mg/kg (N = 84)	Placebo (N = 85)
Gender, n (%)		
Female	45 (54%)	49 (58%)
Male	39 (46%)	36 (42%)
Race, n (%)		
Black or African American	46 (55%)	43 (51%)
White	27 (32%)	26 (31%)
Asian	6 (7%)	6 (7%)
Other	5 (6%)	10 (12%)
Genotype, n (%)		
HbSS	58 (69%)	58 (68%)
HbSC	11 (13%)	12 (14%)
HbS/beta^{+} - thalassemia	8 (10%)	8 (9%)
HbS/beta^{0} - thalassemia	5 (6%)	6 (7%)
Other	2 (2%)	1 (1%)
Ethnicity, n (%)		
Not Hispanic or Latino	54 (64%)	57 (67%)
Hispanic or Latino	22 (26%)	18 (21%)
Other (not reported/unknown)	8 (10%)	10 (12%)
Hydroxyurea use, n (%)		
Yes	62 (74%)	61 (72%)
No	20 (24%)	23 (27%)
Missing	2 (2%)	1 (1%)
Number of VOC leading to healthcare visit in the last 12 months, n (%)		
< 5	62 (74%)	58 (68%)
≥ 5	21 (25%)	27 (32%)
Missing	1 (1%)	0

The percentages for subgroups of race and genotype do not add up to 100% due to rounding to 1 decimal place. The results of the efficacy analysis did not confirm the statistical superiority of ADAKVEO over placebo in reducing VOCs leading to a healthcare visit over the first-year post randomization.

Table 7: Efficacy Results From STAND Trial in Sickle Cell Disease

				Between-Treatment Comparison		
Treatment	**n**	**Adjusted Annualized Rate of VOC**	**(95% CI)**	**Comparison**	**Rates Ratio**	**(95% CI)**
ADAKVEO 5 mg/kg	84	2.49	(1.90, 3.26)	vs Placebo	1.08	(0.76, 1.55)*
Placebo	85	2.30	(1.75, 3.01)			

Treatment	n	Adjusted Annualized Rate of VOC	(95% CI)	Between-Treatment Comparison Comparison	Rates Ratio	(95% CI)

n: Total number of participants included in the analysis.
Obtained from fitting a negative binomial regression model with treatment and randomization stratification factors (baseline VOC and HU/HC) as covariates. The natural log of the observation period was used as offset.

*The 95% CI includes 1, which indicates that the result is not statistically significant.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ADAKVEO (crizanlizumab) injection is a sterile, clear to opalescent, colorless to slightly brownish-yellow solution for intravenous infusion supplied as:

Carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial

The single-dose vial has a rubber stopper and an aluminum cap with a plastic flip-off disk. Each 10 mL vial is made of Type 1 glass.

Storage and Handling

- Store and transport refrigerated at 2°C to 8°C in the original carton to protect from light.
- Do not freeze.
- The expiry date of the product is indicated on the packaging materials.

17 LICENSE HOLDER AND IMPORTER AND ITS ADRESS

Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

18 REGISTRATION NUMBER

168-71-36562-00

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