

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761128Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

BLA Multi-Disciplinary Review and Evaluation  
 BLA 761128  
 ADAKVEO (Crizanlizumab-tmca)

### BLA Multi-Disciplinary Review and Evaluation

<b>Application Type</b>	BLA
<b>Application Number(s)</b>	761128
<b>Priority or Standard</b>	Priority
<b>Submit Date(s)</b>	February 19, 2019; March 15, 2019; March 29, 2019; April 30, 2019; May 16, 2019
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<b>Division/Office</b>	Division of Hematology Products and Office of Oncologic Diseases
<b>Review Completion Date</b>	November 14, 2019
<b>Established/Proper Name</b>	Crizanlizumab-tmca
<b>(Proposed) Trade Name</b>	ADAKVEO®
<b>Pharmacologic Class</b>	Monoclonal antibody
<b>Code name</b>	SEG101
<b>Applicant</b>	Novartis Pharmaceuticals Corporation
<b>Dosage form</b>	Concentrate for solution for infusion
<b>Applicant proposed Dosing Regimen</b>	Administer 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter
<b>Applicant Proposed Indication(s)/Population(s)</b>	For the prevention of vasoocclusive crises (VOCs) in sickle cell disease patients aged 16 years and over.
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	To reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.
<b>Recommended Dosing Regimen</b>	Administer ADAKVEO 5 mg/kg by intravenous infusion over a period of 30 minutes at Week 0, Week 2, and every 4 weeks thereafter

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## Reviewers of Multi-Disciplinary Review and Evaluation

<b>Regulatory Project Manager</b>	Michael Gwathmey
<b>Nonclinical Reviewer</b>	Ramadevi Gudi, PhD
<b>Nonclinical Team Leader</b>	John Leighton, PhD
<b>Office of Clinical Pharmacology Reviewer</b>	Xiang Jiang, PhD
<b>Office of Clinical Pharmacology Team Leader</b>	Olanrewaju Okusanya, PharmD, MS
<b>Clinical Reviewers</b>	Patricia Oneal, MD; Roseanna Setse, MD, PhD
<b>Clinical Team Leader</b>	Tanya Wroblewski, MD
<b>Safety Analyst (if applicable)</b>	Qin Ryan, MD, PhD; Roseanna Setse, MD, PhD
<b>Statistical Reviewer</b>	Yaping Wang, PhD
<b>Statistical Team Leader</b>	Yeh-Fong Chen, PhD
<b>Cross-Disciplinary Team Leader</b>	Tanya Wroblewski, MD
<b>Division Director (DHOT)</b>	John Leighton, PhD
<b>Division Director (DCP1)</b>	Brian Booth, PhD (Acting)
<b>Division Director (OB) or designee</b>	Thomas Gwise, PhD
<b>Supervisory Associate Division Director (DHP)</b>	Albert Deisseroth, MD, PhD
<b>Office Director (or designated signatory authority)</b>	Richard Pazdur, MD (Acting)

## Additional Reviewers of Application

<b>OPQ</b>	Mekonnen LemmaDechassa, PhD; Ramesh Potla, PhD (ATL); Susan Kirshner, PhD (Review Chief)
<b>Microbiology</b>	Max Van Tassell, PhD (DS); Diane Raccasi, PhD (DP); Reyes Cancau-Chacon, PhD (TL); Patricia Hughes, PhD (Branch Chief)
<b>Immunogenicity</b>	Joao Pedras-Vasconcelos, PhD
<b>Facilities</b>	Zhong Li, PhD; Peter Qiu, PhD (TL)
<b>OPDP</b>	Robert Nguyen, PharmD
<b>DMPP</b>	Sharon R. Mills, BSN, RN, CCRP
<b>OSI</b>	Anthony Orenca, MD
<b>OSE/DMEPA</b>	Stephanie DeGraw, PharmD; Hina Mehta, PharmD (TL)
<b>OSE/DRISK</b>	Till Olickal, PharmD, PhD; Liz Everhart, MSN, RN, ACNP (TL)
<b>OSE/DEPI</b>	Peter Waldron, MD; Neha Gada, PharmD (TL)
<b>Associate Director for Labeling</b>	Virginia Kwitkowski, MS, ACNP-BC

OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology

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DMEPA=Division of Medication Error Prevention and Analysis  
DRISK=Division of Risk Management

## Glossary

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AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

## 1 Executive Summary

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### 1.1. Product Introduction

Crizanlizumab-tmca (ADAKVEO<sup>®</sup>, SEG101) is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1. P-selectin is an adhesion molecule expressed on activated endothelial cells and platelets. Its role is critical in the initial recruitment of leukocytes and aggregation of platelets at the site of vascular injury during the inflammatory state associated with vasoocclusive crises (VOCs) of patients with sickle cell disease (SCD).

Crizanlizumab was originally developed by Reprixys Pharmaceutical Corporation, until Novartis acquired the company in November 2016. Up to the time of acquisition, all pre-clinical and clinical studies (including the registrational study CSEG101A2201/SUSTAIN) used Reprixys manufactured crizanlizumab (SelG1). Novartis continued technical development and production of crizanlizumab under the code SEG101 and Novartis-manufactured crizanlizumab, SEG101, is planned for commercialization. SelG1 and SEG101 were shown to be comparable inhibitors and demonstrated similar PK and comparable PD profiles in healthy subjects. For the purposes of this review, crizanlizumab refers to crizanlizumab-tmca or ADAKVEO as well as SEG101 or SelG1.

The Applicant's proposed indication is for the prevention of vasoocclusive crises (VOCs) in sickle cell disease patients aged 16 years and over. The Agency's proposed indication is for the reduction in the frequency of vasoocclusive crises (VOCs) in patients aged 16 years and older with sickle cell disease. The recommended dosage is 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for crizanlizumab-tmca in in adult and pediatric patients aged 16 years and older with sickle cell disease to reduce the frequency of vasoocclusive crisis (VOC). This conclusion was based on the results from a 52-week randomized, multicenter, double-blind, placebo-controlled trial (SUSTAIN). A total of 198 patients with sickle cell disease with a history of 2-10 VOCs in the previous 12 months were eligible for inclusion. Patients were randomized 1:1:1 to ADAKVEO 5mg/kg (N=67), ADAKVEO 2.5mg/kg (N=66), or placebo (N=65) by intravenous infusion over 30 minutes every 2 weeks x2, followed by every four weeks thereafter for 52 weeks of treatment. Efficacy was evaluated in the SUSTAIN study by annual rate of VOCs leading to a healthcare visit. A VOC leading to 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 non-steroidal anti-inflammatory drugs (NSAIDs). Patients with sickle cell disease who received ADAKVEO 5mg/kg had a lower median annual rate of VOC compared to

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patients who received placebo (1.63 vs 2.98) which was statistically significant ( $p=0.010$ ). In summary, crizanlizumab-tmca treatment was associated with a clinically meaningful and statistically significant decrease in annual rates of VOCs compared to placebo.

### 1.3. Benefit-Risk Assessment

#### Benefit-Risk Summary and Assessment

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the  $\beta$ -globin gene which progresses into a complex disease characterized by acute and chronic inflammation. There are limited treatment options and a high unmet medical need. Vasoocclusive crisis are an acute, recurrent complication of sickle cell disease that causes significant morbidity and organ damage. VOCs are the most frequent cause of emergency room visits and hospitalizations and are associated with early mortality. Nearly every clinical manifestation of SCD correlates with the white blood cell (WBC) count. Since leukocytosis is common among patients with SCD and is accompanied by elevated levels of circulating inflammatory cytokines including tumor necrosis factor (TNF- $\alpha$ ), interleukin (IL)-1, and IL-8 along with adhesion molecules like, vascular cell adhesion molecule-1 (VCAM), selectins, laminin, thrombospondin, fibronectin and  $\alpha\beta$ 3 integrin, there has been a considerable effort directed toward designing therapeutics to alleviate the clinical severity of SCD. The adhesion interactions between sickle red blood cells (RBCs), leukocytes, platelets and the vascular endothelium cause vasoocclusion, ischemia, and reperfusion injury that result in acute vasoocclusive pain episodes, acute chest syndrome (ACS) and, over time, ischemic organ damage. VOCs are typically managed symptomatically with analgesics and other supportive therapies. The only FDA-approved therapies to reduce the frequency of VOCs in patients with SCD are hydroxyurea/hydroxycarbamide (HU/HC) (Droxia; Bristol Myers Squibb) and L-Glutamine (Endari; Emmaus Medical, Inc.). The use of these agents is complicated by the side effects leading to intolerance or unwillingness to use these therapies, thus leading to continued occurrence of VOCs. Therefore, an unmet medical need exists for the treatment of patients with SCD.

The efficacy of crizanlizumab was evaluated in the Phase 2, randomized, multicenter, placebo-controlled, double-blind study (SUSTAIN) of 198 patients with Hgb SS, SC, S/Beta0 Thalassemia and S/Beta+ Thalassemia between the ages of 16 to 63 years of age with a history of 2-10 vasoocclusive crises in the previous twelve months. 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 52 weeks. Crizanlizumab was administered by intravenous infusion over 20 minutes on Week 0, 2 and every four weeks thereafter. Patients were allowed to receive crizanlizumab with or without hydroxyurea and were allowed to receive occasional transfusions and pain medications on an as needed basis. Randomization was stratified by hydroxyurea (HU) usage and number of crises (2-4 or 5-10). The primary efficacy endpoint was the annualized rate of VOCs leading to a healthcare visit.

The primary evaluation population was the patients who received the 5mg/kg dose compared to placebo. The patients recruited in the study had complications associated with sickle cell disease and other comorbidities including history of acute chest syndrome (18%), pulmonary

hypertension (8%), priapism (7%), psychiatric manifestations (25%) including depression and anxiety, hypertension (17%), and cholelithiasis (17%). The median age was 29 years (range 16, 63) in the crizanlizumab arm and a median age of 26 (range 16, 56) in the placebo arm. Overall, sixty-two (62%) of patients were on hydroxyurea while 65% of patients had a baseline history of 2-4 VOCs.

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 vasocclusive 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 during the 52-week study compared to 17% of placebo-treated patients. The median time to first VOC from randomization was 4.1 months in the ADAKVEO 5mg/kg arm compared to 1.4 months in the placebo.

In general, crizanlizumab was well tolerated. Among the 66 patients that received the recommended dose (5mg/kg), 83% were exposed for 6 months or longer, 61% were exposed for approximately one year, and 42 (64%) were treated with crizanlizumab in combination with hydroxyurea. The most frequently reported adverse reactions (ARs) with an incidence rate of at least 10% in the safety pool were nausea, arthralgia, back pain and pyrexia. The majority of the ARs were mild or moderate (grade 1 or 2). Severe events (grade 3 and above) were observed for pyrexia and arthralgia (1 patient/1.5% each; both grade 3). Serious adverse reactions were reported in 2 patients (3%) treated with crizanlizumab both reactions were pyrexia. Discontinuations due to adverse events (AEs) were rare, reported for 2.7 % of patients in the safety pool. No patients discontinued due to an adverse drug reaction. No cases of drug-induced liver injury due to crizanlizumab were observed. None of the four on-treatment deaths of crizanlizumab-treated patients were considered related to the study treatment by the Investigator or by Novartis and supported by the reviewers of this application.

As with other therapeutic proteins, there is potential for immunogenicity there is a potential for infusion-related reactions (IRRs) and immunogenicity. IRRs were observed in 2 patients (1.8%) in the safety pool, neither of which was serious or required discontinuation. Detection of treatment-induced anti-drug antibodies (ADA) was reported in 1 patient (0.9%); there was no evidence for altered PK, safety or efficacy with ADA development.

In conclusion, sickle cell disease is a serious and life-threatening condition associated with recurrent vasoocclusive pain or crises episodes and chronic hemolytic anemia. The benefit-risk of crizanlizumab 5mg/kg administered over a 30 minute intravenous infusion at Week 0, Week 2 and every 4 weeks thereafter provides meaningful clinical benefit with an acceptable risk profile for patients with sickle cell disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>Sickle cell Disease (SCD) is a systemic disease characterized by acute and chronic vascular occlusion. The pathogenesis of sickle cell disease is due to a complex interplay between adequate blood flow and vessel obstruction involving abnormal polymerization of deoxygenated hemoglobin S (HbS), endothelial cell activation, and acute and chronic inflammation.</li> <li>Sickle cell disease is a life-threatening, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States.</li> <li>Vaso-occlusive crisis is an acute, recurrent, unpredictable complication of SCD that induces tissue ischemia and severe pain. 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.</li> <li>The cumulative effect of recurrent vasoocclusive episodes and chronic hemolytic anemia result in multiple end-organ complications and overall decreased life expectancy in patients with SCD.</li> <li>Patients report that the health effects of sickle cell disease, including excruciating and incapacitating effects of episodic pain crises and acute chest syndrome affects all aspects of their lives. The debilitating symptoms and complex treatment needs limit their</li> </ul>	<p>Sickle Cell Disease is a serious and life-threatening condition with significant morbidity and mortality and reduced life expectancy.</p> <p>The excruciating and incapacitating symptoms and complex treatments of SCD impact all aspects of the patients' lives.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>ability to perform in school, pursue careers, have a family, and maintain relationships. [The Voice of the Patient: Sickle Cell Disease; Report Date October 2014]</p> <ul style="list-style-type: none"> <li>• Patients also report that the disease takes an emotional toll as patients face challenges with the healthcare system, stigma within society, financial hardships, and worry about their future. Both young and old live with constant reminders that they are not able to live a normal life. [The Voice of the Patient: Sickle Cell Disease; Report Date October 2014]</li> <li>•</li> </ul>	
<p><a href="#">Current Treatment Options</a></p>	<p>There are two FDA-approved medications for patients with sickle cell disease, however use of these agents can be complicated by severe side effects (myelosuppression and malignancies) and many patients cannot tolerate or are unwilling to accept the risks of these approved treatments.</p> <ul style="list-style-type: none"> <li>○ Endari® (L-Glutamine ) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.</li> <li>○ Droxia (Hydroxyurea) is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises.</li> </ul> <p>Hematopoietic stem cell transplantation (HSCT) offers potential cure; however, only a small percentage of patients are eligible for this treatment option.</p>	<p>A significant unmet medical need exists for new drugs for the treatment of SCD.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>Management of acute sickle cell episodes is generally only supportive.</p> <ul style="list-style-type: none"> <li>○ Blood transfusions and red cell exchanges: RBC transfusion are used to treat anemia, while RBC exchange transfusions are used to prevent or treat the complications arising from the presence of HbS. Red cell exchange can reduce the HbS percentage without a significant increase in hematocrit or blood viscosity or provision of excess iron.</li> <li>○ Pain medications (including NSAIDs and opiates) are used for acute pain relief.</li> <li>○ Other supportive therapies include: intravenous fluids, supplemental oxygen, etc.</li> </ul>	
<p><u>Benefit</u></p>	<ul style="list-style-type: none"> <li>● Study A2201 (SUSTAIN), a Phase 2, randomized, multicenter, placebo-controlled, double-blinded study of 198 patients with Hgb SS, SC, S/Beta0 Thalassemia and S/Beta+ Thalassemia between the ages of 16 to 63 years of age was conducted.</li> <li>● 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 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.</li> <li>● 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</li> </ul>	<p>Crizanlizumab treatment was associated with a clinically meaningful and statistically significant decrease in annual rates of VOCs compared to placebo.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>= 0.010).</p> <ul style="list-style-type: none"> <li>• Reductions in the frequency of VOCs were observed among patients regardless of sickle cell disease genotype and/or hydroxyurea use.</li> <li>• Thirty-six percent (36%) of patients treated with ADAKVEO 5 mg/kg did not experience a VOC during the 52-week study compared to 17% of placebo-treated patients.</li> <li>• The median time to first VOC from randomization was 4.1 months in the ADAKVEO 5mg/kg arm compared to 1.4 months in the placebo.</li> </ul>	
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>• The most frequently reported adverse reactions (ARs) with an incidence rate of at least 10% in the safety pool were back pain, nausea, pyrexia, and arthralgia.</li> <li>• Severe ARs (grade 3 and above) were observed for pyrexia and arthralgia (1 patient/1.5% each; both grade 3).</li> <li>• Discontinuations due to ARs were rare.</li> <li>• Infusion-related reactions (IRRs) and immunogenicity were observed in 2 patients (1.8%) in the safety pool, neither of which was serious or required discontinuation.</li> <li>• Detection of treatment-induced anti-drug antibodies (ADA) was reported in 1 patient (0.9%).</li> <li>• None of the four on-treatment deaths of crizanlizumab-treated patients were considered related to the study treatment.</li> <li>• The safety of long-term treatment (beyond 1 year) with ADAKVEO is unknown.</li> </ul>	<p>The product label adequately addresses the risks of using this product in patients for the reduction in the frequency of vasoocclusive crises in sickle cell disease patients aged 16 years and older.</p> <p>Long term follow-up and safety with the use of this drug will be an important consideration. Postmarketing requirements will be recommended to address the long-term safety of this product.</p>

#### 1.4. Patient Experience Data

In the SUSTAIN trial, patient-reported outcomes were assessed using the SF-36v2 and the brief pain inventory (BPI). Both tools were collected at study visits prior to and during the Treatment and Follow-Up Evaluation Phases. The patient reported outcome endpoints were exploratory and thus were not included in the prescribing information.

##### Patient Experience Data Relevant to this Application

<input checked="" type="checkbox"/>	<b>The patient experience data that were submitted as part of the application include:</b>	Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input checked="" type="checkbox"/>	Patient reported outcome (PRO)	Section 8.12 Efficacy Results – Secondary or exploratory COA (PRO) endpoints
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data that were not submitted in the application, but were considered in this review:</b>	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input checked="" type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	2/7/2014 FDA Sickle Cell Disease PFDD Meeting

		<a href="https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings#sicklecell">https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings#sicklecell</a>
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify):	
<input type="checkbox"/>	<b>Patient experience data was not submitted as part of this application.</b>	

**X**

Cross Discipline Team Leader  
 Tanya Wroblewski MD

## 2 Therapeutic Context

### 2.1. Analysis of Condition

Sickle-cell disease (SCD) is a life-threatening, hereditary, chronic hemolytic anemia that affects nearly 100,000 individuals in the United States (Yawn, Buchanan et al. 2014). A single point mutation in the hemoglobin  $\beta$ -globin chain of affected persons produces mutant hemoglobin molecules (Hemoglobin S [Hb S]). The most common form of sickle-cell disease (homozygous Hb SS) accounts for 60%-75% of sickle cell disease in the United States. Approximately 25% of patients have coinheritance of Hb S with another  $\beta$ -globin chain variant such as sickle-Hb C disease and sickle  $\beta$ -thalassemia.

During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting in intermittent vaso-occlusive events and chronic hemolytic anemia. Vaso-occlusion occurs as a result of the formation of multicellular aggregates that block blood flow in small blood vessels, resulting in tissue ischemia & reperfusion damage to downstream tissues which lead to recurrent acute pain/crises episodes. Vaso-occlusive pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (Platt, Thorington et al. 1991, Gill, Sleeper et al. 1995). The cumulative effect of recurrent vasoocclusive episodes and sustained hemolytic anemia result in multiple end-organ complications including diastolic heart disease, pulmonary hypertension, splenic dysfunction; hepatobiliary disease and chronic kidney disease.

SCD is associated with decreased life expectancy (Platt 1994, Lanzkron, Carroll et al. 2013, Elmariah, Garrett et al. 2014, Maitra, Caughey et al. 2017). Acute chest syndrome (ACS) is a

serious acute complication and a leading cause of mortality in both children and adults with SCD (Vichinsky, Neumayr et al. 2000, Bakanay, Dainer et al. 2005). Other causes of death in patients with SCD include infections (Adamkiewicz, Sarnaik et al. 2003) kidney failure and cerebrovascular events (Platt 2005, Verduzco and Nathan 2009).

Children have higher rates of death from infection and sequestration crises (Manci, Culberson et al. 2003). Cardiopulmonary complications represent a major mortality risk in adults (Fitzhugh, Lauder et al. 2010). Currently, the management of sickle cell crises (SCC) episodes is generally supportive and includes symptomatic treatment with intravenous fluids, analgesics, oxygen and RBC transfusion support. Hematopoietic stem cell transplantation (HSCT) and gene therapy offer potential cure; however, only few patients are eligible for these treatment option. Hydroxyurea (HU) was approved in 1998 and 2017; for reducing the frequency of sickle cell crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months) and for reducing the frequency of painful crises and the need for blood transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises, respectively . L- glutamine (approved in 2017) is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

Adhesive interactions between circulating sickle red blood cells (RBCs), leukocytes, and endothelial cells are major pathophysiologic events in sickle cell disease (SCD) (Ataga 2017). Endothelial cell P-selectin, a member of the selectin family of cell adhesion molecules,2 plays a key role in leukocyte recruitment as well as the adhesion of sickle RBCs to the endothelium. Presynthesized P-selectin is stored in the Weibel-Palade bodies in endothelial cells and rapidly translocated to the cell surface in response to extracellular stimuli such as hypoxia (Embury 2004, Frenette 2004) . Expression levels of P-selectin are elevated in patients with SCD. The interactions between P-selectin and its ligands are likely to contribute to cell adhesion between multiple types of cells (i.e. leukocytes, endothelial cells and platelets), which results in the impairment of microvascular circulation presumably involved in the development of painful vaso-occlusive episodes. The adherence of sickle erythrocytes and leukocytes to the endothelium is substantially reduced when P-selectin is blocked in transgenic mice expressing human HbS .Because P-selectin-mediated cell adhesion is believed to impair the microvascular flow in SCD, the inhibition of blood cell-endothelial cell interactions by anti-P-selectin aptamer likely contributes to the increase in microvascular flow velocities; hence, contributing to the reduction in the risk of vaso-occlusion, inflammation, and sickle cell-related pain crises (Polanowska-Grabowska R 2010, Turhan 2002).]

