CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761128Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761128
PDUFA Goal Date	November 16, 2019
OSE RCM #	2019-1064; 2019-1075
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	October 09, 2019
Subject	Review to determine if a REMS is necessary
Established Name	crizanlizumab
Trade Name	Adakveo
Name of Applicant	Novartis Pharmaceuticals Corporation
Therapeutic Class	IgG2 kappa humanized anti-P-selectin monoclonal antibody 100 mg/10
Formulation(s)	mL (10 mg/mL) injection solution in a single-dose vial
Dosing Regimen	Administer 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity crizanlizumab is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a Biologic Licensing Application (BLA) 761128 for crizanlizumab with the proposed indication for the prevention of vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and over. The serious risks associated with the use of crizanlizumab are infusion-related reactions, laboratory test interference and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

DRISK and Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of crizanlizumab outweigh its risks. Sickle cell disease is an inherited, lifelong blood disorder that can cause significant morbidity and early mortality. VOCs are the most common acute, recurrent, unpredictable, and painful manifestation of SCD. VOCs are a major cause of morbidity and organ damage, and the most frequent cause of emergency room visits and hospitalizations. Despite the advances in early detection and preventive/symptomatic treatments, mainly in developed countries, progress has been limited and even with the best care, quality of life remains poor with life expectancy reduced by about 20-30 years in a high-income setting. As treatment options for VOCs are limited, and despite available therapies, most patients continue to experience VOCs and related complications, or are unable to tolerate/unwilling to comply with therapies such as hydroxyurea/-carbamide. In light of the high burden of disease, there remains a clear medical need for effective and safe therapies for the prevention of vaso-occlusive events/crises. In the clinical trial, crizanlizumab appeared efficacious in both its primary and secondary outcomes. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of crizanlizumab to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older sickle cell disease. The most concerning adverse reactions observed with the use of crizanlizumab are of infusion-related reactions, laboratory test interference and embryo-fetal toxicity. If crizanlizumab is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with crizanlizumab, as well as information to be included in section 17, Patient Counseling Information and a PPI, to inform patients and increase the prominence of this information and promote its mitigation.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) crizanlizumab is necessary to ensure the benefits outweigh its risks. Novartis Pharmaceuticals Corporation submitted a Biologic Licensing Application (BLA) 761128 for crizanlizumab with the proposed indication for the prevention of vaso-occlusive crises (VOCs) in sickle cell disease patients aged 16 years and over.[1] The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information and a Patient Package Insert (patient labeling or PPI).

2 Background

2.1 PRODUCT INFORMATION

Crizanlizumab is a NME BLA type 351(a) pathway application.[a] It is a IgG2 kappa humanized monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1. Binding P-selectin on the surface of the activated endothelium and platelets has been shown to effectively block interactions between endothelial cells, platelets, red blood cells, and leukocytes.[1] Crizanlizumab is prepared as 100 mg/10 mL (10 mg/mL) injection solution in a single-dose vial to be administered intravenously. The recommended dose of crizanlizumab is 5 mg/kg by intravenous infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter.[b] Crizanlizumab was granted orphan drug designation on June 22, 2008, and breakthrough therapy designation on December 20, 2018. Crizanlizumab is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for crizanlizumab (BLA 761128) relevant to this review:

- 06/22/2008: Orphan Drug designation granted
- 03/02/2011: Investigation New Drug (IND) 110752 submission for crizanlizumab (SEG101) was received.
- 12/20/2018: Breakthrough therapy designation granted.
- 05/16/2019: BLA 761128 submission for crizanlizumab with the proposed indication for the prevention of VOCs in sickle cell disease patients aged 16 years and over, received.
- 08/28/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for crizanlizumab.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Sickle cell disease (SCD) is an inherited, lifelong blood disorder that causes individuals to produce abnormal hemoglobin, causing their red blood cells to become rigid and sickle-shaped. SCD is a group of genetic blood disorders caused by a single missense mutation (Glu6Val) in the β-globin gene, which early on progresses to a systemic disease resulting in complications such as vaso-occlusion, multi-organ damage, and early death.[2] Some patients are constantly ill and display most of the clinical and laboratory sub phenotypes of this disease; others have few overt signs and symptoms. However, it is