## 2.2. Analysis of Current Treatment Options

The clinical complications of SCD result from a cascade of events that starts with the polymerization of HbS. Thus, the goal of disease-modifying therapies is to decrease Hgb S

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concentration, either by increasing HbF levels (HU) or increasing HbA levels (transfusion). Curative options, such as hematopoietic stem cell transplantation (HSCT) and gene therapy, strive to eliminate the production of HbS. Supportive therapies, such as antibiotic prophylaxis, have increased survival of children by preventing death from overwhelming infection, but have not increased overall life expectancy for people living with SCD. With the increasingly widespread use of disease-modifying and curative therapies, the life expectancy will increase and approach that of the average American in the near future.

**Table 1: Summary of Treatment Armamentarium Relevant to Sickle Cell Disease**

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]				
Droxia (Hydroxyurea)	For reducing the frequency of SCD crises in adult patients with SCD and reducing the frequency of painful crises and the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises (generally at least 3 during the preceding 12 months)/For reducing the frequency of painful crises and the need for blood transfusions in patients age 2 and older who have sickle cell anemia with recurring moderate to severe painful crises	1998/2017	15-20 mg/kg/day as a single daily dose	<u>MSH Study</u> : Resulted in a 44% reduction of VOCs and fewer episodes of ACS and fewer RBCs transfusions, higher hemoglobin and HbF levels, lower reticulocyte, neutrophil, and platelet counts <u>BABYHUG Study</u> : Rates of VOCs, ACS, and unscheduled erythrocyte transfusions decreased who received HU
Endari (L-Glutamine)	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	2017	< 30 kg: 5 g twice daily, 30- 65 kg: 10 g twice daily, >65 kg: 15 g twice daily	<u>GLUSCC09-01 Study</u> : # of VOCs were reduced by 25% in the L-glutamine group compared to placebo
Other Treatments – [Combine by Pharmacologic Class, if relevant]				
Hematopoietic stem cell transplantation (HSCT)	n/a		Offers possible cure in patients eligible for this treatment.	<u>Blood 2011</u>
RBC Transfusions and RBC Exchange Transfusions	n/a	n/a	Treatment of anemia and reduction in Hb S %.	
Penicillin	Reduce the rate of invasive pneumococcal disease in children less than 5	N/A	Children <3 years: Oral: 125 mg twice daily Children ≥3 years: Oral:	<u>PROPS Study (1986)</u> : 84% reduction in incidence of infection

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Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information
	years of age		250 mg twice daily until age 5	compared with placebo (13 of 110 patients vs. 2 of 105; P = 0.0025), with no deaths from pneumococcal septicemia
Folic Acid	Increase erythrocyte production in individuals with SCD at risk of folate deficiency	N/A	Any patient with SCD	No differences in hematologic indices or clinical complications compared to placebo

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Crizanlizumab-tmca (ADAKVEO®) is a new molecular entity and is not currently marketed in the United States or elsewhere.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

Selexys Pharmaceuticals, Inc. requested a pre-IND meeting with FDA for IND 110752 on January 28, 2011. The Agency granted the meeting, sent preliminary responses, and the meeting was cancelled by the Sponsor. IND 110752 was submitted to FDA on 02/28/11. On 04/01/11, the Agency concluded that the proposed Phase 1, placebo-controlled, double-blind, first-in human, ascending single-dose and multiple-dose clinical study of intravenous administered SelG1 in healthy subjects was safe to proceed. A Type B Pre-Phase 2 meeting was held with the Sponsor on 04/26/12 to discuss the development of SelG1 for the treatment of vasoocclusive crisis in patients with sickle cell disease as well as a proposed Phase 2 clinical trial (i.e. "A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12 month Study to Assess Safety and Efficacy of SelG1 in Patients with Sickle Cell Disease Who have Had 2 to 12 Acute Sickle-Related Painful Crises within the Preceding 12 months"). The Agency has a telephone conversation on November 26, 2013 with Dr. Russell Rother, stating that the protocol, SelG1-00005, "A Phase II, Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SELG1 in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises", required a partial clinical hold due to inadequate safety evaluation to support the treatment of pediatric patients with sickle cell disease; hence, no patients younger than 18 years of age could be enrolled into the trial. On November 18, 2016, there was a change in sponsorship from Selexys Pharmaceuticals, Inc. to Novartis Pharmaceuticals, Co. The product name was changed to SEG101 (crizanlizumab). The Agency recommended pooled clinical pharmacokinetic/ pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated exposure-response analyses for dose optimization as well as human PK/PD data demonstrating that the differences would not impact safety and efficacy using the Selexys-manufactured SelG1 mAb versus the Novartis-manufactured mAb proposed to be used in the Phase III clinical trial.

(b) (4)

SelG1 received Orphan Designation (#08-2597) for the treatment of vasoocclusive crisis in patients with sickle cell disease on July 22, 2008. With this designation, Novartis is exempted from the submission and approval of a Pediatric Study Plan as required under the Pediatric Research Equity Act (PREA). (b) (4)

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[REDACTED] (b) (4)

On December 20, 2018, Breakthrough Therapy Designation was granted to crizanlizumab on the basis of prevention of vasoocclusive crises (VOC) in patients with sickle cell disease.

A pre-BLA meeting was held on August 9, 2018, to discuss the content of the Applicant's planned BLA application. A face-to-face Type B Meeting held November 14, 2018 proposing a rolling submission.

The Applicant was granted rolling submission and review of their planned BLA on February 7, 2019. [REDACTED] (b) (4)

[REDACTED] Six separate submissions comprising the original BLA were received on February 19, March 15, March 29, April 30, May 10 and May 16, 2019 respectively.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

Two clinical sites were selected for inspection in support of BLA 761228. Site inspections occurred and included review of: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, correspondence, and informed consent documents. CRFs were compared with source data to assess that the primary study endpoint was verifiable at the study site.

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
Sickle Cell Center, Augusta University 989 St. Sebastian Way (EF Bldg.) Augusta, GA 30912	Abdullah Kutlar, M.D.	Site# 102/10	August 19-21, 2019	VAI (Voluntary Action Indicated): Clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.
East Carolina University Brody School of Medicine Leo W. Jenkins Cancer Center 600 Moye Blvd. Greenville, NC 27834	Darla Liles M.D.	Site# 122/11	August 12-15, 2019	VAI (Voluntary Action Indicated): Clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

As per the OSI overall assessment of findings and recommendations (final letter 05 September 2019 by Anthony Orenca, MD, FACP) finds that the two sites inspected are in compliance with Good Clinical Practice and based on clinical inspections are considered to be reliable in support of the requested indication.

#### 4.2. **Product Quality**

Novel excipients: No

Any impurity concern: None

See CMC review by Mekonnen Lemma Dechassa, Ph.D., and Ramesh Potla, Ph.D. for details related to product quality.

#### 4.3. **Clinical Microbiology**

Refer to the CMC review by Max Van Tassell, PhD (DS) and Diane Raccasi, PhD. (DP)

#### 4.4. **Devices and Companion Diagnostic Issues**

There are no companion diagnostic devices required for the use of crizanlizumab-tmca.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

Crizanlizumab (also known as SelG1 or SEG101) is a humanized IgG2 kappa monoclonal antibody directed against P-selectin. Selectins (L, P, and E) are found in leukocytes, platelets and endothelial cells that line blood vessels and are involved in trafficking of cells of the innate immune system, T-lymphocytes and platelets. Through interactions with physiological ligand P-selectin glycoprotein ligand-1 (PSGL-1), selectins initiate binding between leukocytes, platelets, and the endothelium at sites of inflammation. In sickle cell disease, P-selectin-dependent interactions between sickled red blood cells, platelets, leukocytes, and the microvasculature can result in vasoocclusion and painful crisis.

Crizanlizumab bound to human and cynomolgus monkey platelets expressing P-selectin but did not bind to platelets expressing P-selectin from dog or rat. The Applicant did not characterize the pharmacological activity of crizanlizumab to other selectins in human or nonclinical animal models. For this reason, “selectin blocker” was chosen as the established pharmacological class for crizanlizumab. In vitro, crizanlizumab was shown to block neutrophil rolling on P-selectin under shear stress in the microcirculation in a dose-dependent manner. The inhibitory effect of crizanlizumab on binding of human and cynomolgus P-selectin to its ligand (PSGL-1) was comparable between two species. A tissue cross-reactivity study showed similar crizanlizumab binding distributions between human and cynomolgus monkey tissues. Specifically, crizanlizumab binding was seen in platelets in the blood and spleen, and in blood vessels in the majority of tissues examined of both human and cynomolgus monkey.

The toxicity of crizanlizumab was evaluated in GLP-compliant 4- and 26-week toxicology studies in cynomolgus monkeys. Monkeys received crizanlizumab intravenously, once every 2-weeks up to 25.2 mg/kg in the 4-week study and once every 4-weeks up to 50 mg/kg in the 26-week study. There were no crizanlizumab-related toxicities observed in the 4-week study. In the 26-week study, one male given 50 mg/kg/dose died during the dosing phase due to pulmonary hemorrhage secondary to aspiration of gastric contents while recumbent. This animal had clinical signs of emesis and lateral recumbency prior to death. Histopathology findings include mononuclear cell infiltration in multiple tissues including injection site, decreased lymphocytes in spleen, hemorrhage in the heart. In two females (one each from the dosing phase and the recovery phase) given 50 mg/kg/dose, inflammation of the vessels was observed in multiple organs including heart, kidney, liver, stomach, colon, ovary, and vagina. Inflammation of the vessels was characterized by transmural migration of mixed inflammatory cells, often with thickening of the vessel wall, and typically affected small to medium sized arteries. Crizanlizumab exposure levels at 50 mg/kg was  $AUC_{0-504h}$  274500  $\mu\text{g}\cdot\text{h}/\text{mL}$ , resulting in approximately 13.5-fold higher exposure than in humans receiving the 5 mg/kg dose of crizanlizumab ( $AUC_{tau}$  20400  $\mu\text{g}\cdot\text{h}/\text{mL}$ ). According to the Applicant, inflammation of the

vessels was considered a secondary effect that likely represented an off-target immune complex-mediated reaction of a nonhuman primate to the humanized antibody (Type III hypersensitivity reaction). In a type III hypersensitivity reaction, circulating antigen-antibody complexes deposit in vessel walls and elicit an immune response through activation of the complement cascade and activation of neutrophils and macrophages through Fc receptors.

Because of the inflammation observed in monkeys, DHP requested consults from Division of Applied Regulatory Science (DARS) and the Division of Cardiovascular and Renal Products (DCRP). According to DARS and DCRP, the findings may be due to drug-related immune-mediated vascular injury; however, the applicant did not provide data showing immune complex deposition at the site of injury to support the conclusion. There is evidence that the vasculature in SCD patients is in a chronically inflamed state and in an animal model of SCD that P-selectin is directly involved in the adhesion between blood elements and the endothelium in SCD<sup>1, 2</sup>. There were no clinical findings of vasculitis with crizanlizumab. Of note, one of two animals had neutralizing antibodies with corresponding decreases in PD effects and exposure. The review team included information on the vascular inflammation in monkeys to the USPI. Thus, no additional studies are needed to assess vascular inflammation in monkeys.

In an enhanced pre- and post-natal development study in cynomolgus monkeys, crizanlizumab was administered to pregnant dams once every 2-weeks, at dose levels of 10 or 50 mg/kg. The maternal exposures (AUC<sub>0-336h</sub>) on gestation day (GD) 146 at 10 and 50 mg/kg were 29000 and 163000 µg\*h/mL, respectively resulting in exposures of 2.8 and 16-fold greater than those observed clinically at the recommended dose of 5 mg/kg given every 4 weeks. The fetal exposures were between 0.02 and 0.03-fold the average clinical C<sub>max</sub> of 124 µg/mL based on gender combined fetal C<sub>max</sub> of 2270 and 3640 ng/mL on birth day (BD) 28 at 10 and 50 mg/kg, respectively. There was no maternal toxicity at the crizanlizumab doses tested. There were non-dose related increases in third-trimester pregnancy losses in crizanlizumab treated monkeys compared to concurrent control and/or mean historical control. There was macroscopic evidence of placental infarcts characterized by pale white or tan multiple foci with 10-60% of the placental disks effected, resulting in inadequate uteroplacental perfusion to the fetus. In addition, there was presence of anti-drug antibodies (ADA), and dose reactions (salivation and emesis, transient loss of consciousness and reddened skin) in some of the aborted monkeys. The cause for the fetal losses in monkeys is unknown but may be related in part due to the development of anti-drug antibodies against crizanlizumab-tmca.

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<sup>1</sup> Wood KC et al 2004. Endothelial cell P-selectin mediates a proinflammatory and prothrombotic phenotype in cerebral venules of sickle cell transgenic mice. *Am J Physiol Heart Circ Physiol* 286: H1608–H1614

<sup>2</sup> Mayades TN et al (1993). Leukocyte rolling and extravasation are severely compromised in P-selectin deficient mice. *Cell*:74:541-554.

There were no malformations (external or visceral) in the aborted fetuses. There were increased infant losses in crizanlizumab treated monkeys compared to concurrent controls. Infant losses are likely related to maternal-induced trauma and/or neglect; a common background finding in monkeys<sup>3, 4</sup>. The frequency of maternal neglect in this study (5/35, 14.3%) was consistent with testing facility historical control range (0 to 16.7%). In infants that died early, there were no morphometric measurements, external evaluations, visceral (including heart) evaluations, skeletal evaluations, gross pathology, and/or histopathology. Crizanlizumab crossed the placental barrier in pregnant monkeys but transfer to milk is unknown.

In surviving infants of crizanlizumab treated dams, there were no effects of crizanlizumab exposure on neurobehavioral, physical or clinical pathology parameters throughout the postnatal observation period, and no gross or histopathological findings associated with crizanlizumab administration at scheduled termination. Crizanlizumab was detectable in the serum of infants from 10 and 50 mg/kg treated dams through at least Postnatal Day 28.

No dedicated fertility studies were conducted. There were no effects on reproductive organs in males or females in the 26-week general toxicology study.

## 5.2. Referenced NDAs, BLAs, DMFs

None

## 5.3. Pharmacology

### Primary pharmacology

The binding of crizanlizumab (SelG1) to P-selectin was analyzed using SensiQ Pioneer, an SPR-based biosensor system (Study No. 2010122301). The Kinetic analysis of crizanlizumab was performed to obtain affinity constants (KD) in comparison to the parental anti-human P-selectin antibody G1 (precursor of humanized SelG1). The binding affinity (KD) of crizanlizumab to soluble P-selectin was comparable to G1.

Antibody	ka ( $\times 10^6 \text{ M}^{-1}\text{s}^{-1}$ )	kd ( $\times 10^{-2} \text{ s}^{-1}$ )	KD (nM)	Res. SD (RU)
G1	6.3 $\pm$ 2	5.6 $\pm$ 2	8.94 $\pm$ 3	3.39
SelG1	2.22 $\pm$ 1	1.306 $\pm$ 6	5.89 $\pm$ 2	4.48

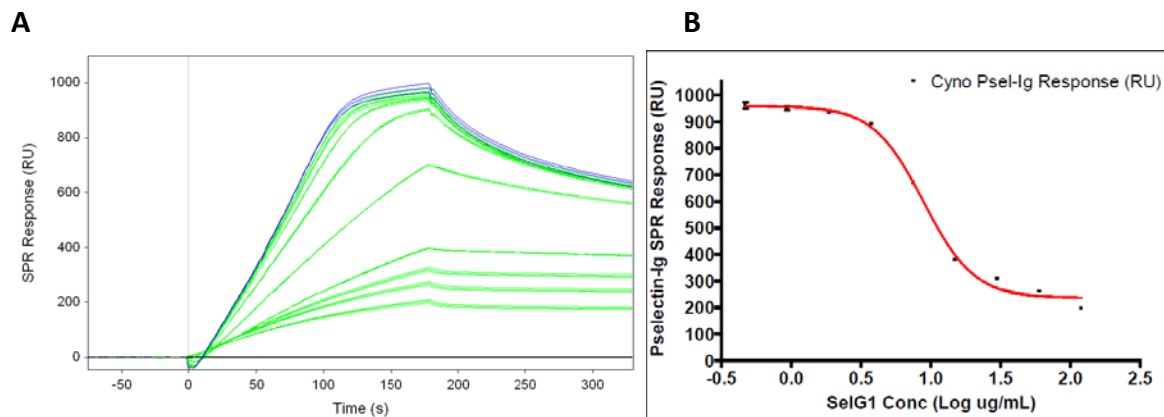
(Table excerpted from BLA)

<sup>3</sup> McCormack et al (2006) Maternal Care Patterns and Behavioral Development of Rhesus Macaque Abused Infants in the First 6 Months of Life. *Developmental Psychobiology* 10, 537-550

<sup>4</sup> Carroll K.A. et al (1998) Infant Abuse and Neglect in Monkeys A Discussion of Definitions, Epidemiology, Etiology, and Implications for Child Maltreatment: Reply to Cicchetti (1998) and Mason (1998) *Psychological Bulletin* 123, (3) 234-237

The inhibitory effect of crizanlizumab on binding of human and cynomolgus P-selectin-Ig chimeras (Psel-Ig, positive controls) to GSP-6 (PSGL-1 ligand) was compared using SensiQ Pioneer (Study No. 2012091401). A dose-response plot was analyzed by plotting P-selectin-Ig binding response versus crizanlizumab concentration. The inhibitory effect (EC50) of crizanlizumab on the binding of human and cynomolgus P-selectin to immobilized GSP-6 (PSGL-1) was comparable between two species (EC50 6.77  $\mu\text{g}/\text{mL}$  and 8.9  $\mu\text{g}/\text{mL}$  for human and cynomolgus Psel-Ig, respectively).

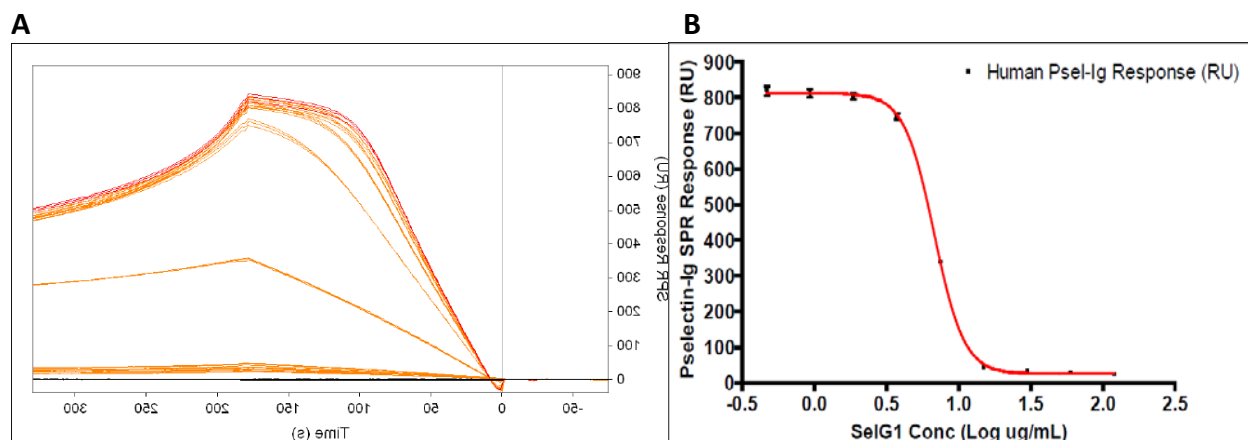
**Figure 1: Inhibitory effects of crizanlizumab on cynomolgus P-selectin binding to GSP-6**



**A:** Blue curves illustrate positive control (cynomolgus Psel-Ig only) and green curves illustrate SelG1-inhibited samples (cynomolgus Psel-Ig and varying concentrations of SelG1). (Figures excerpted from BLA)

**B:** Dose Response plot of Cynomolgus P-selectin-Ig Binding vs. SelG1 concentration

**Figure 2: Inhibitory effects of crizanlizumab on human P-selectin binding to GSP-6**



**A:** Red curves illustrate positive control (human Psel-Ig only) and orange curves illustrate SelG1-inhibited samples (human Psel-Ig and varying concentrations of SelG1). (Figures excerpted from BLA)

**B:** Dose Response plot of Human P-selectin-Ig Binding vs. SelG1 concentration

The ability of crizanlizumab to block neutrophil rolling on P-selectin under shear stresses in the microcirculation was assessed (Study No. DR-10). Human neutrophils ( $10^6$ /ml in HBSS containing 0.5% human serum albumin) isolated from healthy donors were perfused over purified platelet membranes (mP-selectin) in a parallel-plate flow chamber under shear stress at 1.0 dyn/cm<sup>2</sup> pressure. Following few minutes, the accumulated number of rolling neutrophils was measured with a videomicroscopy system coupled to a digitized image analysis system <sup>(b) (4)</sup>. The study results showed that crizanlizumab inhibited neutrophil rolling in this assay in a dose-dependent manner over a concentration range of 0.625 µg/ml to 20 µg/ml.