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

rare for an affected individual to escape the consequences of HbS polymerization that drives sickle vaso-occlusion and the hemolytic anemia that continues even when acute events are quiescent.[3] Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease and can lead to tissue ischemia and damage, potentially resulting in serious complications.[4] VOCs are the most common acute, recurrent, unpredictable, and painful manifestation of SCD. VOCs are a major cause of morbidity and organ damage, and the most frequent cause of emergency room visits and hospitalizations. VOCs are significantly associated with early mortality, and among the most common causes of death in patients with SCD.[5,6] Sickle-cell anemia is particularly common among people whose ancestors come from sub-Saharan Africa, India, Saudi Arabia, and Mediterranean countries. Because of population movements, the distribution of SCD has spread far beyond its origins.[7] SCD is a heterogeneous disease affected by environmental factors and genetic variability. SCD genotypes include homozygous hemoglobin SS (HbSS), hemoglobin sickle cell disease (HbSC), hemoglobin sickle beta zero (HbSβ0)-thalassemia, hemoglobin sickle beta plus thalassemia (HbSβ+)-thalassemia, and others. The most common and most severe form of SCD, known as sickle cell anemia, presents in patients with the homozygous HbSS genotype. Patients with heterozygous genotypes (with the exception of HbSβ0-thalassemia) usually have a less severe form of the disease, however, individual patients may present with severe SCD regardless of their genotype.[8] It is estimated that in the United States, the population of sickle cell disease is approximately 100,000 and likely to increase. Current projections estimate that the number of newborns with SCD globally will exceed 400,000 by 2050.[9,c] The most common genotype is homozygous hemoglobin SS (HbSS), and common heterozygous conditions are hemoglobin sickle beta zero thalassemia, hemoglobin sickle beta plus thalassemia (hemoglobin sickle beta plus thalassemia), and hemoglobin sickle cell disease (HbSC). SCD is a multisystem disorder and the most common genetic disease in the United States, affecting 1 in 500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans.[10] About 1 in 12 African Americans carry the autosomal recessive mutation, and approximately 300,000 infants are born with sickle cell anemia annually.[11] Sickle cell disease has no cure and is associated with life-threatening complications. The life expectancy in sickle cell disease is reduced overall (perhaps by 20 to 30 years) compared to normal adults.[11,d]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Sickle cell anemia management can be considered in two categories, health maintenance, and management of complications. The goal of health maintenance is to screen and identify risk factors and early signs of complications. There is evidence that pneumococcal vaccination, penicillin prophylaxis (early infancy until at least age five), and education of the management of fever have considerably reduced mortality and morbidity from invasive infections. Routine screening with transcranial Doppler (TCD) of large intracranial blood vessels may predict the risk of stroke in children with sickle cell disease, but this may not be universally available. Further, the treatment (chronic transfusion therapy) is not feasible in many developing nations.[12]

Management of sickle cell complications is tailored to the type of complication. VOC management consists of rapid pain assessment, early initiation of analgesic therapy and maintaining this analgesia

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

(consider PCA pump), and hydration until there is symptom relief.[13] For most patients with mild pain, acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) may suffice, but for moderate and severe pain, opiates with or without NSAIDs are indicated.[11] More recently Ketamine in sub-dissociative doses has shown to reduce opiate use.[14] Patients presenting with fever should be immediately assessed for life-threatening infections including the performance of complete blood count (CBC) with differential, reticulocyte count, blood culture, and urine culture if urinary tract infection (UTI) is suspected, and broad-spectrum antibiotic therapy should be initiated. For most other complications like acute chest syndrome, splenic sequestration, and strokes, meticulous supportive care (oxygen, judicious fluid administration) and transfusion therapy are needed. Among patients who have frequent and severe complications, hydroxyurea has been shown to offer significant benefit.[15] Hematopoietic stem cell transplantation (HST) (bone marrow transplantation) shows great promise as a cure for sickle cell disease.[9] Antihistamines (diphenhydramine, hydroxyzine) may reduce itching caused by the opiates and may have some opioid-sparing effect. For acute chest syndrome, empirical antibiotics (cephalosporin and macrolide), adequate analgesics, oxygen supplementation, simple or exchange transfusion, beta-agonist inhalations, and incentive spirometry may be needed.[11]