**Table 2: SelG1 neutrophil rolling assay**

No.	Antibody	ug/ml	Cells/Field				Average	SD
			Field 1	Field 2	Field 3	Field 4		
1	BufferOnly	0	70	65	80	73	72.0	6.3
2	Isotype Control	20	62	77	67	67	68.3	6.3
3	SelG1-20	20	1	1	1	0	0.8	0.5
4	SelG1-10	10	0	1	1	3	1.3	1.3
5	SelG1-5	5	3	5	4	7	4.8	1.7
6	SelG1-2.5	2.5	22	26	23	19	22.5	2.9
7	SelG1-1.25	1.25	44	52	48	32	44.0	8.6
8	SelG1-0.625	0.625	58	60	45	59	55.5	7.0

(Table excerpted from BLA)

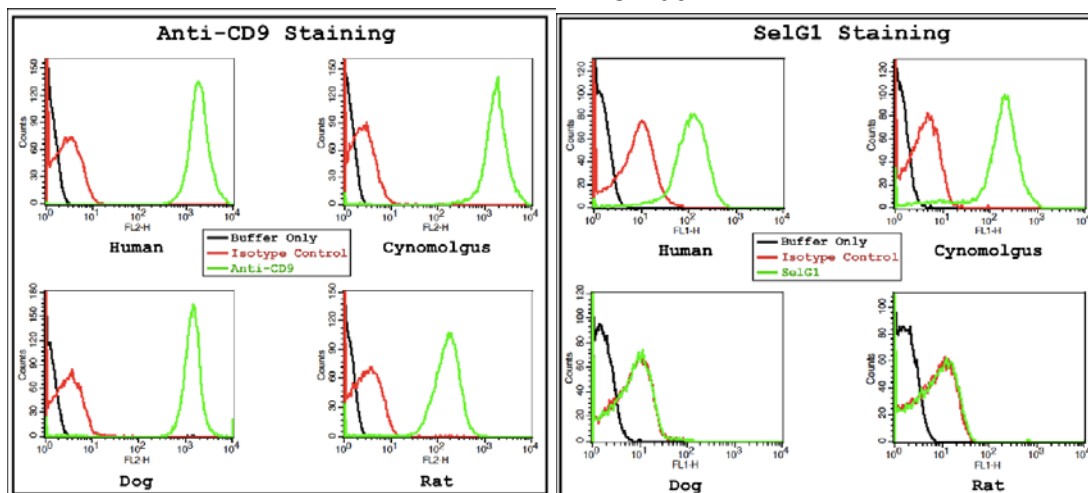
### Secondary Pharmacology

#### **Study title/Study No.: Species cross-reactivity testing of SelG1/DR-03**

The purpose of this study was to determine the ability of crizanlizumab to cross-react with platelets expressing P-selectin from human, cynomolgus, dog, and rat using assessed using a fluorescence-activated cell sorting (FACS) method. The cell-type identity of the platelets from all species was confirmed by their interaction with the anti-CD9 antibody, which cross-reacts with CD9 from all the tested species. Crizanlizumab bound to human and cynomolgus monkey platelets expressing P-selectin, but did not bind to platelets expressing P-selectin from dog or rat. Thus, monkey is an appropriate toxicological animal model to study crizanlizumab.

Figure-3:

**A: Cell-type identity of the platelets (green) from all species bound to anti-CD9 mAB** **B: SelG1 bound (green) to platelets from human and cynomolgus monkey but not to dog or rat.**



(figures excerpted from BLA)

### Safety Pharmacology

Safety pharmacology endpoints were included in the 4- and 26-week repeat dose studies in monkeys.

### 5.4. ADME/PK

Pharmacokinetic parameters were extrapolated from single- or repeat-dose IV bolus administration studies in cynomolgus monkeys at the tested crizanlizumab doses of 2 mg/kg to 50 mg/kg.

#### Key findings:

- The T<sub>max</sub> values of crizanlizumab ranged from 0.25 hours to 6 hours at 2-50 mg/kg.
- The mean C<sub>max</sub> and AUC values increased in a roughly dose-proportional manner across the animal studies. Crizanlizumab can cross the blood-placental barrier in monkeys as shown in the ePPND study.
- 
- The half-life (T<sub>1/2</sub>) of crizanlizumab in cynomolgus monkeys ranged between 57.9 hours to 149 hours (2.4 days to 6.2 days).
- The mean volume of distribution (V<sub>z</sub> or V<sub>ss</sub>) of crizanlizumab ranged between 23.5 mL/kg and 53.5 mL/kg (did not exceed the blood volume of 60 mL/kg of cynomolgous monkey).

- The mean clearance (CL) of crizanlizumab ranged between 0.18 mL/hr/kg and 0.55 mL/hr/kg.
- Crizanlizumab crossed the placenta based on the infant-to-maternal concentration ratios of 6.9 and 4.5 at 10 mg/kg and 50 mg/kg, respectively, at birth Day 28 (BD28).
- No specific distribution, metabolism or excretion studies were conducted.

Type of study		Major findings		
<b>Absorption</b>				
The comparative PK/PD between the two variants (Reprixys SelG1 and Novartis SEG101) of crizanlizumab were assessed following administration of a single IV bolus of 5 mg/kg or 10 mg/kg in cynomolgus monkeys (Study Nos. R1900014/1570356).				
Group	No. of Animals Female	Dose Level <sup>a</sup> (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
1 (SEG101 Antibody)	4	5	8.7	0.57
2 (SEG101 Antibody)	4	10	8.7	1.15
3 (SELG1 Antibody)	4	5	10.8	0.46
4 (SELG1 Antibody)	4	10	10.8	0.93
<p>After dosing, animals were observed for a period of 28 days (Day 29 terminal euthanasia). Blood samples (approximately 1.0 mL) for pharmacokinetic and pharmacodynamic analyses were collected prior to dosing and 0.25, 6, 24, 72, 120, 168, 196, 336, 504, and 672 hours postdose. Pharmacodynamic analysis was performed using SPR method.</p> <p>The two variants of crizanlizumab, SEG101 show higher mean serum concentrations and PK parameters than SelG1 at all time points at the dose of 5 mg/kg, while at 10 mg/kg, the mean serum concentrations of SEG101 and SelG1 appeared similar at all time points. Overall the geometric mean ratios (SEG101/SelG1) of C<sub>max</sub> and AUC ranged between 1.1 and 1.7 at the tested doses.</p> <p><b>Mean serum concentration-time profiles of crizanlizumab in a PK/PD bridging study in cynomolgus monkeys</b></p> <p>Data presented as arithmetic mean ± standard deviation (SD) (Figure excerpted from BLA)</p>				

**Summary of PK parameters of crizanlizumab following administration of a single IV bolus dose in cynomolgus monkeys**

PK parameters	5 mg/kg SEG101 (n = 4) <sup>a</sup>	5 mg/kg SelG1 (n = 4) <sup>a</sup>	10 mg/kg SEG101 (n = 4) <sup>a</sup>	10 mg/kg SelG1 (n = 4) <sup>a</sup>
Tmax (hr) <sup>b</sup>	3.1 (3.3) <sup>b</sup>	1.7 (2.9) <sup>b</sup>	1.7 (2.9) <sup>b</sup>	0.25 (0.0) <sup>b</sup>
Tmax (hr) <sup>c</sup>	3.1 (0.25-6.0) <sup>c</sup>	0.25 (0.25-6.0) <sup>c</sup>	0.25 (0.25-6.0) <sup>c</sup>	0.25 (0.25-0.25) <sup>c</sup>
Cmax (µg/mL)	188.9 (44.3)	149.3 (20.5)	401.1 (87.0)	331.6 (33.4)
AUClast (hr*µg/mL)	19272.8 (3147.9)	11833.7 (3612.5)	34952.1 (2555.3)	31989.0 (5572.4)
AUCinf (hr*µg/mL)	19960.1 (3304.6)	12280.5 (3359.3)	36399.1 (2681.7)	33468.5 (4585.2)
CL (mL/hr/kg)	0.26 (0.04)	0.43 (0.1)	0.28 (0.02)	0.30 (0.04)
Vz (mL/kg)	30.3 (3.5)	34.7 (6.1)	36.5 (4.5)	40.9 (6.5)
T1/2 (hr)	84.9 (22.8)	57.9 (11.7)	92.0 (12.2)	95.8 (25.6)

Data presented as arithmetic mean (standard deviation), unless noted.

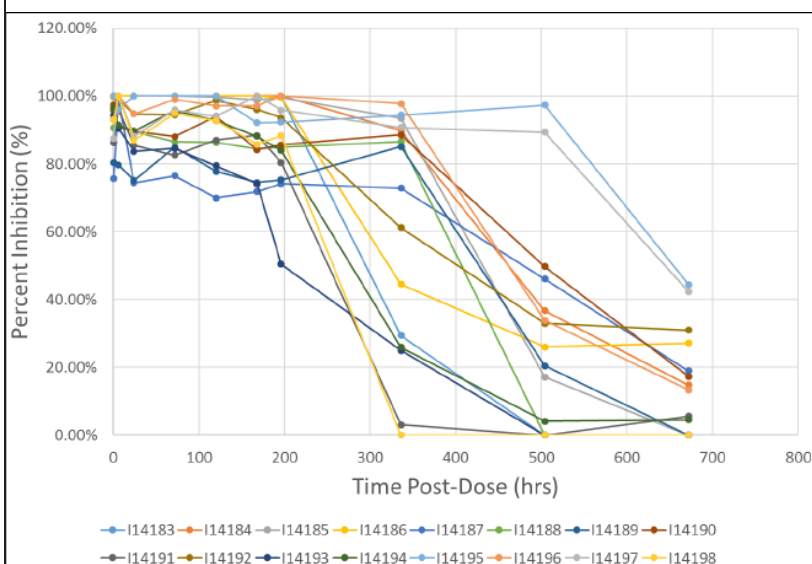
<sup>a</sup> Sample size (n) = 4 female cynomolgus monkeys per dosing group. <sup>b</sup>Tmax presented as arithmetic mean (standard deviation).

<sup>c</sup>Tmax presented as median (range).

*(Table excerpted from BLA)*

Animals administered 5 mg/kg SEG101 had complete P-selectin inhibition (100% inhibition up to 196 hr post dose). In all animals, ≥ 69% inhibition with reduced inhibition at 336 hr post dose.

**Inhibition of P-selectin following single dose administration of SEG101 in monkeys**



*(Figure excerpted from BLA)*

Animal numbers: Group 1: 14183-14186, Group 2: 14187-14190, Group 3: 14191-14194, Group 4: 14195-14198.

TK data from general toxicology studies	Refer to Section 5.5
-----------------------------------------	----------------------

## 5.5. Toxicology

### 5.5.1. General Toxicology

#### Study title/ Study number: 26-Week Intravenous Injection Toxicity and Toxicokinetic Study (Seven Doses) with SelG1 in Cynomolgus Monkeys with a 4-Week Recovery Phase/8259995

##### Key Study Findings:

- Inflammation of the vessels in multiple tissues at 50 mg/kg/dose.
- The exposure multiples based on AUC values at 5 mg/kg in SCD patients was 13.5-fold at 50 mg/kg/day (e.g., 274,500 hr\*µg/mL divided by 20,400 hr\*µg/mL).

Conducting laboratory and location:



GLP compliance: Yes

##### Methods

Dose and frequency of dosing: 0, 5, 25, 50 mg/kg/dose and once every 4 weeks for a total of 7 doses (Days 1, 29, 57, 85, 113, 141, and 169 of the dosing phase)

Route of administration: Intravenous (bolus) injection

Formulation/Vehicle:



Species/Strain: Cynomolgus monkey

Number/Sex/Group: 5 (3 – main study; 2 – recovery) for dose level 0 and 50 mg/kg

3 (only main study) for dose level 5 and 25 mg/kg

Age: 4 to 8 years

Satellite groups/ unique design: None

Deviation from study protocol: No

affecting interpretation of results:

#### Observations and Results: changes from control

Parameters	Major findings
Mortality	One male (animal # 104856) given 50 mg/kg/dose died on Day 141 of the dosing phase due to pulmonary hemorrhage secondary to aspiration of gastric contents

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	while recumbent. This animal had clinical signs of emesis and lateral recumbency prior to death. Histopathology findings show mononuclear cell infiltration at the injection site, gall bladder, kidney, lung, mandibular salivary gland and prostate, decreased lymphocytes in spleen, parasite in stomach (protozoan), and hemorrhage in heart.
<b>Clinical Signs</b>	Unremarkable
<b>Body Weights</b>	Unremarkable
<b>Food Consumption</b>	Unremarkable
<b>Ophthalmoscopy</b>	Unremarkable
<b>ECG</b>	Unremarkable
<b>Blood Pressure Measurements</b>	Unremarkable
<b>Neurological Examinations</b>	Unremarkable
<b>Physical Examinations</b>	Unremarkable
<b>Vital Signs</b> (body temperature, respiration rate, or heart rate)	Unremarkable
<b>Male Reproductive Assessment</b> (Testicular measurements, sperm motility, density, total count, and morphology)	Unremarkable
<b>Female Reproductive Assessment</b> (vaginal swabs, number or mean duration of menstrual cycles)	Unremarkable
<b>Hematology</b>	Unremarkable
<b>Clinical Chemistry</b>	Unremarkable
<b>Peripheral Blood Immunophenotyping</b> (total T-lymphocytes, helper T-lymphocytes, cytotoxic T-lymphocytes, B cells, natural killer cells were measured)	Unremarkable
<b>Urinalysis</b>	Unremarkable
<b>Gross Pathology</b>	Unremarkable
<b>Organ Weights</b>	Unremarkable
<b>Histopathology</b>	Minimal to moderate inflammation of the vessels of several tissues (including heart, kidney, liver, stomach, colon, ovary, and vagina) in one female (animal # 104872) at 50 mg/kg/dose in the terminal sacrifice and one female (Animal # 104875) in the recovery sacrifice. Inflammation of the vessels was characterized by transmural migration of mixed inflammatory cells, often with thickening of the vessel wall, and typically affected small to medium sized arteries; however, portal veins were also affected in the liver of the terminal sacrifice female. Areas of inflammation were typically characterized by segmental or nodular involvement, and did not affect the entire length of the observable vessel. Applicant suggests that this finding is related

	<p>to off-target immune-complex mediated reaction to primate antihuman antibody. However, no evidence was provided showing that immune complex deposition was associated with the vascular lesions.</p> <p><b>Summary of microscopic findings for animals 104872 and 104875</b></p> <table border="1"> <thead> <tr> <th>Animal</th> <th>Tissue</th> <th>Findings</th> </tr> </thead> <tbody> <tr> <td colspan="3"><b>104872 Female (terminal sacrifice) 50 mg/kg/dose</b></td> </tr> <tr> <td rowspan="15"></td> <td>Cecum</td> <td>Inflammation, vessel; slight; multifocal; submucosa</td> </tr> <tr> <td>Colon</td> <td>Inflammation, vessel; slight; multifocal; submucosa</td> </tr> <tr> <td>Femur</td> <td>Physis closed; Present</td> </tr> <tr> <td>Gall Bladder</td> <td>Infiltrate, mononuclear cell; minimal; multifocal</td> </tr> <tr> <td rowspan="2">Heart</td> <td></td> <td>Inflammation, vessel; slight; multifocal;</td> </tr> <tr> <td></td> <td>coronary artery Intravenous Injection Site, Right Saphenous vein; Hemorrhage; slight; focal; subcutis</td> </tr> <tr> <td>Kidney:</td> <td>Inflammation, vessel; 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<b>Pharmacodynamic Analysis</b>	<p style="text-align: center;"><b>Number of animals with &gt;75% inhibition of P-selectin</b></p> <table border="1"> <thead> <tr> <th>Sex</th> <th colspan="4">Male</th> <th colspan="4">Female</th> </tr> <tr> <th>Dose mg/kg/dose</th> <th>0</th> <th>5</th> <th>25</th> <th>50</th> <th>0</th> <th>5</th> <th>25</th> <th>50</th> </tr> </thead> <tbody> <tr> <td>Days 8-169<sup>c</sup></td> <td>0/5</td> <td>2/3</td> <td>1/3</td> <td>1/5</td> <td>0/5</td> <td>2/3</td> <td>1/3</td> <td>2/5</td> </tr> </tbody> </table>				Sex	Male				Female				Dose mg/kg/dose	0	5	25	50	0	5	25	50	Days 8-169 <sup>c</sup>	0/5	2/3	1/3	1/5	0/5	2/3	1/3	2/5																						
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<b>Toxicokinetics</b>	<p>Animals that were positive for ADAs generally had lower concentrations of crizanlizumab observed.</p> <p style="text-align: center;"><b>Mean toxicokinetic parameters for SelG1 in monkey serum - Day 1</b></p> <table border="1"> <thead> <tr> <th>Sex</th> <th colspan="3">Male</th> <th colspan="3">Female</th> </tr> <tr> <th>Dose mg/kg/dose</th> <th>5</th> <th>25</th> <th>50</th> <th>5</th> <th>25</th> <th>50</th> </tr> </thead> <tbody> <tr> <td>AUC<sub>0-504h</sub> (µg*hr/mL)</td> <td>25300</td> <td>109000</td> <td>333000</td> <td>13300</td> <td>74900</td> <td>216000</td> </tr> <tr> <td>C<sub>max</sub> (µg/mL)</td> <td>312</td> <td>1180</td> <td>2550</td> <td>255</td> <td>957</td> <td>2080</td> </tr> <tr> <td>T<sub>1/2</sub> (hr)</td> <td>104</td> <td>144</td> <td>167</td> <td>63.4</td> <td>101</td> <td>131</td> </tr> <tr> <td>CL (mL/hr/kg)</td> <td>0.192</td> <td>0.373</td> <td>0.215</td> <td>0.326</td> <td>0.140</td> <td>0.221</td> </tr> <tr> <td>V<sub>ss</sub> (mL/kg)</td> <td>18.7</td> <td>28.2</td> <td>32.3</td> <td>37.0</td> <td>24.1</td> <td>28.7</td> </tr> </tbody> </table>				Sex	Male			Female			Dose mg/kg/dose	5	25	50	5	25	50	AUC <sub>0-504h</sub> (µg*hr/mL)	25300	109000	333000	13300	74900	216000	C <sub>max</sub> (µg/mL)	312	1180	2550	255	957	2080	T <sub>1/2</sub> (hr)	104	144	167	63.4	101	131	CL (mL/hr/kg)	0.192	0.373	0.215	0.326	0.140	0.221	V <sub>ss</sub> (mL/kg)	18.7	28.2	32.3	37.0	24.1	28.7
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**General toxicology; additional studies**

SelG1 was assessed in a non-GLP single dose tolerability and toxicokinetics intravenous dose range finding study (Study no. R8220237), and a 4-week intravenous bolus administration toxicity and toxicokinetic study in cynomolgus monkeys with a 2-week recovery period. (Study no. SelG1-00002). The results are summarized below.

**Study Title/Study no. Single-Dose Tolerability and Toxicokinetics Intravenous Bolus Administration Study with SelG1 in Cynomolgus Monkeys/R8220237**

Cynomolgous monkeys (1/sex for each dose) were administered with crizanlizumab as a single bolus dose via intravenous injection to cynomolgus monkeys at 0, 1.3, 6.5 and 13.7 mg/kg. Animals were sacrificed on Day 28 for dosing phase.

**Key study findings:**

- No SelG1-induced toxicities were seen at any dose.
- SelG1 was capable of maintaining greater than 50% inhibition of P-selectin binding to PSGL-1 was observed at  $\geq 6.5$  mg/kg at Day 14.

**Study Title/Study no. 4-Week Intravenous Bolus Administration Toxicity and Toxicokinetic Study with SelG1 in Cynomolgus Monkeys with a 2-Week Recovery Period/SelG1-00002**

Cynomolgus Monkeys (5/sex for control and high dose and 3/sex low dose and mid dose) were given IV bolus administration at doses of 0, 2, 5 and 25.2 mg/kg/dose weekly every 2 weeks. Animals were sacrificed on Day 28 for dosing phase.

**Key Study Findings:**

- No SelG1-induced toxicities were seen at any dose.
- NOAEL was 25.2 mg/kg, the highest dose tested.
- 5 and 25.2 mg/kg SelG1 provided almost complete inhibition of P-selectin binding to PSGL-1 throughout the dosing interval.

**5.5.2. Genetic Toxicology**

Genotoxicity studies are not considered relevant for a biological product in accordance with ICH S6.

**5.5.3. Carcinogenicity**

The Applicant submitted a waiver request to conduct carcinogenicity studies for crizanlizumab to the FDA in 2017. In the submission the Applicant provided supportive information from nonclinical study reports for #8220205 (Tissue Cross Reactivity), #SelG1-00002 (4-week monkey study), and #8259995 (26-week monkey study), which are summarized below.

1. Crizanlizumab binds to P-selectin only in human and nonhuman primates, and does not bind P-selectin in rat or dog.
2. Crizanlizumab is not pharmacologically active in rodents.
3. In the 26-week monkey study, there were no test article-related changes in peripheral blood immunophenotyping (total T cells, helper T cells, cytotoxic T cells, B cells, and natural killer cells); no increases in organ weights; and there was no evidence of tissue hyperplasia or dysplasia, cell proliferation or lymphoproliferative changes.