Despite the advances in early detection and preventive/symptomatic treatments, mainly in developed countries, progress has been limited and, even with the best care, quality of life remains poor, and life expectancy is still reduced by about 20-30 years in a high-income setting. As treatment options for VOCs are limited, and despite available therapies, most patients continue to experience VOCs and related complications, or are unable to tolerate/unwilling to comply with therapies such as hydroxyurea/-carbamide. In light of the high burden of disease, there remains a clear need for effective and safe therapies for the prevention of vaso-occlusive events/crises.

4 Benefit Assessment

The efficacy of crizanlizumab was evaluated in a 52-week, phase II, randomized, multicenter, placebo-controlled, double-blind trial (SUSTAIN; study A2201 [NCT01895361]). A total of 198 patients with sickle cell disease, any genotype (HbSS, HbSC, HbSeta^0-thalassemia, HbSeta$^+$-thalassemia, and others), and a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. Patients received crizanlizumab with or without hydroxyurea and were allowed to receive occasional transfusions on an as needed basis, as well as pain medications [i.e., acetaminophen, NSAIDs, and opioids]. Patients were randomized 1:1:1 to crizanlizumab 5 mg/kg (N = 67), crizanlizumab 2.5 mg/kg (N = 66), or placebo (N = 65) 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). VOCs were defined as those leading to a healthcare visit, which captured all acute episodes of pain with no other cause than a vaso-occlusive 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.

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for crizanlizumab. Treatment with crizanlizumab 5 mg/kg had a lower median annual rate of VOC compared to placebo (1.63 vs. 2.98), which was statistically significant (p = 0.010). Clinically significant reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use as

shown in Table 1.[1,16,e] Treatment with crizanlizumab 5 mg/kg also resulted in a greater than 2-fold increase in the proportion of patients with no VOC (36% compared to 17% of placebo subjects), a 3-fold delay in the time to first VOC (Standard median of 4.07 of crizanlizumab 5 mg/kg subjects compared to Standard median of 1.38 of placebo subjects), a 2-fold delay in time to second VOC from randomization (Standard median of 10.32 of crizanlizumab 5 mg/kg subjects compared to Standard median of 5.09 of placebo subjects) and a numerical reduction in median annual rate of days hospitalized compared to placebo.[16,e]

Table 1: Results from SUSTAIN Clinical Trial in Sickle Cell Disease[a,1,16,e]

Event	**Crizanlizumab 5 mg/kg (n = 67)**	**Placebo (n = 65)**	**Treatment Difference Estimate**
Annual rate of VOC[b,a]	1.63	2.98	HL = -1.01 (-2.00, 0.00)
Annual rate of days hospitalized[b,a]	4.00	6.87	

Abbreviations: HL, Hodges-Lehmann; VOC, vaso-occlusive crises; OR, odds-ratio; HR, hazard ratio.
[a]VOCs were as assessed by an independent review committee.
[b]Standard median, HL median difference (95% CI).

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for crizanlizumab. The safety analysis of crizanlizumab primarily focuses in 175 patients with sickle cell disease (any genotype including HbSS, HbSC, HbSeta^0-thalassemia, and HbSeta$^+$-thalassemia) in SUSTAIN and study A2202. The safety of crizanlizumab was evaluated in the SUSTAIN trial (study A2201) (phase II, randomized, double-blind, placebo-controlled study) and study A2202 (phase II, single-arm, open-label, pharmacokinetics/pharmacodynamics/safety study). In the SUSTAIN trial, patients received crizanlizumab 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. In study A2202, patients received crizanlizumab 5 mg/kg (N=45) by intravenous infusion. Among the 111 patients that received the recommended dose (5 mg/kg), 75 (68%) patients were treated with crizanlizumab in combination with hydroxyurea.[1]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Deaths

A total of 6 deaths in the crizanlizumab arm were reported in the clinical development program. In Study A2201, on-treatment deaths were rare and balanced between arms. Two patients died in the 5 mg/kg treatment arm: 1 patient due to sickle cell anemia with VOC and 1 patient due to endocarditis and sepsis in the context of catheter/port contamination; one patient died in the 2.5 mg/kg treatment arm due to acute chest syndrome, aspiration, respiratory failure, and angiopathy. Two patients died in the placebo treatment arm: 1 patient due to right ventricular failure and 1 patient due to sickle cell anemia with VOC, ischemic stroke, coma, sepsis, and venous thrombosis of the right lower limb.[17] One additional death was reported in Study A2202; the patient was treated with crizanlizumab 7.5 mg/kg. Two months and three days after the first dose and 25 days after last dose the subject presented to the emergency department unresponsive and in asystole with suspected respiratory arrest leading to cardiac arrest. The sponsor commented that, based on the available information, the patient was on narcotics with positive urine screens for opioids and barbiturates. At baseline the patient had cirrhosis and chronic renal failure. Baseline liver and renal function tests, as well as urine screening for drug substances during the 3 visits were not known; however, the patient had increased liver enzymes and serum creatinine levels after receiving 3 doses of study medication. Also, the patient was in cardiac failure at the time of death. Autopsy results and cause of death were not available.[18]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 24 of patients (21.6%; n=111) receiving crizanlizumab 5 mg/kg subjects in safety pool compared with 8 of placebo subjects (12.9%, n=62). Serious adverse reactions in >1% of patients who received crizanlizumab included pneumonia (3 patients), pyrexia, endocarditis, and urinary tract infection (2 patients each). Dosage interruptions due to an adverse reaction occurred in 7 of patients (6.3%; n=111) who received crizanlizumab 5 mg/kg subjects in safety pool compared with 1 of placebo subject (1.6%, n=62). In the safety pool, AEs leading to discontinuation were reported in 3 of patients (2.7%; n=111) receiving crizanlizumab 5 mg/kg subjects in safety pool compared with 2 of placebo subjects (3.2%, n=62).[17]

(b) (4)

5.1 INFUSION-RELATED REACTIONS (IRR)

In the safety pool (n=111), 28 (25.2%) patients had IRR events. In clinical trials, infusion-related reactions (defined as occurring within 24 hours of infusion) were observed in 2 (1.8%) patients treated with crizanlizumab 5 mg/kg. Most events were reported in 1 or 2 patients only, except for headache and nausea (8 patients each, 7.2%), arthralgia (5 patients, 4.5%), back pain (4 patients, 3.6%), fatigue and myalgia (3 patients each, 2.7%). Only 1 of these events (headache) was considered to be related to study treatment as per investigator assessment. None of the events were grade 3 or 4 in severity. In the safety pool, 2 (1.8%) patients had IRR events using the “severe reactions” search. The PT (preferred term) reported for both patients was infusion related reaction (1 grade 1 and 1 grade 2, none serious). Both patients had interruption of crizanlizumab, and the event resolved without sequelae at data cutoff. The first patient received only 1 infusion and the event was reported verbatim as “elevation of temperature during infusion” without additional details; no further information on why the study drug was not continued was provided (“discontinued study due to other / unblinding”). The second patient was reported with the verbatim, “enuresis while sleeping during infusion”, and was coded as an infusion

related reaction. The applicant stated that none of these AEs were suggestive of severe allergic or anaphylactic reactions and most patients continued their treatment without need for premedication.[19] If approved, the risk of infusion related reactions will likely be communicated with in the Warnings and Precautions section of the label.[1]