The FDA agreed with the Applicant's plan to conduct no further nonclinical work with

BLA Multi-Disciplinary Review and Evaluation  
BLA 761128  
ADAKVEO (Crizanlizumab-tmca)

crizanlizumab to assess carcinogenic risk, and supports their decision to evaluate the carcinogenicity risk with long-term clinical follow-up and continued pharmacovigilance monitoring.

4. The executive carcinogenicity assessment committee at the FDA concurred with the Applicant's plan based on lack of binding/pharmacologic activity in rodents.

#### 5.5.4. Reproductive and Developmental Toxicology

##### **Fertility and Early Embryonic Development**

No fertility and early embryonic development studies were submitted.

##### **Embryo-Fetal Development**

No embryo-fetal development studies were submitted.

##### **Prenatal and Postnatal Development**

##### **Study title/ number: Enhanced Pre-Postnatal Toxicity Study of SEG101 Administered by Intravenous Injection in Pregnant Cynomolgus Monkeys with 6-Month Postnatal Evaluation/1770674**

##### **Key Study Findings**

- Increased 3rd trimester abortions and stillbirths occurred in crizanlizumab treated dams (25%) versus controls dams (0%).
- SEG101 crossed placenta.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

##### **Methods**

Dose and frequency of dosing:

0, 10 or 50 mg/kg/dose and once every 2 weeks

Route of administration:

IV slow bolus injection.

Formulation/Vehicle:

(b) (4)

Species/Strain:

Cynomolgus monkeys

Age (females)

4.2 to 9.6 years (at start of dosing)

Number/Sex/Group:

16 pregnant females

Satellite groups:

None

Study design:

- ❖ Dams were dosed from gestation day (GD) 20-22 (based on day of pregnancy confirmation by ultrasound) until parturition (GD152-174).
- ❖ Pregnancy was monitored by ultrasonography every 2 weeks.
- ❖ Dams were allowed to deliver naturally and rear infants until postpartum day (PPD) 182±1.
- ❖ Dams were monitored for viability, clinical signs, food consumption, body weight, clinical pathology, postpartum, TK,

immunogenicity (ADA),  
 pharmacodynamics,

- ❖ Infants were monitored for viability, clinical signs, body weight, teratology and neurobehavioral assessments, and evaluation of clinical pathology, birth observations, immunogenicity, pharmacodynamics, and toxicokinetic parameters.

Toxicokinetics

Adults females all groups:

Adult female sample collection time points		
Group nos.	Study day	Time points (relative to dosing)
All	GD20-22 (first dose)	Pre, 0.25, 6, 24, 168 and 336 hr Post (prior to 2nd dose)
	Each dose day (GD48 to GD132)	Pre
	GD146	Pre, 0.25, 6, 24, 168 and 336 hr Post (prior to GD160 dose, if applicable)
	PPD28	NA
	PPD91	NA
	Day of abortion/pregnancy loss confirmation (including stillbirth and any C-sections) and infant losses.	As applicable
Unscheduled necropsy of adult female	As applicable	NA

Deviation from study protocol affecting interpretation of results:

Reported deviations do not appear to affect overall study interpretation.

Justification for selection of doses:

50 mg/kg/dose was selected as the high dose on the basis of expectations to achieve exposure above the human equivalent pharmacologically effective dose used in the clinic (5 mg/kg) and a 5-fold dose increase from the low dose.

**Observations and Results**

Generation	Major Findings
F0 Dams	<p><b>Survival:</b> There were no preterm deaths at 10 and 50 mg/kg/dose SEG101. One adult female (1509) in control was euthanized on PPD109 after a history of chronic diarrhea and weight loss and had macroscopic and microscopic findings of mixed cell inflammation of the large intestine.</p> <p><b>Clinical signs:</b></p> <ul style="list-style-type: none"> <li>• Red vaginal discharge was observed across all groups with no dose response (% of affected animals 25, 19, and 13 at 0, 10, and 50 mg/kg, respectively).</li> <li>• Abortion in one control female (Day 33), in two 10 mg/kg females (Days 60-70) and in five 50 mg/kg females (Days 33-132).</li> <li>• Stillbirth in four 10 mg/kg females (Days 143-160) and one 50 mg/kg females (Days 162).</li> </ul>

- Infant loss in one control (BD1), two (BD1) in 10 mg/kg and two (BD1 and BD5) in 50 mg/kg

**Dose reactions:** Salivation and emesis were observed in 1 female at 10 mg/kg (2507), and 2 females (3508 and 3516) at 50 mg/kg. Transient loss of consciousness and reddened skin (petechiae) were observed for 2 days postdose. Each of the 3 affected females had developed ADAs to SEG101 prior to the occurrence of the dose reactions. Female #2507 at 10 mg/kg delivered a live infant (GD104), both females at 50 mg/kg aborted (3508 on GD102 and 3516 on GD132).

**Body weights:** No SEG101 related effects on body weight were observed.

**Food consumption:** No SEG101 related effects on feed consumption were observed.

**Clinical pathology:** Unremarkable

**Uterine content:** Forty-eight pregnant females (16 per group) were enrolled on study. A total of 15 group 1 (control), 10 group 2 (10 mg/kg), and 10 group 3 (50 mg/kg) infants were delivered. All were delivered by natural birth except for 2 infants that were delivered by C-section, one in the control group and one in the 10 mg/kg group. There were no SEG101-related effects on gestation length or pregnancy/postpartum outcomes that were considered related to maternal administration of Seg101.

**Summary of pregnancy and infant loss**

Crizanlizumab Dose	0 mg/kg	10 mg/kg	50 mg/kg	Historical control incidences mean (range) <sup>a</sup>
1 <sup>st</sup> Trimester	1/16 (6.3%) 1516 (GD33)	0	2/16 (12.5%) 3505 (GD33) 3510 (GD45)	30/350 (8.6%) 0-15.8%
2 <sup>nd</sup> Trimester	0	2/16 (12.5%) 2514 (GD60) 2506 (GD70)	0	6/396 (1.5%) 0 to 10.0%
3 <sup>rd</sup> Trimester	0	4/16 (25.0%) 2504 (GD143) 2510 (GD155) 2503 (GD157) 2505 (GD160)	4/16 (25.0%) 3508 (GD102) 3513 (GD102) 3516 (GD132) 3504 (GD162)	46/391(11.8%) 0 to 28.6%
Infant loss	1/15 (6.7%) 1514/1146 (GD144/BD2)	2/10 (20%) 2515/2151 (GD160/BD1) 2166/2516 (GD158/BD1)	2/10 (20%) 3066/3506 (GD143/BD5) 3076/3507 (GD145/BD1)	28/296 (9.5%) <sup>b</sup> (0 to 20.0%)

<sup>a</sup>Based on 22 ePPND studies conducted at the testing facility from 2008 to 2017.

<sup>b</sup>Testing facility historical data excluding maternal neglect is: mean 5.1% ; range 0 – 16.7%. The frequency of maternal neglect in this study (5/35, 14.3%) was consistent with testing facility historical control range (0 to 16.7%).

**Necropsy observation:** Necropsies were performed for dams that had fetal loss (stillbirth/aborted) or infant loss postpartum. There were no SEG101-related organ weight changes, macroscopic, and/or microscopic pathology findings for adult females that aborted or had an infant death prior to the scheduled necropsy, or for those that survived to scheduled terminal euthanasia.

**Toxicokinetics (TK):** Exposure to SEG101 in maternal animals during gestation increased dose proportionally from 10 to 50 mg/kg. The increases in SEG101 mean Cmax and AUC0-336 values were dose proportional. No accumulation of SEG101 was observed after multiple doses every other week of SEG101 in pregnant monkeys during gestation.

**Mean maternal TK on GD 20-22 and GD 146**

*(Table excerpted from BLA)*

Day	Dose Group	Dose Level (mg/kg)	Cmax (µg/mL)	Cmax/D [(µg/mL)/(mg/kg)]	AUC0-336 (µg·h/mL)	AUC0-336/D [(µg·h/mL)/(mg/kg)]
GD 20-22	2	10	243	24.3	22100	2210
	3	50	1350	26.9	137000	2740
GD 146	2	10	254	25.4	29000	2900
	3	50	1230	24.6	163000	3250

- SEG101 crossed placental barrier, and no sex differences were observed in infant toxicokinetics.
- The mean infant:maternal monkey concentration ratios were 6.94 at 10 mg/kg and 4.52 at 50 mg/kg, on PPD/BD28.

**Mean maternal and fetal TK**

*(Table excerpted from BLA)*

Postpartum: Maternal and infant animals							
Day of post-dose sample collection	Doses (mg/kg)	Sex	Infant		Maternal		Infant:Maternal concentration ratio at BD28 <sup>a</sup>
			Infant animal (N)	Concentration at BD28 (ng/mL)	Maternal animal (N)	Concentration at BD28 (ng/mL)	
BD28	10	Male	3	2650 (599)	3	375 (382)	5.4
		Female	5	1990 (985)	5	186 (162)	8.5
		Gender combined	8	2270 (854)	8	280 (282)	6.9
BD28	50	Male	3	3910 (306)	3	2070 (1440)	2.6
		Female	5	3480 (1740)	5	1840 (1970)	6.0
		Gender combined	8	3640 (1350)	8	1930 (1680)	4.5

Footnotes: IV = intravenous; N = Number of animals; n = Number of animals with evaluable PK parameters; -, Not available. Accumulation ratio (AR) = [Cmax or AUC0-336 GD146] / [Cmax or AUC0-336 GD20-22]. GD, Gestation Day; BD, Birth Day.

Data are presented as arithmetic mean ± standard deviation (SD).

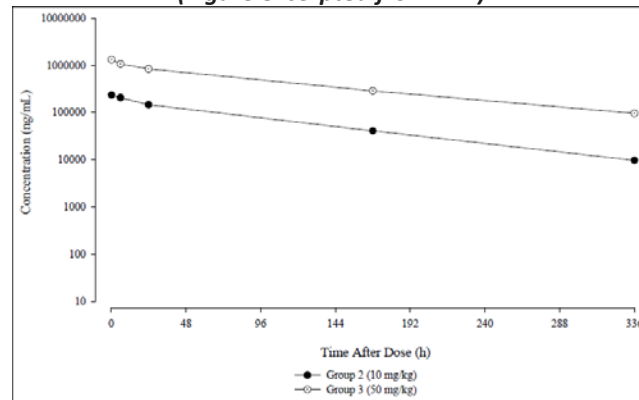
<sup>a</sup> SD values are not presented for the ratios, since SD may not be relevant to indicate data variability for ratios.

Animals with positive anti-test article antibody (AHA) were excluded from the descriptive statistics and TK interpretation due to the crizanlizumab exposure being generally lower than the AHA negative animals.

Source: [1770674-Appendix 5]

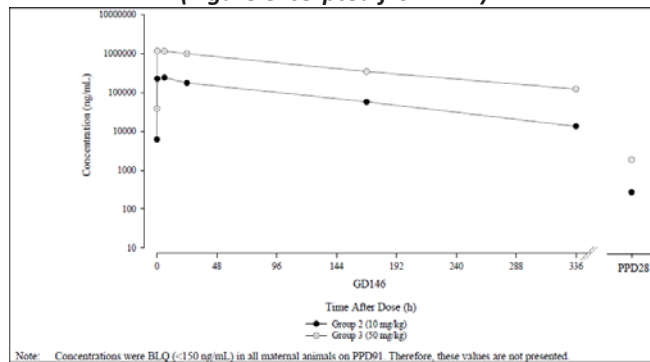
Following birth, SEG101 concentrations were measurable in maternal monkeys through PPD28 at 10 and 50 mg/kg and were measurable in infant monkeys through BD56 at a maternal dose level of 10 mg/kg and BD70 at a maternal dose level of 50 mg/kg. No drug was detected in control animals at any time point below the lower limit of quantitation (< 150 ng/mL).

**Mean Concentrations (ng/mL) of SEG101 in Maternal Monkey Serum: GD20-22**  
*(Figure excerpted from BLA)*



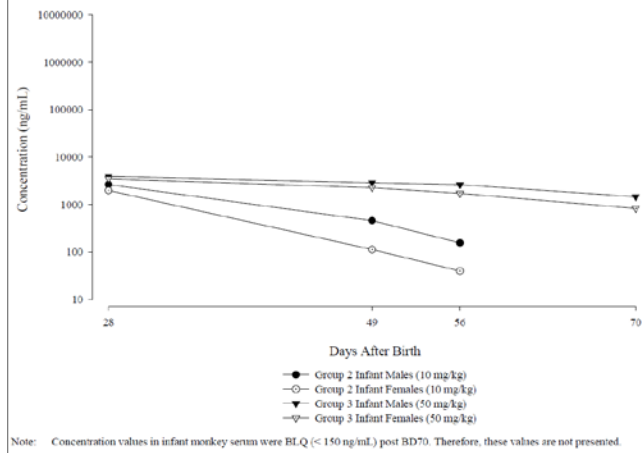
**Mean Concentrations (ng/mL) of SEG101 in Maternal Monkey Serum: GD146 and PPD28**

*(Figure excerpted from BLA)*



**Mean Concentrations (ng/mL) of SEG101 in Infant Monkey Serum: BD28 to BD70**

*(Figure excerpted from BLA)*



**Anti-drug antibodies (ADA):**

ADAs were detected in 3/16 (19%), 8/16 (50%), 11/16 (69%) given 0, 10, and 50 mg/kg, respectively. During the gestational phase, 4/16 (25%) females in each of 10 and 50 mg/kg doses tested positive for ADAs and showed increased clearance relative to ADA-negative animals. These animals were excluded from descriptive statistics and interpretation of TK analysis to represent actual drug exposure. On PPD182±2, remaining animals generally tested positive for ADAs, indicating maternal animals generally developed ADAs over the course of the study. The incidence of ADA in infants was lower than maternal monkeys.

**Maternal animals testing positive for ADA  
(Table excerpted from BLA)**

Dose group	Dose level (mg/kg)	Maternal animal	Increased CL beginning on	ADA-positive beginning on
2	10	2506	GD20-22	GD48
		2507	GD62	GD76
		2510	GD48	GD48
		2515	GD62	GD76
3	50	3504	GD76	GD76
		3508	GD48	GD48
		3513	GD62	GD76
		3516	GD62	GD76

CL = chloride; ADA = anti-drug antibody.

**Abnormal placenta:**

Macroscopic evidence of abnormal placenta was identified in 3 females at 10 mg/kg (adult female/fetus nos. 2503/2031, 2504/2046, and 2513/2136) and 2 females at 50 mg/kg (3508/3086 and 3513/3131), respectively. Abnormal placenta was characterized by pale white or tan multiple foci with 10-60% of the

placental disks effected resulting in inadequate uteroplacental perfusion to the fetus.

**Summary of abnormal placenta, ADAs, dose reactions in dams with fetal loss/infant loss**

Dose/animal#	Birth status	Abnormal placental	ADA	Dose reactions
0 mg/kg/1501	Live birth	-	-	-
0 mg/kg/1502	Live birth	-	-	-
0 mg/kg/1503	Live birth	-	-	-
0 mg/kg/1504	Live birth	-	-	-
0 mg/kg/1505	Live birth	-	-	-
0 mg/kg/1506	Live birth	-	-	-
0 mg/kg/1507	Live birth	-	-	-
0 mg/kg/1508	Live birth	-	-	-
0 mg/kg/1509	UNEC	-	-	-
0 mg/kg/1510	Live birth	-	-	-
0 mg/kg/1511	Live birth	-	-	-
0 mg/kg/1512	Live birth	-	X	-
0 mg/kg/1513	Live birth	-	-	-
0 mg/kg/1514	Infant loss <sup>a</sup>	-	-	-
0 mg/kg/1515	Live birth	-	X	-
0 mg/kg/1516	Abortion	X		
10 mg/kg/2501	Live birth	-	-	-
10 mg/kg/2502	Live birth	-	-	-
10 mg/kg/2503	Stillbirth	X	-	-
10 mg/kg/2504	Stillbirth	X	-	-
10 mg/kg/2505	Stillbirth	-	X	-
10 mg/kg/2506	Abortion	-	X	-
10 mg/kg/2507	Live birth	-	X	X
10 mg/kg/2508	Live birth	-	X	-
10 mg/kg/2509	Live birth	-	X	-
10 mg/kg/2510	Stillbirth	-	X	-
10 mg/kg/2511	Live birth	-	-	-
10 mg/kg/2512	Live birth	-	-	-
10 mg/kg/2513 <sup>b</sup>	Live birth	X	-	-
10 mg/kg/2514	Abortion	-	X	-
10 mg/kg/2515	Infant loss	-	X	-
10 mg/kg/2516	Infant loss	-	-	-
50 mg/kg/3501	Live birth	-	X	-
50 mg/kg/3502	Live birth	-		-
50 mg/kg/3503	Live birth	-	X	-
50 mg/kg/3504	Stillbirth	-	X	
50 mg/kg/3505	Abortion	-	-	-
50 mg/kg/3506	Infant loss	-	-	-
50 mg/kg/3507	Infant loss	-	-	-
50 mg/kg/3508	Abortion	X	X	X
50 mg/kg/3509	Live birth		X	

	<table border="1"> <tr> <td>50 mg/kg/3510</td> <td>Abortion</td> <td>-</td> <td>-</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3511</td> <td>Live birth</td> <td>-</td> <td>X</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3512</td> <td>Live birth</td> <td>-</td> <td>X</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3513</td> <td>Abortion</td> <td>X</td> <td>X</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3514</td> <td>Live birth</td> <td>-</td> <td>X</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3515</td> <td>Live birth</td> <td>-</td> <td>X</td> <td>-</td> </tr> <tr> <td>50 mg/kg/3516</td> <td>Abortion</td> <td>-</td> <td>X</td> <td>X</td> </tr> </table> <p><sup>a</sup>Preterm delivery. Maternal neglect leading to infant, unscheduled necropsy BD2.  <sup>b</sup>Animal# 2513 had focus, pale, tan, central, 2x1cm, &lt;10% disk area. According to the Applicant, the extent of disk area affected ≥ (25 %) and/or centralized location of these areas, consistent with infarcts macroscopically, were considered abnormal and representative of a chronicity that could have affected fetal condition/viability prior to observed gestation day of fetal losses.  “-“ = no comment or not applicable</p> <p><b>Adult females (PPD182±2):</b></p> <ul style="list-style-type: none"> <li>No SEG-101-related organ weights, macroscopic or microscopic findings were noted.</li> <li>ADAs were detected in SG101-treated animals on PPD28 and PPD180.  PPD28: 2/7 animals in 10 mg/kg and 2/9 animals in 50 mg/kg.  PPD182 ± 2: 3/7 animals in 10 mg/kg and 8/9 animals in 50 mg/kg.</li> </ul>	50 mg/kg/3510	Abortion	-	-	-	50 mg/kg/3511	Live birth	-	X	-	50 mg/kg/3512	Live birth	-	X	-	50 mg/kg/3513	Abortion	X	X	-	50 mg/kg/3514	Live birth	-	X	-	50 mg/kg/3515	Live birth	-	X	-	50 mg/kg/3516	Abortion	-	X	X
50 mg/kg/3510	Abortion	-	-	-																																
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50 mg/kg/3512	Live birth	-	X	-																																
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50 mg/kg/3515	Live birth	-	X	-																																
50 mg/kg/3516	Abortion	-	X	X																																
F1 Generation	<p><b>Survival:</b></p> <p><b>Fetal loss</b></p> <ul style="list-style-type: none"> <li>Dams one/15 (6.3%) in control, six/16 (37.5%) in 10 mg/kg and six/16 (37.5%) in 50 mg/kg had fetal loss.</li> <li>The remaining offspring were born alive (7M/8F out of 15 control females, 4M/6F out of 10 females at 10 mg/kg, and 3M/7F out of 10 females at 50 mg/kg).</li> <li>The increases in third-trimester pregnancy losses in both in SG101-treated monkeys were (25%) above relative to concurrent control (0%) and mean historical controls (11.8%).</li> <li>No SEG101-related changes in fetal measurements, fetal external or visceral evaluations, microscopic findings, heart evaluations were noted.</li> </ul> <p><b>Infant loss</b></p> <ul style="list-style-type: none"> <li>There were 5 infant deaths in the study. One/15 in control (6.7%, died on BD2), two/10 (20% died in BD1) in 10 mg/kg and two/10 (20% died in BD1 and BD5) in 50 mg/kg.</li> <li>The frequency of infant loss in the SG101-treated dams was above the concurrent control and above mean historical control (9.5%), but well within the historical control range (0 to 20%). There was one other infant that did not reach its scheduled terminal necropsy. Unscheduled necropsy of control infant no. 1091 on BD109 was conducted of necessity due to demise of the infant’s mother.</li> <li>All 5 infant losses were determined to be related to maternal-induced trauma and/or neglect. This determination was based on observations documented in the study report including weakening/decreased activity</li> </ul>																																			

	<p>of the infants, loss of strength, and inability to suckle/nurse; cold and bite/puncture wounds on the limbs/tails; Inflated lungs, loss of body weight, abrasions on the face, slight discoloration of the lips, vocalizing, purple around the lips and tongue, cold to touch, and decreased activity.</p> <ul style="list-style-type: none"> <li>• The frequency of maternal neglect in this study (5/35, 14.3%) was consistent with testing facility historical control range (0 to 16.7%).</li> <li>• For infants that died or were euthanized, there were no SEG101-related findings in morphometric measurements, external evaluations, visceral (including heart) evaluations, skeletal evaluations, gross pathology, and/or histopathology. In the infant no. 3066 (50 mg/kg) euthanized on BD5, bile pigment was observed in the liver, mild mixed cell infiltration and type II pneumocyte hyperplasia in the lung and minimal lymphoid decreased cellularity in the thymus.</li> </ul> <p style="text-align: center;"><b>Summary of maternal neglect leading to infant unscheduled necropsy</b></p> <table border="1" data-bbox="380 835 1429 1520"> <tr> <td data-bbox="380 835 639 915"><b>Group 1 (0 mg/kg - Controls)</b></td> <td data-bbox="639 835 911 915">1514/1146 (preterm delivery GD144; infant euthanized BD2)</td> <td data-bbox="911 835 1429 915">The infant loss resulted from preterm delivery and maternal neglect, leading to weakening of the infant, loss of strength, and inability to suckle/nurse.</td> </tr> <tr> <td data-bbox="380 915 639 1073"><b>Group 2 (10 mg/kg)</b></td> <td data-bbox="639 915 911 1073">2515/2151 (GD160 – infant euthanized BD1)</td> <td data-bbox="911 915 1429 1073">Alive but was cold and had bite/puncture wounds on the leg/hand/tail; placed in an incubator to warm, needed oxygen due to difficulty breathing (became cyanotic when off oxygen), and was soon recognized to require euthanasia for humane reasons. Necropsy findings confirmed maternal-inflicted trauma.</td> </tr> <tr> <td data-bbox="380 1073 639 1209"><b>Group 2 (10 mg/kg)</b></td> <td data-bbox="639 1073 911 1209">2516/2166 (GD158 – infant found dead BD1)</td> <td data-bbox="911 1073 1429 1209">Inflated lungs at necropsy confirmed this infant had been born alive. Bite wounds/injuries indicative of maternal-induced trauma were present (most fingers missing both hands, crushed skull, head lacerations).Necropsy findings confirmed maternal-inflicted trauma.</td> </tr> <tr> <td data-bbox="380 1209 639 1346"><b>Group 3 (50 mg/kg)</b></td> <td data-bbox="639 1209 911 1346">3506/3066 (preterm delivery GD143; maternal neglect – infant euthanized BD5)</td> <td data-bbox="911 1209 1429 1346">Pattern of maternal neglect over a period of 5 days postpartum. The infant had declined in body weight from 233.6 g on BD1 to 197.8 g on BD4 (15% decrease). The final decision to euthanize the infant was based on continuing and persistent lack of maternal care.</td> </tr> <tr> <td data-bbox="380 1346 639 1520"><b>Group 3 (50 mg/kg)</b></td> <td data-bbox="639 1346 911 1520">3507/3076 (preterm delivery GD145; maternal neglect – infant euthanized BD1)</td> <td data-bbox="911 1346 1429 1520">Pattern of maternal neglect, infant had abrasions on the face and slight discoloration of the lips, vocalizing, purple around the lips and tongue, cold to touch, weak, and had decreased activity. Euthanized based on ongoing and consistent maternal behavior/infant neglect and the status of the infant’s condition.</td> </tr> </table> <p><b>Infants -Postpartum</b></p> <ul style="list-style-type: none"> <li>• There were no SEG101-related clinical signs, body weights, external assessments or morphometric, grip strength, clinical pathology in the infants.</li> <li>• Neurobehavioral assessment: The Applicant performed neurobehavioral assessments on infants on BD7 and BD 14. The Applicant states that results were considered within the range of normal variability for</li> </ul>	<b>Group 1 (0 mg/kg - Controls)</b>	1514/1146 (preterm delivery GD144; infant euthanized BD2)	The infant loss resulted from preterm delivery and maternal neglect, leading to weakening of the infant, loss of strength, and inability to suckle/nurse.	<b>Group 2 (10 mg/kg)</b>	2515/2151 (GD160 – infant euthanized BD1)	Alive but was cold and had bite/puncture wounds on the leg/hand/tail; placed in an incubator to warm, needed oxygen due to difficulty breathing (became cyanotic when off oxygen), and was soon recognized to require euthanasia for humane reasons. Necropsy findings confirmed maternal-inflicted trauma.	<b>Group 2 (10 mg/kg)</b>	2516/2166 (GD158 – infant found dead BD1)	Inflated lungs at necropsy confirmed this infant had been born alive. Bite wounds/injuries indicative of maternal-induced trauma were present (most fingers missing both hands, crushed skull, head lacerations).Necropsy findings confirmed maternal-inflicted trauma.	<b>Group 3 (50 mg/kg)</b>	3506/3066 (preterm delivery GD143; maternal neglect – infant euthanized BD5)	Pattern of maternal neglect over a period of 5 days postpartum. The infant had declined in body weight from 233.6 g on BD1 to 197.8 g on BD4 (15% decrease). The final decision to euthanize the infant was based on continuing and persistent lack of maternal care.	<b>Group 3 (50 mg/kg)</b>	3507/3076 (preterm delivery GD145; maternal neglect – infant euthanized BD1)	Pattern of maternal neglect, infant had abrasions on the face and slight discoloration of the lips, vocalizing, purple around the lips and tongue, cold to touch, weak, and had decreased activity. Euthanized based on ongoing and consistent maternal behavior/infant neglect and the status of the infant’s condition.
<b>Group 1 (0 mg/kg - Controls)</b>	1514/1146 (preterm delivery GD144; infant euthanized BD2)	The infant loss resulted from preterm delivery and maternal neglect, leading to weakening of the infant, loss of strength, and inability to suckle/nurse.														
<b>Group 2 (10 mg/kg)</b>	2515/2151 (GD160 – infant euthanized BD1)	Alive but was cold and had bite/puncture wounds on the leg/hand/tail; placed in an incubator to warm, needed oxygen due to difficulty breathing (became cyanotic when off oxygen), and was soon recognized to require euthanasia for humane reasons. Necropsy findings confirmed maternal-inflicted trauma.														
<b>Group 2 (10 mg/kg)</b>	2516/2166 (GD158 – infant found dead BD1)	Inflated lungs at necropsy confirmed this infant had been born alive. Bite wounds/injuries indicative of maternal-induced trauma were present (most fingers missing both hands, crushed skull, head lacerations).Necropsy findings confirmed maternal-inflicted trauma.														
<b>Group 3 (50 mg/kg)</b>	3506/3066 (preterm delivery GD143; maternal neglect – infant euthanized BD5)	Pattern of maternal neglect over a period of 5 days postpartum. The infant had declined in body weight from 233.6 g on BD1 to 197.8 g on BD4 (15% decrease). The final decision to euthanize the infant was based on continuing and persistent lack of maternal care.														
<b>Group 3 (50 mg/kg)</b>	3507/3076 (preterm delivery GD145; maternal neglect – infant euthanized BD1)	Pattern of maternal neglect, infant had abrasions on the face and slight discoloration of the lips, vocalizing, purple around the lips and tongue, cold to touch, weak, and had decreased activity. Euthanized based on ongoing and consistent maternal behavior/infant neglect and the status of the infant’s condition.														

	<p>neonatal cynomolgus monkeys, and scores were comparable between control and SEG101-exposed infants.</p> <p><b>Infants (BD180 ± 2):</b></p> <ul style="list-style-type: none"> <li>• There were no SEG101-related clinical signs, clinical pathology, morphometric measurements, body weights, external evaluations, visceral (including heart) evaluations, skeletal evaluations, organ weights, gross pathology, and/or histopathology. Infant no. 2081 (10 mg/kg), had macroscopic multifocal pale tan foci correlated with regionally extensive hepatocellular vacuolation at the edge of the lobe of the liver.</li> <li>• Mean SEG101 concentration values were measurable in maternal and infant monkeys on PPD28 and BD28, respectively, indicating that SEG101 was able to cross the placental barrier following administration once every 2 weeks to maternal monkeys. The mean infant: maternal monkey concentration ratios on PPD/BD28 were 6.94 at 10 mg/kg and 4.52 at 50 mg/kg.</li> <li>• ADAs were detected in 2 animals in 10 mg/kg and 3 animals in 50 mg/kg.</li> </ul> <p><b>Pharmacodynamics – adult females and infants</b></p> <p>Serum samples were analyzed for ex vivo P-selectin inhibition using a surface plasmon resonance assay. The amount of BLQ decreased with increasing dose level of SEG101 from group 1 (0 mg/kg) to group 3 (50 mg/kg) in both adults and infants.</p> <p style="text-align: center;"><b>Summary of BLQ samples in each group</b> (Table excerpted from BLA)</p> <table border="1" data-bbox="381 1297 1419 1654"> <thead> <tr> <th>Group (dose level)</th> <th>No. of tested samples</th> <th>No. of BLQ samples</th> <th>% of BLQ samples in the group</th> </tr> </thead> <tbody> <tr> <td>Group 1 (0 mg/kg) Adult</td> <td>161</td> <td>93</td> <td>57.8%</td> </tr> <tr> <td>Group 1(0 mg/kg) Infant</td> <td>59</td> <td>35</td> <td>59.3%</td> </tr> <tr> <td>Group 2 (10 mg/kg) Adult</td> <td>161</td> <td>35</td> <td>21.7%</td> </tr> <tr> <td>Group 2 (10 mg/kg) Infant</td> <td>30</td> <td>7</td> <td>23.3%</td> </tr> <tr> <td>Group 3 (50 mg/kg) Adult</td> <td>152</td> <td>20</td> <td>13.2%</td> </tr> <tr> <td>Group 3 (50 mg/kg) Infant</td> <td>42</td> <td>6</td> <td>14.3%</td> </tr> </tbody> </table> <p>BLQ = below limit of quantitation.</p>	Group (dose level)	No. of tested samples	No. of BLQ samples	% of BLQ samples in the group	Group 1 (0 mg/kg) Adult	161	93	57.8%	Group 1(0 mg/kg) Infant	59	35	59.3%	Group 2 (10 mg/kg) Adult	161	35	21.7%	Group 2 (10 mg/kg) Infant	30	7	23.3%	Group 3 (50 mg/kg) Adult	152	20	13.2%	Group 3 (50 mg/kg) Infant	42	6	14.3%
Group (dose level)	No. of tested samples	No. of BLQ samples	% of BLQ samples in the group																										
Group 1 (0 mg/kg) Adult	161	93	57.8%																										
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Group 2 (10 mg/kg) Infant	30	7	23.3%																										
Group 3 (50 mg/kg) Adult	152	20	13.2%																										
Group 3 (50 mg/kg) Infant	42	6	14.3%																										
F2 Generation	Not evaluated																												

### 5.5.5. Other Toxicology Studies

#### Study title/Study no.: Hemolytic Potential Testing of SelG1/DR-02

The hemolytic potential of SelG1 at 10 and 100 mg/mL was tested on human blood using spectrophotometry to quantitate released hemoglobin. Saponin was used as a positive control while the negative control was left untreated. A hemoglobin level greater than 500 mg/dl was considered positive indication of hemolysis. The results show that there was no difference seen in the amount of released hemoglobin between the SelG1-treated samples and the negative control.

**Table 3: The concentration of hemoglobin in each sample (an indicator for hemolysis)**

Sample	A <sub>380</sub>	A <sub>415</sub>	A <sub>450</sub>	Concentration of hemoglobin in the original sample (mg/dl)
Untreated (1:5)	0.2653	0.3146	0.3106	2.2
SelG1 10 ug/ml (1:5)	0.3506	0.3767	0.3663	1.5
SelG1 100 ug/ml (1:5)	0.2880	0.3293	0.3240	2.0
Saponin 1% (1:5000)	0.0617	0.2239	0.0323	14,859.6

*(Table excerpted from BLA)*

#### Study title/Study no.: Study to Assess the Potential Cross Reactivity of SelG1 with a Selected Panel of Human and Cynomolgus Monkey Tissues/8220205

Biotin labeled SelG1 at 10µg/mL, 5µg/mL and 2.5µg/mL was evaluated for tissue cross reactivity with prepared cryo-sections from a selected panel of human and cynomolgus monkey tissues. The vascular component of human lung and colon were used as the positive control preparation. The smooth muscle component of the same human lung and colon preparations were used as the negative control preparation. Tissues included sections from adrenal gland, blood cells, bone marrow, breast, brain, endothelium, eye, fallopian tube, gastrointestinal tract, heart, kidney, liver, lung, lymph node, ovary, pancreas, parathyroid, salivary gland, peripheral nerve, pituitary, placenta, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid, tonsil, ureter, and uterus.

Granular cytoplasmic staining was observed with biotinylated SelG1 in blood vessels in the majority of tissues examined and in platelets in the blood and spleen of both human and cynomolgus monkey. Granular cytoplasmic staining was also seen in megakaryocytes in the bone marrow of cynomolgus monkey (megakaryocytes not present in human samples). In general, the staining observed in cynomolgus monkey was of a lower intensity than that observed in the human.

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Ramadevi Gudi, PhD  
Nonclinical Primary Reviewer

John Leighton, PhD  
Nonclinical Supervisor

## 6 Clinical Pharmacology

### 6.1. Executive Summary

Clinical Pharmacology Section of the BLA submission includes pharmacokinetics/ pharmacodynamics (PK/PD) studies of crizanlizumab after single dose and repeat doses in both healthy subjects and patients with sickle cell disease (SCD) to support the proposed crizanlizumab dosing regimen of 5 mg/kg administered as an intravenous (IV) infusion over 30 minutes on Week 0, Week 2, and every 4 weeks thereafter. No therapeutic individualization for intrinsic or extrinsic factors is recommended.

The data from a phase 1 PK/PD comparability study and a phase 2 PK/PD study allowed for bridging the Novartis-manufactured crizanlizumab (SEG101) to Reprixys-manufactured crizanlizumab (SelG1).

#### Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in BLA 761128. This BLA is approvable from a clinical pharmacology perspective provided that the Applicant and the FDA reach an agreement regarding the labeling language. See details in section 11. Post-marketing commitments and requirements are detailed in section 6.2.2.

### 6.2. Summary of Clinical Pharmacology Assessment

The adequacy of the clinical pharmacology program in the overall crizanlizumab development plan is summarized in the table below.

Review Issue	Sufficiently Supported?	Recommendations and Comments
Proposed dosing regimen of 5 mg/kg at Week 0, Week 2, and every 4 weeks thereafter for general patient population	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	The primary evidence of effectiveness comes from the pivotal phase 2 Study CSEG101A2201 (SUSTAIN). The proposed dosing regimen is supported by the a statistically significant reduction in median annual rate of vaso-occlusive crises (VOC) leading to a healthcare visit compared to placebo (1.63 vs 2.98 p=0.010) in SCD patients.
Effect of immunogenicity on PK, efficacy, and safety	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	<b>Labeling Recommendation:</b> Inconclusive due to low incidence (1.6%) of treatment-emergent anti- crizanlizumab antibody formation in limited number of healthy subjects (N = 61).

#### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Crizanlizumab is a 146 kDa humanized IgG2 monoclonal antibody (mAb) 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 block interactions between endothelial cells, platelets, red blood cells, and leukocytes.

The PK parameters of Novartis-manufactured crizanlizumab (SEG101) and Reprixys-manufactured crizanlizumab (SelG1) in healthy subjects and SCD patients following 5 mg/kg dose treatment are presented in Table 2:

**Table 2. PK parameters for crizanlizumab 5 mg/kg treatment in healthy subjects and SCD patients**

Population	PK parameters	Novartis-manufactured crizanlizumab SEG101 Arithmetic mean (CV%)	Reprixys-manufactured crizanlizumab SelG1 Arithmetic mean (CV%)
*Healthy subjects	C <sub>max</sub> (mg/mL)	0.16 (15.3%)	0.15 (19.8%)
	AUC <sub>last</sub> (mg*hr/mL)	33.6 (12.6%)	26.5 (17.2%)
	AUC <sub>inf</sub> (mg*hr/mL)	34.6 (13.1%)	27.3 (18.8%)
	CL (mL/hr)	11.7 (16.2%)	14.8 (23.1%)
	T <sub>1/2</sub> (days)	10.6 (20.5%)	9.4 (32.9%)
**SCD patients	C <sub>max</sub> (mg/mL)	0.12 (25.5%)	N/A
	AUC <sub>tau</sub> (mg*hr/mL)	20.4 (23.5%)	N/A
	T <sub>1/2</sub> (days)	7.6 (28.5%)	N/A

Source: Study SEG101A2102 CSR, Table 11-6 & Table 11-7; Study SEG101A2202 CSR, Table 14.2-6 & Table 14.2-7.

\*PK parameters of crizanlizumab in healthy subjects were obtained following a single dose treatment.

\*\*PK parameters of crizanlizumab in SCD patients were obtained at steady-state.

The immunogenicity of crizanlizumab was evaluated using MSD bridging assay. In Study 2102, 1 of the 61 (1.6%) evaluable healthy subjects tested positive for a treatment-induced anti-crizanlizumab. The effect of immunogenicity on PK, efficacy, and safety of crizanlizumab cannot be determined due to low incidence of treatment-emergent anti-crizanlizumab antibody formation in limited number of healthy subjects.

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The proposed dosing regimen of crizanlizumab is 5 mg/kg IV infusion on Week 0, Week 2, and every 4 weeks thereafter.

### Therapeutic Individualization

No therapeutic individualization for intrinsic or extrinsic factors is recommended.

### Outstanding Issues

Two clinical pharmacology PMR studies will be issued:

- Assess Neutralizing anti-drug antibody (NADA) responses with a validated NADA assay. NADA response will be evaluated in all confirmed ADA positive samples from studies CSEG101 A2102, A2202 and the primary analysis of A2301. Provide a final report and include information on the level of crizanlizumab in each sample at each sampling point.

Study/Trial Completion: 12/2025

Final Report Submission: 12/2025

- Assess immunogenicity of crizanlizumab, including anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) in all crizanlizumab-treated subjects in Study A2301. Evaluate the effect of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy, and safety of crizanlizumab. In the primary analysis study report include: the complete immunogenicity data set, information on the drug product lots administered to each patient, the ADA status and titers, the NADA status and the level of drug in each patient’s test sample at the specific sampling point.

Study/Trial Completion: 12/2025

Final Report Submission: 12/2025

### 6.3. Comprehensive Clinical Pharmacology Review

#### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Crizanlizumab is a humanized IgG2 mAb (146, (b) (4) Da (b) (4) molecular mass)
Aqueous solubility	Not available. Crizanlizumab is supplied as a concentrate for solution for infusion at a concentration of 10 mg/mL.
PHARMACOLOGY	
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.
Active moiety	As a mAb, major circulating metabolite is not expected for crizanlizumab.
QT/QTc prolongation	As a mAb, crizanlizumab is not expected to cause QT prolongation. No clinically relevant changes from baseline in the QTc interval observed SCD patient population.
GENERAL INFORMATION	

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<b>Bioanalytical assay</b>	<p>Two validated enzyme-linked immunosorbent assays (ELISA) were developed to measure the concentrations of crizanlizumab in the serum samples collected from both patients and healthy subjects in the clinical studies included in this BLA (see Section 19.5.1).</p> <p>A validated surface plasmon resonance (SPR)-based PD assay was developed to measure the inhibition of P-Selectin-PSGL-1 interaction by crizanlizumab in the serum samples collected from both patients and healthy subjects in the clinical studies included in this BLA (see Section 19.5.1).</p>
<b>Patient PK vs. healthy subject (HS) PK</b>	At 5 mg/kg, the mean terminal elimination half-life ( $t_{1/2}$ ) of crizanlizumab was 7.6 days and 10.6 days in SCD patients and healthy subjects, respectively.
<b>Steady-state exposure at the proposed dosing regimen</b>	<p>Crizanlizumab 5mg/kg Q4W exhibited minimal accumulation at steady-state in SCD patients. At steady state:</p> <ul style="list-style-type: none"> <li>▪ <math>C_{MAX} \approx 0.12</math> mg/mL (25.5% CV)</li> <li>▪ <math>AUC_{tau} \approx 20.4</math> mg·hr/mL (23.5% CV)</li> </ul>
<b>Minimal effective dose or exposure</b>	In the Phase 2 Study A2201, crizanlizumab 5 mg/kg demonstrated a statistically significant reduction in median annual rate of VOC leading to a healthcare visit compared to placebo in SCD patients; whereas crizanlizumab 2.5 mg/kg did not demonstrate a statistical significance.
<b>Maximum tolerated dose or exposure</b>	MTD was not reported. No death, SAE, or severe AE was reported in healthy subjects received crizanlizumab treatment (single doses of 0.2, 0.5, 1, 5 mg/kg or two doses of 8 mg/kg). In SCD patients treated with crizanlizumab at 5 mg/kg, the majority of the adverse drug reactions (ADRs) were mild to moderate in severity (grade 1 or 2). No patients discontinued due to ADRs.
<b>Dose proportionality</b>	The mean crizanlizumab $C_{max}$ , $AUC_{last}$ , or $AUC_{inf}$ increased in a dose proportional manner over the dose range of 5 to 7.5 mg/kg in healthy subjects.
<b>Accumulation</b>	Crizanlizumab 5mg/kg Q4W exhibited minimal accumulation at steady-state in SCD patients.
<b>Variability</b>	Based on Study A2202, inter-subject variability (%CV) of crizanlizumab at 5 mg/kg was 25.5% for $C_{MAX}$ and 25.3% for $AUC_{tau}$ in SCD patients.
<b>ABSORPTION</b>	
<b>Bioavailability</b>	Not applicable as crizanlizumab is administered IV as a 30-minute infusion
<b><math>T_{MAX}</math></b>	Median $T_{MAX} = 0.5$ h (End of infusion)
<b>Food effect</b>	Not applicable, as crizanlizumab is administered IV
<b>DISTRIBUTION</b>	
<b>Volume of distribution (Vd)</b>	$V_{ss} \approx 4.26$ L (25.1% CV) after a single crizanlizumab 5 mg/kg intravenous infusion in healthy subjects.
<b>Substrate of transporter systems</b>	N/A
<b>ELIMINATION</b>	

<b>Terminal elimination half-life and clearance</b>	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 subjects. The mean (% CV) elimination $t_{1/2}$ of crizanlizumab was 7.6 (28.5%) days during dosing interval in patients with sickle cell disease.
<b>Metabolism</b>	As a monoclonal antibody, crizanlizumab is expected to be metabolized into small peptides by catabolic pathways.
<b>Excretion</b>	N/A
<b>Drug interaction liability</b>	N/A

### 6.3.2. Clinical Pharmacology Questions

#### Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes.