5.2 LABORATORY TEST INTERFERENCE

Interference with automated platelet counts (platelet clumping) when blood samples were collected in tubes containing Ethylenediaminetetraacetic Acid (EDTA) were observed following administration of crizanlizumab. This may lead to unevaluable or falsely decreased platelet counts. There is no evidence that it causes a true reduction in circulating platelets or has an effect on platelet aggregation in vivo. Labeling instructs to run the blood samples as soon as possible (i.e., within 4 hours of blood collection) or draw blood samples in tubes containing citrate. Labeling also recommends the estimation of platelet count via peripheral blood smear, when needed. If approved, the risk of laboratory test interference will likely be communicated in the Warnings and Precautions and Drug Interactions sections of the label.[1]

5.3 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, crizanlizumab can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, administration of crizanlizumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased fetal loss at maternal exposures (AUC) approximately (b) (4) times the AUC in patients receiving the recommended dose (b) (4)

(b) (4)

6 Expected Postmarket Use

According to the current proposed indication, if approved, crizanlizumab will be used in both inpatient and outpatient settings such as infusion centers or home infusion and will be prescribed by various types of healthcare providers such as hematologists or experienced general pediatricians, internists, family practitioners, and emergency medicine physicians.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for crizanlizumab beyond routine pharmacovigilance and labeling. The applicant proposed a PI that includes Warnings and Precautions to address the risks of infusion-related reactions, laboratory test interference and embryo-fetal toxicity, as well as a PPI.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for crizanlizumab, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for crizanlizumab will be various types of healthcare providers such as such as

hematologists or experienced general pediatricians, internists, or family practitioners, and emergency medicine physicians. The risks identified are risks that these providers have likely encountered in their practice experience.

Crizanlizumab is a IgG2 kappa humanized monoclonal antibody, with the proposed indication for the prevention of VOCs in sickle cell disease patients aged 16 years and over.[1] At the time of this writing, labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that crizanlizumab shows clinically meaningful benefit to sickle cell disease patients, and recommends approval of crizanlizumab to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older sickle cell disease.[f,17]

Sickle cell disease is an inherited, lifelong blood disorder that can cause significant morbidity and early mortality. VOCs are the most common acute, recurrent, unpredictable, and painful manifestation of SCD. VOCs are a major cause of morbidity and organ damage, and the most frequent cause of emergency room visits and hospitalizations. VOCs are significantly associated with early mortality, and among the most common causes of death in patients with SCD. Despite the advances in early detection and preventive/symptomatic treatments, mainly in developed countries, progress has been limited and even with the best care, quality of life remains poor, and life expectancy is still reduced by about 20-30 years in a high-income setting. As treatment options for VOCs are limited, and despite available therapies, most patients continue to experience VOCs and related complications, or are unable to tolerate/unwilling to comply with therapies such as hydroxyurea/-carbamide. In light of the high burden of disease, there remains a clear need for effective and safe therapies for the prevention of vaso-occlusive events/crises. Crizanlizumab appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of crizanlizumab outweigh its risks. The most concerning adverse reactions observed with the use of crizanlizumab are of infusion-related reactions, laboratory test interference and embryo-fetal toxicity. If crizanlizumab is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with crizanlizumab, as well as information to be included in section 17, Patient Counseling Information and in the PPI to inform patients and increase the prominence of this information and promote its mitigation. At this time, none of these risks will receive a boxed warning in the label. Additionally, the applicant will be required to conduct the post-marketing required (PMR) study to (b) (4)

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of crizanlizumab. The management of the risks associated with crizanlizumab treatment will be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

[f] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is updated and significant changes to the proposed label made by FDA prior to negotiations.

10 References

(b) (4)

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[16] Wang Y. Statistical Review Presentation. Mid-Cycle Meeting, dated August 16, 2019.

(b) (4)

[18] Novartis Pharmaceuticals Corporation. SCS Appendix 2: Deaths and SAEs in Ongoing Studies. In: Clinical Study Reports of crizanlizumab, dated April 30, 2019.

[19] Novartis Pharmaceuticals Corporation. Summary of Clinical Safety of crizanlizumab, dated April 30, 2019.

[20] Late-Cycle Meeting, dated October 04, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
10/09/2019 02:24:54 PM

ELIZABETH E EVERHART
10/09/2019 02:39:08 PM
I concur.

CYNTHIA L LACIVITA
10/09/2019 06:07:58 PM