The pivotal study A2201 was a phase 2, double blind, placebo-controlled, parallel-group study to assess the efficacy and safety of crizanlizumab in SCD patients. Patients (N = 198) were randomized 1:1:1 to receive IV infusions of crizanlizumab (2.5 mg/kg or 5 mg/kg) or placebo by IV infusion on Week 0, Week 2, and every 4 weeks (Q4W) thereafter. Refer to Section 19.5.1 for additional details.

As detailed in Section 8.1, Crizanlizumab 5 mg/kg led to a statistically significant reduction in median annual rate of vaso-occlusive crises (VOC) leading to a healthcare visit compared to placebo (1.63 vs 2.98 p=0.010). Crizanlizumab 2.5 mg/kg didn't lead to a statistically significant reduction in median annual rate of VOC leading to a healthcare visit compared to placebo (2.01 vs 2.98 p=0.180). Additional details regarding the efficacy can be found in Section 8.1 (Efficacy).

#### Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

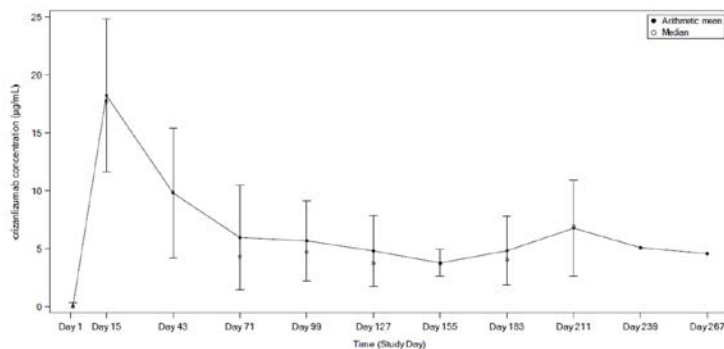
Yes. The Applicant's proposed dosing regimen of 5 mg/kg on Week 0, Week 2, and every 4 weeks thereafter is approvable for the intended patient population of adults and pediatric patients aged 16 years and older with sickle cell disease from a clinical pharmacology perspective. The proposed dosing regimen is supported by the observed PK data described below as well as efficacy data from the pivotal phase 2 Study A2201, and safety data from phase 2 Studies A2201 and A2202, in Sections 8.1 and 8.2.

#### Dose selection rationale

Per Applicant, dose selection was based on results of the phase 1 FIH Study A2101 in healthy subjects (N = 27) and the pivotal phase 2 Study A2201 in adult patients (N = 198) with SCD, which evaluated crizanlizumab dosing regimens ranging from 0.2 to 8 mg/kg.

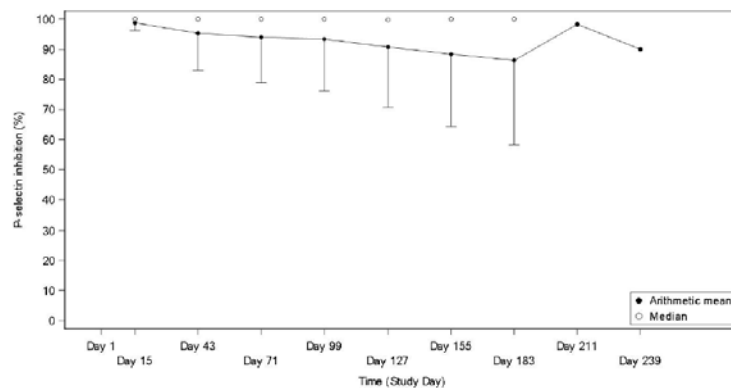
While crizanlizumab 5 mg/kg was shown to be safe and efficacious in patients with SCD in Study A2201 by demonstrating a clinically relevant and statistically significant difference in the annual rate of VOCs leading to a health care visit (See Section 8.1), it is likely that crizanlizumab 5 mg/kg Q4W may not provide sufficient P-selectin inhibition by the end of the dosing interval. As reported in Study A2202, the mean trough crizanlizumab concentrations (Figure 2) and mean trough% P-selectin inhibition (Figure 3) of crizanlizumab following 5 mg/kg treatment in SCD patients were about 5.7 µg/mL (ranged from 3.8 to 9.8 µg/mL) and 91.2% (ranged from 86.3% to 98.8%), respectively.

**Figure 2. Trough serum concentration-time profiles for crizanlizumab (SEG101) 5 mg/kg treatment in SCD patients**



Source: Study SEG101A2202 CSR, Figure 11-2. Crizanlizumab 5 mg/kg was administered at W0, W2 and at Q4W thereafter. Data is presented as median and arithmetic mean (SD).

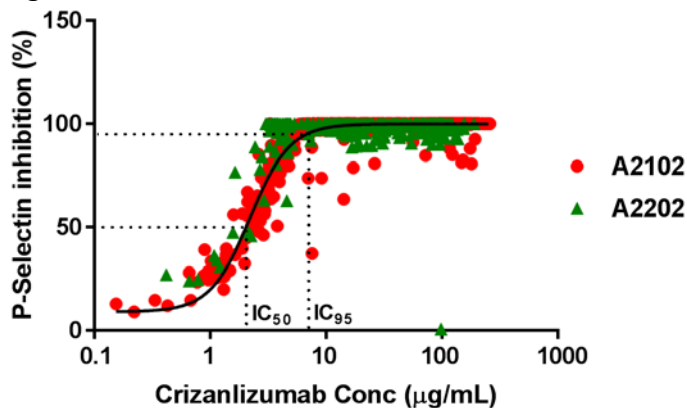
**Figure 3. Trough serum PD (%P-selectin inhibition)-time profiles for crizanlizumab (SEG101) 5 mg/kg treatment in SCD patients**



Source: Study SEG101A2202 CSR, Figure 11-4. Crizanlizumab 5 mg/kg was administered at W0, W2 and at Q4W thereafter. Data is presented as median and arithmetic mean (SD).

The FDA's analysis showed that the estimated ex vivo  $IC_{50}$  and  $IC_{95}$  values for crizanlizumab (SEG101) in healthy subjects from Study 2102 were 2.6  $\mu\text{g/mL}$  and 6.6  $\mu\text{g/mL}$ , respectively (Figure 4). The concentration-response relationship of crizanlizumab (SEG101) in SCD patients from Study 2202 exhibited a consistent trend. However, due to lack of concentration-response relationship data at lower crizanlizumab concentration range, the ex vivo  $IC_{50}$  and  $IC_{95}$  values couldn't be reliably estimated and were not used in the final analysis.

**Figure 4. Estimation of Ex vivo  $IC_{50}$  for crizanlizumab (SEG101)**



Source: FDA analysis

Comparison between the observed  $C_{\text{trough}}$  PK/PD data in SCD patients following crizanlizumab 5 mg/kg (Figure 2, Figure 3) and the estimated  $IC_{95}$  value indicated that at least 25% increase in

crizanlizumab dose may be necessary in order to achieve sufficient P-selection inhibition (i.e.,  $\geq 95\%$ ) at steady state C<sub>trough</sub> (i.e.,  $\geq 6.6 \mu\text{g/mL}$ ).

In Study 2102, the PK and PD of crizanlizumab (SEG101) have been evaluated in healthy subjects at the dose levels 5 mg/kg (Figure 5) and 7.5 mg/kg (Figure 6). The mean crizanlizumab C<sub>max</sub>, AUC<sub>last</sub>, or AUC<sub>inf</sub> increased in a dose proportional manner over the dose range of 5 to 7.5 mg/kg in healthy subjects (Table 3, Figure 5A, Figure 6A). Crizanlizumab 5 mg/kg and 7.5 mg/kg both demonstrated nearly complete P-selectin inhibition (i.e.,  $\approx 100\%$ ) up to Day 29, as manifested by the similar AU<sub>EC29days</sub> (66600 % inhibition\*hr for 5 mg/kg, 67200 % inhibition\*hr for 7.5 mg/kg). However, % P-selectin inhibition following 7.5 mg/kg treatment continued to be greater than that following 5 mg/kg treatment at Day 43 (100% vs. 94.9%) and at Day 57 End of Treatment disposition (99.3% vs. 55.6%) (Table 4, Figure 5B, Figure 6B), suggesting that the duration of complete P-selection inhibition (i.e.,  $\geq 95\%$ ) may be extended by increase of crizanlizumab dose.

In summary, the proposed dosing regimen of crizanlizumab 5 mg/kg at Week 0, Week 2, and every 4 weeks thereafter for general patient population is reasonable from a clinical pharmacology perspective. FDA analysis suggested that further increase of dose (e.g., 7.5 mg/kg) may improve the efficacy of crizanlizumab in SCD patients.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

The effect of renal or hepatic impairment on the pharmacokinetics of crizanlizumab is unknown. (b) (4)

See details in Section 19.5.1. The Applicant should update their population PK analysis using PK data from Study 2201, Study A2202 and Study A2301 with fully validated assays, and assess the effect of intrinsic factors (e.g., renal or hepatic impairment, disease, age, sex, body weight) and extrinsic factors (e.g., concomitant drugs) on crizanlizumab exposure.

Immunogenicity

Serum samples were collected from Studies A2101, A2201, A2102 and A2202 for the analysis of anti-drug antibodies (ADAs) to crizanlizumab at scheduled time points. The ADA assay used in Studies A2101, A2201 is not validated, so immunogenicity data from these two studies was rejected. The ADA assay used in Studies A2102, A2202 is validated, and the ADA data from these two studies has been used to support immunogenicity labeling. Refer to OBP review for more detailed information.

In their response to FDA submitted on 09/18/2019 (SDN 35), the Applicant provided the updated immunogenicity information: In Study 2102, 1 of the 61 (1.6%) evaluable healthy subjects tested positive for a treatment-induced anti-crizanlizumab. In Study 2202, none of the 45 evaluable SCD patients tested positive for treatment-induced anti-crizanlizumab antibodies.

The effect of immunogenicity on PK, efficacy, and safety of crizanlizumab cannot be determined due to low incidence (1.6%) of treatment-emergent anti-crizanlizumab antibody formation in limited number of healthy subjects (N = 61). The FDA concluded that the Applicant should conduct PMC studies to assess immunogenicity of crizanlizumab, including anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA), in all crizanlizumab-treated patients with fully validated assays; evaluate the effect of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy and safety of crizanlizumab; and update ADAKVE label with the updated immunogenicity information.

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

There are no relevant food-drug or drug-drug interactions. However, crizanlizumab interferes with automated platelet counts (platelet clumping) when blood samples are collected in tubes containing ethylenediaminetetraacetic acid (EDTA) which may lead to unevaluable or falsely decreased platelet counts. The Applicant states that this is an ex vivo phenomenon that is EDTA- and time-dependent, without any indication of a platelet clumping, true reduction in circulating platelets or pro-aggregant effect in vivo. Based on their in vitro study results, the Applicant proposes that blood samples should be analyzed within 4 hours of blood collection or blood samples should be collected in tubes containing citrate to mitigate this effect. When needed, estimate platelet count via peripheral blood smear.

**Are Reprixys-manufactured crizanlizumab (SelG1) and Novartis-manufactured crizanlizumab (SEG101) comparable?**

Reprixys-manufactured crizanlizumab (SelG1) was used in the phase 1 FIH Study A2101 with healthy subjects and the pivotal phase 2 Study A2201 with SCD patients. Novartis-manufactured crizanlizumab (SEG101) is the to-be-marketed product and was used in the phase 2 PK/PD Study A2202 with SCD patients, and is planned for registration/commercialization. A PK/PD comparability study (Study A2102) with healthy subjects was used to bridge the SelG1 formulation to to-be-marketed SEG101 formulation.

Study A2102 was a randomized, parallel group, single-dose, single-center study that assessed the PK/PD of SEG101 (test) compared to SelG1 (reference) in 61 adult healthy subjects following a single IV infusion of crizanlizumab (SelG1 or SEG101) at 5 mg/kg . An additional exploratory group of seven healthy subjects received SEG101 at 7.5 mg/kg. A summary of the PK parameters from the study is shown in Table 3. A summary of the PD parameters from the study are shown in Table 4.

The PK results showed that systemic exposure (i.e., AUC) for SEG101 was 28% greater than SelG1 (Table 3, Figure 5A). This PK difference also translated to a difference in PD response. SEG101 and SelG1 both demonstrated nearly complete P-selectin inhibition (i.e., ≈ 100%) by

Day 29, as manifested by the similar AUEC29days (66600 % inhibition\*hr for SEG101, 67100 % inhibition\*hr for SelG1). However, % P-selectin inhibition following SEG101 treatment continued to be slightly greater than that following SelG1 treatment at Day 43 (94.9% vs. 91.2%) and at Day 57 End of Treatment disposition (55.6% vs. 45.7%) (Table 4, Figure 5B).

**Table 3. PK parameters for crizanlizumab 5 mg/kg and 7.5 mg/kg treatments**

Product	Arithmetic mean values (CV%)			Geo-mean ratio* (90% CI)		
	C <sub>max</sub> (mg/mL)	AUC <sub>last</sub> (mg.hr/mL)	AUC <sub>inf</sub> (mg.hr/mL)	C <sub>max</sub>	AUC <sub>last</sub>	AUC <sub>inf</sub>
SelG1 5 mg/kg (Reference)	0.15 (19.8%)	26.5 (17.2%)	27.3 (18.8%)	-	-	-
SEG101 5 mg/kg (Test)	0.16 (15.3%)	33.6 (12.6%)	34.6 (13.1%)	1.11 (1.03, 1.20)	1.28 (1.20, 1.36)	1.28 (1.20, 1.37)
SEG101 7.5 mg/kg	0.22 (11.3%)	52.5 (10.2%)	56.2 (10.6%)	-	-	-

Source: Study SEG101A2102 CSR, Table 11-5, Table 11-6 & Table 11-11.

\* Geo-mean ratio is calculated as Test (SEG101 5 mg/kg)/Reference (SelG1 5 mg/kg)

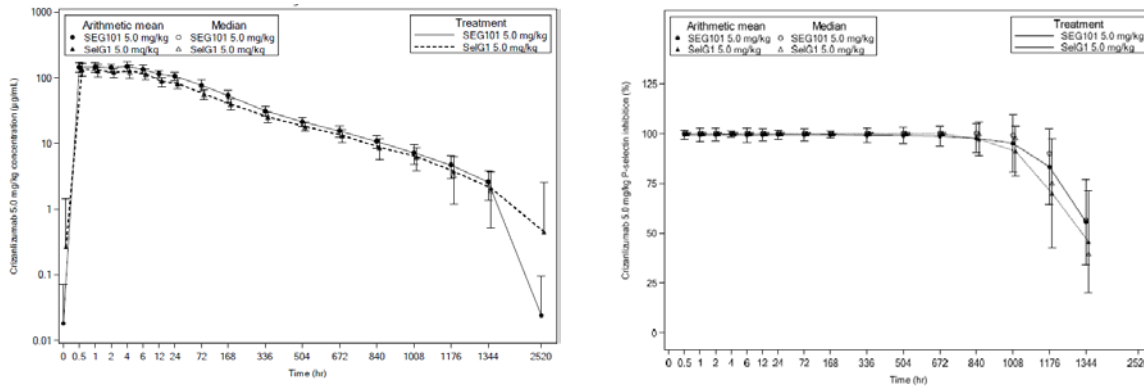
**Table 4. PD parameters (%P-selectin inhibition) for crizanlizumab 5 mg/kg and 7.5 mg/kg treatments**

Product	Arithmetic mean values (CV%)			
	AUEC29days (% inhibition*hr)	Day 29 (% inhibition)	Day 43 (% inhibition)	Day 57 (EOT) (% inhibition)
SelG1 5 mg/kg (Reference)	67100 (0.2%)	99.8 (0.4%)	91.2 (13.8%)	45.7 (56.1%)
SEG101 5 mg/kg (Test)	66600 (3.3%)	98.7 (5.0%)	94.9 (15.4%)	55.6 (38.7)
SEG101 7.5 mg/kg	67200 (0.0%)	100 (N/A)	100 (N/A)	99.3 (1.1%)

Source: Study SEG101A2102 CSR, Table 11-9, Table 11-10, Table 11-13 & Table 14.2-3.4.

**Figure 5. Serum PK (A) and PD (%P-selectin inhibition) profiles (B) for crizanlizumab (SEG101 and SelG1) 5 mg/kg treatments in healthy subjects**

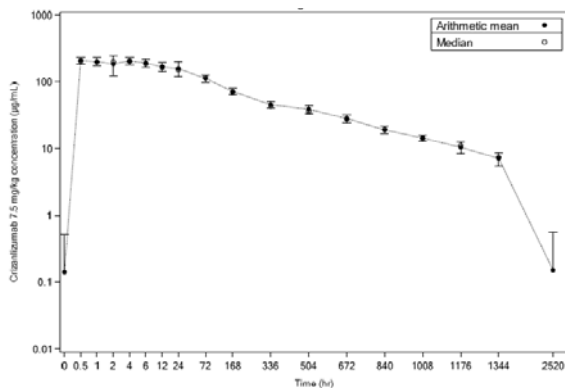
(A). (B).



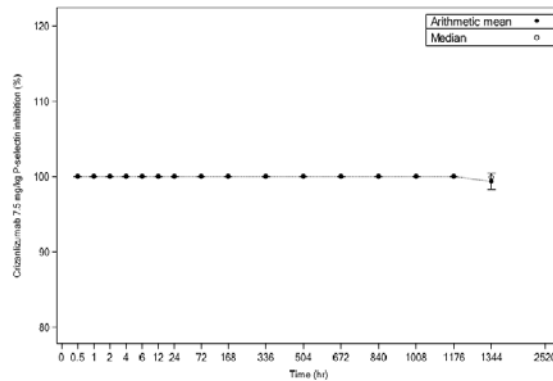
Source: Study SEG101A2102 CSR, Figure 11-2 & Figure 11-5. Data is presented as median and arithmetic mean (SD).

**Figure 6. Serum PK (A) and PD (%P-selectin inhibition) profiles (B) for crizanlizumab (SEG101) 7.5 mg/kg treatment in healthy subjects**

(A).



(B).



Source: Study SEG101A2102 CSR, Figure 11-6 & Figure 11-8. Data is presented as median and arithmetic mean (SD).

Study A2201 reported that the C<sub>trough</sub> values of crizanlizumab (SelG1) following 5 mg/kg treatment ranged from 10.5 to 15.0 µg/mL. Study A2202 reported that the C<sub>trough</sub> values of crizanlizumab (SEG101) following 5 mg/kg treatment ranged from 3.8 to 9.8 µg/mL. The PK samples of these two studies were analyzed by two different assays. FDA evaluation suggested such discrepancy may be caused by differences in two bioanalytical assays applied for the respective studies. In Study A2201, the serum concentration of crizanlizumab was determined by a validated ELISA assay, which has a calibration curve ranging from 0.625 ng/mL to 10.0 ng/mL, and all serum samples were diluted at 1:500 or 1:5000. In Study A2202, the serum concentration of crizanlizumab was determined by another validated ELISA assay, which has a calibration curve ranging from 150 ng/mL to 5000 ng/mL, and the majority of the C<sub>trough</sub> serum samples were diluted at the ratio of 1:50 or less. See details in Section 19.5.1.

The safety data from Study A2201 and Study A2202 suggested that SEG101 and SelG1 exhibited similar safety profiles (Table 5). At least one AE was reported for 35.7% of healthy subjects receiving SEG101 5 mg/kg and for 36.4% of healthy subjects who received SelG1 5 mg/kg, all grade 1 or 2. No deaths and no grade 3/4 AEs were reported during the study.

**Table 5. Adverse events by preferred term for crizanlizumab 5 mg/kg treatments**

Preferred term	SEG101 5.0 mg/kg N=28		SelG1 5.0 mg/kg N=33		All Subjects N=61	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Number of subjects with at least one event	10 (35.7)	0	12 (36.4)	0	22 (36.1)	0
Headache	2 (7.1)	0	2 (6.1)	0	4 (6.6)	0
Viral upper respiratory tract infection	3 (10.7)	0	0	0	3 (4.9)	0
Paraesthesia	1 (3.6)	0	1 (3.0)	0	2 (3.3)	0
Affective disorder	0	0	1 (3.0)	0	1 (1.6)	0
Arthropod bite	1 (3.6)	0	0	0	1 (1.6)	0
Dermatitis	1 (3.6)	0	0	0	1 (1.6)	0
Dizziness	1 (3.6)	0	0	0	1 (1.6)	0
Dysmenorrhoea	0	0	1 (3.0)	0	1 (1.6)	0
Feeling abnormal	1 (3.6)	0	0	0	1 (1.6)	0
Foreign body in ear	1 (3.6)	0	0	0	1 (1.6)	0
Hot flush	0	0	1 (3.0)	0	1 (1.6)	0
Joint dislocation	1 (3.6)	0	0	0	1 (1.6)	0
Limb discomfort	0	0	1 (3.0)	0	1 (1.6)	0
Lip blister	0	0	1 (3.0)	0	1 (1.6)	0
Musculoskeletal discomfort	0	0	1 (3.0)	0	1 (1.6)	0
Nasal congestion	0	0	1 (3.0)	0	1 (1.6)	0
Nasopharyngitis	0	0	1 (3.0)	0	1 (1.6)	0
Paraesthesia oral	0	0	1 (3.0)	0	1 (1.6)	0
Presyncope	0	0	1 (3.0)	0	1 (1.6)	0
Psychotic disorder	0	0	1 (3.0)	0	1 (1.6)	0
Rash papular	0	0	1 (3.0)	0	1 (1.6)	0
Rhinorrhoea	1 (3.6)	0	0	0	1 (1.6)	0
Swelling face	0	0	1 (3.0)	0	1 (1.6)	0
Vomiting	0	0	1 (3.0)	0	1 (1.6)	0
Vulvovaginal pruritus	1 (3.6)	0	0	0	1 (1.6)	0

Source: Study SEG101A2102 CSR, Table 12-1.

In summary, at the dose level of 5 mg/kg,

- **PK:** Systemic exposure for SEG101 was 28% greater than SelG1.
- **PD:** SEG101 and SelG1 both demonstrated nearly complete (i.e., ≈ 100%) P-selectin inhibition by Day 29.
- **Safety:** SEG101 and SelG1 exhibited similar safety profiles.

In conclusion, the data from a phase 1 PK/PD comparability study A2102 and a phase 2 PK/PD study A2202 allowed for bridging the Novartis-manufactured crizanlizumab (SEG101) to Reprixys-manufactured crizanlizumab (SelG1).

**Are the assays for PK and PD assessments adequate?**

The FDA evaluated the Applicant's bioanalytical methods for crizanlizumab PK and PD assessments. The results are summarized in (Table 6). See details in Section 19.5.1 Summary of Bioanalytical Method Validation and Performance.

**Table 6. Evaluation summary on the Applicant's bioanalytical methods**

Study Number	PK Assays		PD Assays	
	Method validation	In study method performance	Method validation	In study method performance
A2101	Acceptable	Not acceptable	Not acceptable	Not acceptable
A2201		Acceptable		Not acceptable
A2102	Acceptable	Acceptable	Acceptable	Acceptable
A2202		Acceptable		Acceptable

In summary, the assays for PK and PD assessments are adequate to support the approval of this BLA from a clinical pharmacology perspective.

**X**

Xiling Jiang, PhD  
Primary Reviewer

**X**

Olanrewaju Okusanya, PharmD, MS  
Team Leader

## **7 Sources of Clinical Data and Review Strategy**

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### **7.1. Table of Clinical Studies**

The pivotal efficacy study, SUSTAIN/SEG101A2201, was based on the Reprixys crizanlizumab variant, SelG1 product. This study was the primary focus of determining the efficacy and safety of crizanlizumab in patients with sickle cell disease. In addition to SUSTAIN, supportive safety information was provided by Study SEG101A2202, a Phase2, multicenter, open-label study to assess PK/PD of SEG101.

#### Study A2201 (SUSTAIN)

This study was conducted and completed at 60 sites, of which US enrolled 151 patients, Brazil enrolled 40 patients and Jamaica enrolled 7 patients.

#### Study A2202

This study is ongoing and being conducted at 11 sites, of which all patients are located in the United States. Approximately 55 patients are planned in total where 45 patients are enrolled and analyzed at the 5 mg/kg arm. At data cutoff, no patients had been enrolled at 7.5 mg/kg.

**Table 7. Listing of Clinical Trials Relevant to BLA 761128**

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
<b><i>Controlled Studies to Support Efficacy and Safety</i></b>							
CSEG 101A22 01	NCT01895361	A Phase II Multicenter, Randomized, Placebo-controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises (SUSTAIN)	<u>Form:</u> SelG1 single use 10 ml vials 10mg/ML and matching placebo; IV injection Day 1, Day 14 then every 4 weeks <u>Regimen:</u> SelG1:5. mg/kg, SelG1:2.5 mg/kg, placebo	<u>Primary:</u> Rate of SCPC (also referred to as VOC leading to a healthcare visit) per year, patient reported outcomes	<u>Duration:</u> 52 weeks doses	<u>Total:</u> 198 (182b,9w,7o) age: 16- 63 (30.1) years groups: 3 (89m,109 f)	Adolescents and adults sickle cell disease (16-70) patients with sickle cell-related pain crises
<b><i>Studies to Support Safety</i></b>							
CSEG10 1A2202		A Phase 2, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without hydroxyurea/hydroxycarbamide, in sickle cell patients with vaso-occlusive	<u>Form:</u> SelG1 single use 10 ml vials 10mg/ML	<u>Primary:</u> characterize PK and PD (P-selectin inhibition) of	<u>Duration:</u> As long as they derive benefit	<u>Total:</u> approximately 55 patients planned (N=45 at 5	Male or female, 16 to 70 years of age (inclusive) with a confirmed diagnosis of SCD by

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		crisis	and matching placebo; IV injection Day 1, Day 14 then every 4 weeks <u>Regimen:</u> SelG1:5. mg/kg, placebo	crizanlizumab at 5 mg/kg in sickle cell disease (SCD) patients with a history of vaso-occlusive crisis (VOC). <u>Secondary:</u> assess safety and tolerability of crizanlizumab, assess efficacy of crizanlizumab		mg/kg and N=10 at 7.5 mg/kg), 45 patients were enrolled and analyzed at 5 mg/kg (at data cutoff, none had yet been enrolled at 7.5 mg/kg)	hemoglobin electrophoresis or high-performance liquid chromatography who had experienced at least 1 VOC within the 12 months prior to screening,
<b><i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i></b>							
CSEG10 1A2202		A Phase 2, multicenter, open-label study to assess PK/PD of SEG101 (crizanlizumab), with or without hydroxyurea/hydroxycarbamide, in sickle cell patients with vaso-occlusive crisis	<u>Form:</u> SelG1 single use 10 ml vials 10mg/ML and matching placebo; IV injection Day 1, Day 14 then	<u>Primary:</u> characterize PK and PD (P-selectin inhibition) of crizanlizumab at 5 mg/kg in sickle cell disease (SCD) patients with a history	<u>Duration:</u> As long as they derive benefit	<u>Total:</u> approximately 55 patients planned (N=45 at 5 mg/kg and N=10 at 7.5 mg/kg), 45 patients were enrolled and analyzed at 5	Male or female, 16 to 70 years of age (inclusive) with a confirmed diagnosis of SCD by hemoglobin electrophoresis or high-performance liquid chromatography who had

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Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
			every 4 weeks <u>Regimen:</u> SelG1:5. mg/kg, placebo	of vaso-occlusive crisis (VOC). <u>Secondary:</u> assess safety and tolerability of crizanlizumab, assess efficacy of crizanlizumab		mg/kg (at data cutoff, none had yet been enrolled at 7.5 mg/kg)	experienced at least 1 VOC within the 12 months prior to screening,

## 7.2. Review Strategy

The application was submitted electronically. The clinical and statistical reviewers, Patricia Oneal, MD, Rosanna Setse, MD, PhD, and Yaping Wang, PhD, respectively, served as the primary reviewers and conducted a joint review of the efficacy data and safety data in this application, respectively. Reviewer comments are identified individually.

This clinical reviewer's strategy included:

- Review of regulatory histories of BLA 761128 and IND 110752;
- Examination of all clinical study reports and amendments
- Subjecting datasets to queries using JReview and JMP;
- Examination of approximately 300 CRFs, selected at random;
- Studying the Applicant's presentation to the FDA on 21 June 2019;
- Searching published literature relative to sickle cell disease and acute/chronic complications of sickle cell disease as well as patient experiences related to all treatment modalities used in this setting;
- Consulting the FDA Division of Scientific Investigation;
- Review of the Periodic Safety Update Reports and Annual Reports ;
- Review of guidelines and other published literature regarding the diagnosis, treatment, and monitoring of patients with sickle cell disease;
- Review of FDA reviews of previous drugs approved for the treatment of sickle cell disease;
- Review and analysis of raw data conducted throughout studies for responders on the treatment arm;
- Review of pooled safety data from the aforementioned trials to detect additional safety signals.

Analysis by Dr. Setse and Dr. Oneal were performed using JReview 13.1 (b) (4)  
Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers. The statistical evaluation was based on data from Study A2201 (SUSTAIN).

### Data Sources

Analysis datasets, SDTM tabulations and software codes are located on the network with the network path: <\\CDSESUB1\evsprod\BLA761128\761128.enx>

Crizanlizumab was originally developed by Reprixys Pharmaceutical Corporation, until Novartis acquired the company in November 2016. Up to the time of acquisition, all pre-clinical and clinical studies (including the registrational study CSEG101A2201/SUSTAIN) used Reprixys manufactured crizanlizumab(SelG1). Novartis continued technical development and production of crizanlizumab under the code SEG101 and Novartis-manufactured crizanlizumab, SEG101, is planned for commercialization. SelG1 and SEG101 were shown to be comparable inhibitor and demonstrated similar PK and comparable PD profiles in healthy subjects. For the purposes of

this review, crizanlizumab refers to crizanlizumab-tmca or ADAKVEO as well as SEG101 or SelG1.

## **8 Statistical and Clinical and Evaluation**

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### **8.1. Review of Relevant Individual Trials Used to Support Efficacy**

#### **8.1.1. Study A2201**

##### **Trial Design**

Study A2201 is a Phase II Multicenter, Randomized, Placebo-Controlled, Double-Blind Study of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises (SUSTAIN).

The analysis population included patients with sickle cell disease (SCD) who were aged  $\geq 16$  years, with 2-10 vaso-occlusive crises (VOCs) in the past 12 months. Some patients who had been receiving HU must have been taking HU for at least 6 months and the dose stabilized for at least 3 months prior to enrollment. A total of 198 patients were randomized and included in the ITT population as follows by intravenous infusions on Weeks 0 & 2, followed by every four weeks for a total of 52 weeks of treatment:

- SelG1 at 5 mg/kg (5 mg/kg arm): 67 patients,
- SelG1 at 2.5 mg/kg (2.5 mg/kg arm): 66 patients,
- Placebo (placebo arm), 65 patients.

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**Table 8: Study Schedule of Events for Protocol CSEG101-A2201**

Table 4. Study Schedule of Events

Event	Screening Phase (Day -30 to -1)	Treatment Phase				Follow-Up Evaluation Phase (Week 56)
		Day 1 <sup>a</sup>	Day 15 <sup>a</sup>	Weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50 <sup>a</sup>	Week 52	
Informed Consent	X					
Demographics	X					
Medical History	X	X <sup>b</sup>				
Physical Exam	X	X	X <sup>c</sup>	X <sup>c</sup>	X	X <sup>c</sup>
12-Lead ECG	X	X <sup>d</sup>	X	X <sup>e</sup>	X	
Vital Signs	X	X <sup>d</sup>	X	X	X	X
Chest X-ray	X <sup>f</sup>					
AE Evaluations <sup>b</sup>		X	X	X	X	X
PK and PD Blood Samples <sup>l</sup>		X	X	X	X	X
Intensive PK Blood Samples (at subset of predetermined sites ONLY) <sup>j</sup>		X <sup>k</sup>		X <sup>l</sup>		
Immunogenicity (anti-P-selectin antibodies)		X	X	X <sup>m</sup>	X	X
Chem-20, CBC, UA	X	X	X	X	X	X
Additional Laboratory Evaluations: PT, aPTT, INR, reticulocyte count, haptoglobin		X	X	X	X	X
SF-36v2 Questionnaire		X	X	X <sup>o</sup>	X	X
BPI Questionnaire		X	X	X <sup>o</sup>	X	X
Biomarkers of SelG1 Activity (i.e. soluble P-selectin, soluble VCAM-1, high-sensitivity CRP, tissue factor, D-dimer);		X	X	X <sup>m</sup>	X	X
Hemoglobin Variant Screen	X					
HIV Screen	X					
Drug Screen <sup>o</sup>	X					
Pregnancy Test <sup>p</sup>	X <sup>q</sup>	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X
Dose		X	X	X		

Source: Applicant's Clinical Study Report; Module 5.3.5.1

**Table 9: Study Schedule of Events for Protocol CSEG101-A2202**

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	Screening phase	Treatment phase														End of treatment	Follow up phase	
	D-35 to D-1	WK1	WK1 D2	WK1 D4	WK2	WK3	WK7	WK11	WK15	WK15 D2	WK15 D4	WK16	WK17	WK18	Week 19, 23, 27, 31, 4qWk	Within 7 days of last infusion	Last infusion + 105d	
Visit on Day 1 of the week (unless otherwise specified) <sup>a</sup>	X																	
Urine protein/creatinine ratio	X														Wk27 and Wk51 only	X		
Adverse event/ serious adverse event	X	Continuous																
Prior/concomitant medications	X	Continuous																
<b>Biomarkers assessments</b>																		
Pharmacodynamic biomarkers <sup>b</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Wk51 only		
Plasma for soluble markers <sup>b</sup>		X				X			X							Wk27 and Wk51 only		
Blood for pharmacogenetics analysis		X																
<b>Pharmacokinetics</b>																		
PK sampling <sup>c</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>e</sup>		X
<b>Immunogenicity</b>																		
Immunogenicity sampling		X				X	X	X	X							X <sup>e</sup>		X

Table 7-1 Visit evaluation schedule

	Category	Protocol Section 7.2	Screening phase	Treatment phase														End of treatment (EoT)	Follow up phase
				110	120	130	140	150	160	170	180	190	200	210	220	230	240 ...		
Visit Number			1	110	120	130	140	150	160	170	180	190	200	210	220	230	240 ...	1999	2000
Visit on Day1 of the week (unless otherwise specified) <sup>a</sup>			D-28 to D-1	WK1	WK1 D2	WK1 D4	WK2	WK3	WK7	WK11	WK15	WK15 D2	WK15 D4	WK16	WK17	WK18	Wk 19, 23, 27, 31, 4qWk	Within 7 days of last infusion	Last infusion n + 105d
<b>Screening</b>																			
Obtain Study Informed Consent	D	7.1.1	X																
Obtain optional pharmacogenetics Informed Consent	D	7.1.1	X																
<b>Disposition assessment</b>																			
End of phase disposition	D	7	X															X	X
<b>Patient history</b>																			
Demography	D	7.1.2.3	X																
Inclusion/exclusion criteria	D	7.1.2.1	X																
Medical History	D	7.1.2.3	X																
ECOG performance status	D	7.2.2.4	X																
Sickle Cell – Vaso-Occlusive Crisis history	D	7.1.2.3	X																
Alcohol history	D	7.1.2.3	X																

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	Screening phase	Treatment phase														End of treatment	Follow up phase
Visit on Day 1 of the week (unless otherwise specified) <sup>a</sup>	D-35 to D-1	Wk1	Wk1 D2	Wk1 D4	Wk2	Wk3	Wk7	Wk11	Wk15	Wk15 D2	Wk15 D4	Wk16	Wk17	Wk18	Week 19, 23, 27, 31, 4qWk	Within 7 days of last infusion	Last infusion + 105d
Drug Screen (drug, alcohol) <sup>f</sup>	X																
<b>Physical examination</b>																	
Physical examination	X															X	
Abbreviated physical exam		X				X	X	X	X						X		
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																
Weight	X	X				X	X	X	X						X		
<b>Laboratory assessments</b>																	
Hematology	X <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis microscopic or macroscopic	X <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X															X	X
Urine pregnancy test		X				X	X	X	X						X		
Hepatitis testing	X																
HIV test	X																

	Screening phase	Treatment phase														End of treatment	Follow up phase
Visit on Day 1 of the week (unless otherwise specified) <sup>a</sup>	D-35 to D-1	Wk1	Wk1 D2	Wk1 D4	Wk2	Wk3	Wk7	Wk11	Wk15	Wk15 D2	Wk15 D4	Wk16	Wk17	Wk18	Week 19, 23, 27, 31, 4qWk	Within 7 days of last infusion	Last infusion + 105d
<b>Study Drug administration</b>																	
Crizanlizumab i.v.		X					X	X	X	X						X	
<p>a. In case the study drug is interrupted, the dose should be resumed as soon as possible. If the dose is delayed for more than 7 days, all future visits should be rescheduled from the date of the last infusion.</p> <p>b. Assessments to be done at within 14 days of Week 1 Day 1 dosing, if the screening assessments have been done more than 14 days before Week 1 Day 1.</p> <p>c. From Week 51 will be done every 24 weeks (Week 75, 99, 123, 147 and 171)</p> <p>d. Drug results will be captured in database. Blood alcohol screen result will be captured in source</p> <p>e. Within 3 months of Week 1 Day 1 dosing</p> <p>f. Within 6 months of Week 1 Day 1 dosing</p> <p>g. Samples to be collected also at time of VOCs, if possible</p>																	

Source: Applicant’s Clinical Study Report; Module 5.3.3.2]

**Study Endpoints**

The primary efficacy endpoint is annual rate of vaso-occlusive crises (VOCs), which was defined as an acute episode of pain with no other cause than a vasoocclusive event that requires a medical facility visit and treatment and needed to be adjudicated by the Crisis Review Committee (CRC) comprised of 3 independent hematologists. Note that Acute chest syndrome, hepatic sequestration, splenic sequestration and priapism (requiring a visit to a medical facility),

were by definition, also be considered VOC for analysis purposes.

The key secondary endpoints included annual rate of days hospitalized, time to First VOC, time to second VOC and a patient-reported outcome (PRO) measured by Brief Pain Inventory (BPI) Questionnaire.

### **Statistical Analysis Plan**

For Primary Endpoint:

The annual rate of VOC = total number of VOC  $\times$  365/(end date – date of randomization + 1), where the End date = Last dose date + 14 days. For patients never dosed, End date = the end of study date. The annual rate of VOC calculation accounted for early dropouts or lost to follow-up by extrapolating the VOC rate of every patient to one year. In particular, if a patient who dropped out on Day 21 after randomization and he/she had the 3 times of VOC during these 20 days, then his annual rate of VOC=31.29 (i.e., 3  $\times$  365/35).

The null hypothesis is that the distribution of annual rate of VOC in patients treated with SelG1 and Placebo are identical. The alternative hypothesis is that the distribution of annual rate of VOC in patients treated with SelG1 and Placebo are different.

A stratified Wilcoxon rank sum test, with randomization strata of HU therapy and categorized VOC history, was used to test the above hypotheses. Medians, median differences, and 95% confidence intervals (CIs) for the median differences were estimated using Hodges-Lehmann method, and the following hierarchical testing procedure was followed:  $\alpha = 0.05$  was utilized to test high dose (5 mg/kg) versus placebo, and if significant, to test low dose (2.5 mg/kg) versus placebo. This controlled the overall alpha level for the study at 0.05 for the primary endpoint.

Sensitivity analyses were performed using different analysis populations (mITT population, PP population, and excluding patients who did not complete 6 months of study drug treatment). Subgroup analysis for primary analysis were conducted separately for HU use, categorized VOC history, and genotype (HbSS versus all other genotypes combined), using the same methods as for the primary analysis.

For Secondary Endpoints:

The annual rate of days hospitalized was analyzed using the stratified Wilcoxon Rank Sum Test. Median time to first VOC and median time to second VOC were estimated by Kaplan-Meier method. To evaluate patient reported outcomes (PRO), change from baseline in the pain severity and pain interference domains of the Brief Pain Inventory (BPI) Questionnaire were compared. Scores of two domains (Pain Severity [worst pain] and Pain Interference) were summarized by treatment arm at each post-Baseline windowed visit.

### **Protocol Amendments**

Study A2201

There were 3 major amendments to the original protocol (Protocol Amendment 1) for Study A2201 dated February 26, 2013. The table below summarizes changes made in each amendment.

Amendment #	Date	Major Changes
2	04/07/2014	<ul style="list-style-type: none"> <li>• Changed minimum age for inclusion to 18 instead of 16</li> <li>• Changed the follow-up from 56 to 58 weeks</li> <li>• Removed death from definition of VOC event</li> </ul>
3	09/26/2014	<ul style="list-style-type: none"> <li>• Changed minimum age for inclusion back to 16 from 18</li> <li>• Use stratified test for analysis of primary endpoint and to identify key secondary endpoint.</li> </ul>
4	04/21/2016	<ul style="list-style-type: none"> <li>• Analysis of the primary efficacy endpoint was modified by taking the randomization strata into consideration. (Inclusion of the randomization stratum in the analysis of the primary endpoint was inadvertently omitted in previous versions).</li> <li>• Annual rate of days hospitalized was elevated from a secondary to key secondary endpoint.</li> <li>• Text was modified throughout the protocol to clarify that for the efficacy endpoints, the rates of the individual endpoints were the “annual rates”.</li> <li>• Anemia-related and hemolysis-related laboratory parameters moved from secondary to exploratory endpoints.</li> <li>• Acute chest syndrome and uncomplicated VOC moved from exploratory to secondary endpoints.</li> </ul>

These amendments were submitted to the Agency and do not appear to have had an impact on the integrity of the trial or interpretation of the results.

**8.1.2. Study Results**

**Compliance with Good Clinical Practices**

Per the Applicant, this trial was designed and monitored in full compliance with current Good Clinical Practices. All studies were closely monitored for compliance to the protocol, relevant SOPs, and applicable regulatory guidance.

### **Financial Disclosure**

Per the Applicant, Financial disclosures were obtained from all Investigators in accordance with Title 21 Code of Federal Regulations (CFR) Part 54. The Applicant did not have any financial arrangements with any of the listed clinical investigators. No disclosable financial information was reported by any of the clinical investigators participating in the trial.

The original sponsor for [REDACTED] <sup>(b) (4)</sup> was Reprixys Pharmaceuticals Corporation. The current sponsor is Novartis. Reprixys Pharmaceuticals Corporation was previously known as Selexys Pharmaceuticals Corporation. Therefore, Selexys Pharmaceuticals Corporation appears on the Financial Disclosure forms (1572s).

### **Data Quality and Integrity**

This application is primarily supported by data from the Phase II multicenter, randomized, double-blind, placebo-controlled, parallel group study (Study A2201). This study was conducted at 51 study centers in the United States, 8 centers in Brazil, and 1 center in Jamaica. Two clinical sites in the US (Site 102 and Site 122) were selected for audit and inspection by OSI. These sites were selected based on the enrollment numbers and the potential impact of results from these sites on the overall study results and FDA's clinical decision making process.

Both clinical sites were reported to be in compliance with Good Clinical Practice. A Form FDA 483 was not issued to either site. See OSI inspection report in DARRTs by Anthony Orenca, M.D. dated 09/05/2019.

OPQ performed a pre-license inspection of the drug substance manufacturing facility for crizanlizumab at Novartis, Basel, Switzerland from August 21-29, 2019. The final report from this inspection is pending in DARRTs.

### **Patient Disposition**

A total of 198 patients were randomized in Study A2201 including 67 patients randomized to receive SelG1 at 5 mg/kg (5 mg/kg arm), 66 patients to receive SelG1 at 2.5 mg/kg (2.5 mg/kg arm), and 65 patients to receive placebo (placebo arm)]. Majority (65.2%) completed the study as planned. Study discontinuation rates were comparable in all study arms: 24 (35.8%), 21 (31.8%) and 24 (36.9%) in subjects treated with SelG1 5 mg/kg, SelG1 at 2.5 mg/kg and placebo. Refer to table 10 for details on disposition.

The most common primary reason for study drug discontinuation was withdrawal by the patient/caregiver/legal guardian, reported for 10.4% of patients in the 5 mg/kg arm, 9.1% in the 2.5 mg.kg arm, and 9.2% in the placebo arm. The exact reasons for these discontinuations were not provided however it is reassuring that these rates were comparable between treatment arms. The proportion of subjects who discontinued treatment due to an adverse event was low

overall (2.5%), and comparable between study treatment arms: 1.5% in the 5 mg/kg arm, 1.5% in the 2.5 mg/kg arm, and 4.6% in the placebo arm.

**Table 10 Patient Disposition Study A2201**

	Crizanlizumab 5mg/kg n(%)	Crizanlizumab 2.5mg/kg n(%)	Placebo n(%)
ITT Population	67(100%)	66(100%)	65(100%)
Completed Study	43(64.2%)	45(68.2%)	41(63.1%)
Discontinued Study	24(35.8%)	21(31.0 %)	24(36.9%)
Reason for Discontinuation			
Adverse Event	1(1.5%)	1(1.5%)	5(2.5%)
Death	2(3.0%)	1(1.5%)	5(2.5%)
Lost to Follow-up	4(6.0%)	4(6.1%)	14(7.1%)
Non-compliance with study	1(1.5%)	3(4.5%)	5(2.5%)
Physician Decision	2(3.0%)	2(3.0%)	6(3.0%)
Withdrawal by patient/caregiver	7(10.4%)	6(9.1%)	19(9.6%)
Other	7(10.4%)	3(4.5%)	4(6.2%)

Five fatalities occurred during the study treatment period including 2 in the 5 mg/kg arm, 1 patient in the 2.5 mg/kg arm, and 2 patients in the placebo arm. See description of SAEs leading to death and in Section 8.2.4 below. None of the deaths were considered related to study treatment by FDA.

### Protocol Violations/Deviations

Overall, there were a considerable number 73 (36.9%) of protocol violations reported for Study A2201. These included. following were considered protocol deviations in Study A2201:

- Subjects who did not receive 12 of 14 planned study doses
- Subjects who did not complete a visit at least 14 days after final dose of study drug
- Subjects who had less than 2 or more than 10 Sickle Cell Related Pain Crises in the previous 12 months

Overall, protocol deviations occurred approximately equally between treatment groups. The most frequent protocol deviation reasons in all treatment groups were “not receiving 12 of 14 planned study doses” – reported for 25 patients (37.3%) in the 5. mg/kg arm, 20 patients (30.3%) in the 2.5 mg/kg arm, and 24 patients (36.9%) in the placebo arm.

### Table of Demographic Characteristics

Most of the demographic and baseline characteristics were similar across the 3 treatment arms except ethnicity and region although the differences observed in these two types of characteristics were not significant to result in different conclusions. Overall, 44.9% of patients (89 patients) in the ITT population were male and 55.1% (109 patients) were female. The overwhelming majority (91.9%) of patients were Black or African American, while only 4.5% White and 3.5% identified as “Other”.

Sickle cell-related pain crises during the 12 months prior to screening were reported by the IXRS for all patients, including 62.6% of patients with 2 to 4 crises and 37.4% with 5 to 10 crises. Hydroxyurea use according to IXRS report was 62.1% of patients. Patient demographics for the ITT population are presented in Table 8 below.

**Table 11: Demographic characteristics of the primary efficacy analysis population**

Demographic Parameters	Treatment Group			Total (N=198), n(%)
	Placebo Group (N=65) n(%)	SelG1 5 mg/kg (N= 67) n(%)	SelG1 2.5 mg/kg (N= 66) n(%)	
<b>Sex</b>				
Male	27 (41.5)	32 (47.8)	30 (45.5)	89 (44.9)
Female	38 (58.5)	35 (52.2)	36 (54.5)	109 (55.1)
<b>Age</b>				
Mean years (SD)	29.3 (10.36)	30.9 (10.89)	30.1 (9.79)	30.1 (10.33)
Median (years)	26.0	29.0	29.0	28.0
Min, max (years)	16, 56	16, 63	17, 57	16, 63
<b>Race</b>				
White	3 (4.6)	4 (6.0)	2 (3.0)	9 (4.5)
Black or African American	60 (92.3)	62 (93.9)	60 (89.6)	182 (91.9)
Asian	0	0	0	0
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other <sup>1</sup>	2 (3.1)	3 (4.5)	2 (3.0)	7 (3.5)
<b>Ethnicity</b>				
Hispanic or Latino	11 (16.9)	20 (29.9)	12 (18.2)	43 (21.7)
Not Hispanic or Latino	53 (81.5)	45 (67.2)	52 (78.8)	150 (75.8)
Unknown	1 (1.5)	2 (3.0)	2 (3.0)	5 (2.5)
<b>Hydroxyurea use (IXRS)</b>				
Yes	40 (61.5)	42 (62.7)	41 (62.1)	123 (62.1)
No	25 (38.5)	25 (37.3)	25 (37.9)	75 (37.9)
<b>Number of VOC in last 12 months (IXRS)</b>				
2 to 4	41 (63.1)	42 (62.7)	41 (62.1)	123 (62.1)
5 to 10	24 (36.9)	25 (37.3)	25 (37.9)	74 (37.4)

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Demographic Parameters	Treatment Group			Total (N=198), n(%)
	Placebo Group (N=65) n(%)	SelG1 5 mg/kg (N= 67) n(%)	SelG1 2.5 mg/kg (N= 66) n(%)	
<b>Region</b> (optional)				
United States	53 (81.5)	46 (68.7)	52 (78.8)	151 (76.3)
South America	12 (18.5)	21 (31.3)	14 (21.2)	47 (23.7)

Source: FDA reviewer analysis.

### Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In Study A2201, study drug compliance was assessed by calculating the percentage of infusions administered relative to the expected number of infusions to be administered during the patient's time on-study and was assessed in the safety population. As expected for a treatment administered by a provider (as opposed to self-administered medication), study drug compliance in Study A2201 was high, with a mean compliance ( $\pm$  SD) of 96.3% (7.09), 96.3% (6.86), and 97.0% (7.73) for the 5 mg/kg arm, the 2.5 mg/kg arm, and the placebo arm, respectively.

### Efficacy Results – Primary Endpoint

The primary efficacy parameter is the annual rate of VOC with the primary analysis carried out using the Intent to treat (ITT) population. All VOC events were adjudicated by an independent crisis review committee. Table 12 contains comparison of the annual rate of VOC according to the ITT population and two sub-populations, where one is for patients who early discontinued from the study and the other is for all but excluding patients who discontinued early.

**Table 12 Annual Rate of VOC**

<b>Intent to Treat</b>	<b>Placebo,</b>	<b>SelG1, 5 mg/kg,</b>	<b>SelG1, 2.5 mg/kg,</b>
	<b>N=65</b>	<b>N=67</b>	<b>N=66</b>
Standard median	2.98	1.63	2.01
<sup>1</sup> Median difference, (95% CI)	---	-1.01, (-2.00, 0.00)	-0.69, (-1.84, 0.02)
<sup>2</sup> p-value	---	0.010	<sup>3</sup> 0.180
<b>Sub-Population</b>	<b>Placebo</b>	<b>SelG1, 5 mg/kg</b>	<b>SelG1, 2.5 mg/kg</b>
(1) Patients who discontinued early from the study, n (%)	N=24 (36.9%)	N=24 (35.8%)	N=21 (31.8%)
Standard median	2.59	1.75	2.01
<sup>1</sup> Median difference, (95% CI)	---	-0.36 (-3.17, 1.37)	-0.51 (-3.91, 1.31)
<sup>2</sup> p-value	---	0.420	0.469
(2) Excluding patients who discontinued early, n (%)	N=41 (63.1%)	N=43 (64.2%)	N=45 (68.2%)
Standard median	2.98	1.18	2.01
<sup>1</sup> Median difference, (95% CI)	---	-1.10 (-2.01, -0.05)	-0.91 (-1.90, 0.03)
<sup>2</sup> p-value	---	0.005	0.236

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

<sup>2</sup>P-values were from a Stratified Wilcoxon Rank Sum Test, with HU therapy (yes, no) and categorized crises history (2 to 4, 5 to 10) as the strata.

<sup>3</sup>No alpha was left for testing any secondary endpoints except the annual rate of days hospitalized because of this insignificant finding.

Source: FDA reviewer analysis.

A stratified Wilcoxon Rank Sum Test was utilized to compare the annual rate of VOC in the 5 mg/kg SelG1 treatment arm with that of placebo. Comparison of the medians for the annual rates of VOC in the 5 mg/kg treatment arm and the placebo treatment arm demonstrated a significant reduction in the rate of VOC (1.63 versus 2.98, respectively and  $p=0.010$ ). The stratified Wilcoxon Rank Sum Test analysis showed that a treatment difference between the 2.5 mg/kg SelG1 arm and the placebo arm, however was not statistically significant ( $p = 0.180$ ).

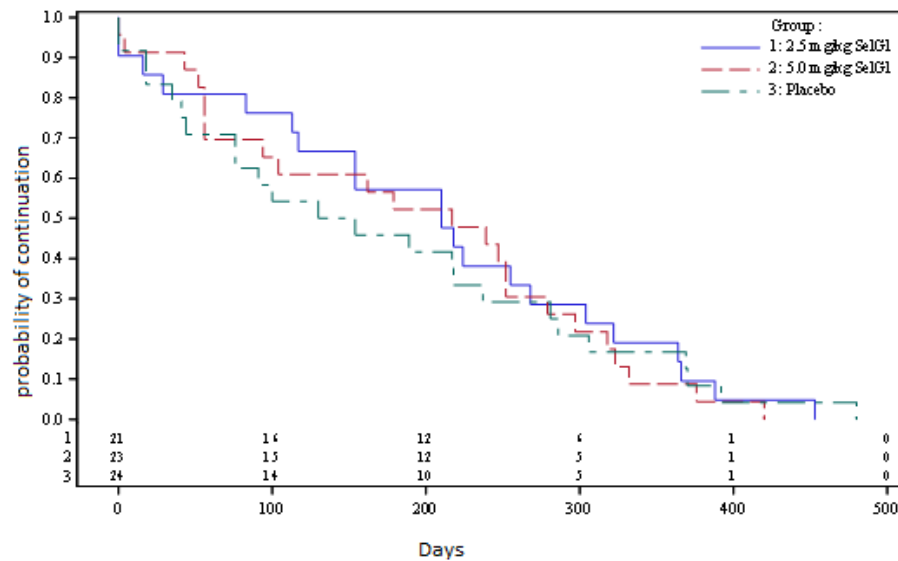
***Reviewer's Comment: Since no statistically significant difference was observed between 2.5 mg/kg SelG1 arm and the placebo arm on the primary endpoint, i.e. annual rate of VOC, no alpha was left for testing any of the key secondary endpoints, including annual rate of days hospitalized, time to First VOC, time to Second VOC and patient-reported outcome.***

***The median reduction in annual rate of VOC leading to healthcare visits was 45% (Hodges Lehmann absolute median difference of -1.01(95% CI: -2.00, 0.00 with  $p=0.010$ ). The presentation of median difference of 45% may be misleading suggesting a reduction in annual VOCs of 45% when this percentage is a median difference and not a reduction. Recommend to not include this median difference in the prescribing information as the presentation of the mean difference may be misleading.***

A substantial number (35%) of the patients randomized in Study A2201 discontinued treatment before the end year evaluation. The rates of discontinuation were 36.9%, 35.8%, and 31.8% for placebo, 5 mg/kg SelG1, and 2.5 mg/kg SelG1 arms, respectively.

As shown in the table above, sensitivity analyses were performed after excluding early discontinued patients (Total N=129), and only for patients who discontinued (Total N=69) early. We found that the medians for the annual rates of VOC in the 5 mg/kg treatment arm demonstrated more reduction in the rate of VOC (1.18 versus 2.98) after excluding discontinued patients compared with placebo. However, the reduction was lower for discontinued patients (1.75 versus 2.59). In addition, a comparison of the time to discontinuation in each arm is provided in Figure 7. The time to discontinuation patterns look similar across the three treatment arms with linear downward trends.

**Figure 7 Time to Discontinuation**



Source: FDA reviewer analysis.

To evaluate the robustness of the primary efficacy results, the actual number of VOC leading to healthcare visit (non-annualized) was also analyzed. The results of the analysis are consistent with the primary endpoint on the annual rate of VOC leading to healthcare visit (see Table 10). The treatment difference remains similar amplitude.

**Table 13 Number of VOC (ITT)**

	Placebo, N=65	SelG1, 5 mg/kg, N=67
Standard median	2.00	1.00
<sup>1</sup> Median difference, (95% CI)	---	-1.00, (-1.00, 0.00)
<sup>2</sup> p-value	---	0.029

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

<sup>2</sup>P-values were from a Stratified Wilcoxon Rank Sum Test, with HU therapy (yes, no) and categorized crises history (2 to 4, 5 to 10) as the strata. Source: FDA reviewer analysis.

Subgroup analysis for the primary endpoint based on ITT population were conducted for HU use, categorized VOC history, gender and region, using the same methods as for the primary analysis.

A comparison of the annual rate of VOC by concomitant HU use is provided in Table 11 below.

**Table 14 Annual Rate of VOC (by concomitant HU)**

ITT	Placebo (N=65)	SelG1, 5 mg/kg (N=67)	SelG1, 2.5 mg/kg (N=66)
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HU use=yes, n (%)	40 (61.5%)	42 (62.7%)	41 (62.1%)
Standard median	3.58	2.43	2.00
<sup>1</sup> Median difference, (95% CI)	---	-1.01, (-2.44, 0.00)	-0.69, (-2.91, 0.00)
HU use=no, n (%)	25 (38.5%)	25 (37.3%)	25 (37.9%)
Standard median	2.00	1.00	2.16
<sup>1</sup> Median difference, (95% CI)	---	-1.02, (-2.00, 0.00)	0.02, (-1.01, 1.12)

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

Source: FDA reviewer analysis.

In patients not receiving concomitant HU, the annual rate of VOC in the 5 mg/kg SelG1 treatment arm demonstrated a significant reduction compared with that of the placebo arm (1.00 versus 2.00). In patients receiving concomitant HU, however, the annual rate of VOC observed in the 5 mg/kg arm relative to the placebo arm was also reduced (2.43 versus 3.58) but did not reach statistical significance. Given that the comparisons of the subgroups were not powered to detect the treatment effect, the lack of statistical significance could be mainly due to lack of study power.

Analysis of the 2.5 mg/kg SelG1 treatment arm showed a lower annual rate of VOC as compared with that of the placebo arm in patients with concomitant HU use (2.00 versus 3.58 ). On the contrary, the observed annual rates of VOC of the 2.5 mg/kg arm were a bit larger than that of the placebo arm in patients without concomitant HU use (2.16 versus 2.00) although the numbers of patients without concomitant HU use in all treatment arms are in general smaller than those with concomitant HU use.

A comparison of the annual rate of VOC by VOC history is provided in Table 15 below.

**Table 15 Annual Rate of VOC (by VOC history)**

ITT	Placebo (N=65)	SelG1, 5 mg/kg (N=67)	SelG1, 2.5 mg/kg (N=66)
VOC history =5 to 10, n (%)	24 (36.9%)	25 (37.3%)	25 (37.9%)
Standard median	5.32	1.97	3.02
<sup>1</sup> Median difference, (95% CI)	---	-2.74, (-5.00, -0.83)	-1.98, (-4.08, 0.04)
VOC history =2 to 4, n (%)	41 (63.1%)	42 (62.7%)	41 (62.1%)
Standard median	2.00	1.14	2.00
<sup>1</sup> Median difference, (95% CI)	---	-0.05, (-1.56, 0.01)	0.00, (-1.01, 0.57)

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

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Source: FDA reviewer analysis.

For patients with an VOC history, those of 2 to 4 had their annual VOC rate in the 5 mg/kg arm relative to the placebo arm reduced (1.14 versus 2.00). Again, the comparisons of the subgroups were not powered to achieve statistical significance.

Analysis of the 2.5 mg/kg SelG1 treatment arm showed a much lower annual rate of VOC as compared with that of the placebo arm in patients with an VOC history of 5 to 10 (3.02 versus 5.32) but not in patients with an VOC history of 2 to 4 (2.00 versus 2.00).

A comparison of the annual rate of VOC by gender and region is provided in Table 16 below.

**Table 16 Annual Rate of VOC (by gender and regions)**

ITT	Placebo (N=65)	SelG1, 5 mg/kg (N=67)	SelG1, 2.5 mg/kg (N=66)
Male, n (%)	27 (41.5)	32 (47.8)	30 (45.5)
Standard median	2.00	2.50	2.00
<sup>1</sup> Median difference, (95% CI)	---	-0.02, (-1.98, 1.02)	-0.04, (-1.99, 1.00)
<sup>2</sup> p-value	---	0.337	0.639
Female, n (%)	38 (58.5)	35 (52.2)	36 (54.5)
Standard median	3.00	1.18	2.10
<sup>1</sup> Median difference, (95% CI)	---	-1.93, (-3.00, -0.75)	-0.96, (-2.01, 0.11)
<sup>2</sup> p-value	---	0.005	0.286
United States, n (%)	53 (81.5)	46 (68.7)	52 (78.8)
Standard median	3.25	2.16	1.97
<sup>1</sup> Median difference, (95% CI)	---	-1.65, (-2.37, 0.02)	-1.0, (-2.01, 0.00)
<sup>2</sup> p-value	---	0.010	0.039
South America, n (%)	12 (18.5)	21 (31.3)	14 (21.2)
Standard median	1.00	1.00	1.19
<sup>1</sup> Median difference, (95% CI)	---	0.00, (-1.00, 1.37)	0.00, (-1.00, 1.60)
<sup>2</sup> p-value	---	0.657	0.772

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

<sup>2</sup>P-values were from a Stratified Wilcoxon Rank Sum Test.

Source: FDA reviewer analysis.

In female patients, the annual rate of VOC in the 5 mg/kg SelG1 treatment arm demonstrated a reduction compared with that of the placebo arm (1.18 versus 3.00). However, in male patients, the median annual VOC rate observed in the 5 mg/kg arm relative to the placebo arm was increased (2.50 versus 2.00). We noted that male patient in placebo had much smaller rate of VOC than female patients in placebo.

In United State patients, the annual rate of VOC in both the 5 mg/kg SelG1 and 2.5 mg/kg SelG1 arms demonstrated significant reductions compared with that of the placebo arm (2.16 versus 3.25, and 1.97 versus 3.25). On the contrary, in South America patients, the median annual VOC rate observed in the 5 mg/kg arm relative to the placebo arm was same (1.00 versus 1.00).

**Reviewer’s comment: The median annual VOC rates in 5 mg/kg SelG1 treatment arm did not show a reduction compared with that of placebo arm, in both male patients and South America patients. The comparisons of these subgroups were not powered to achieve statistical significance.**

**Efficacy Results – Secondary and other relevant endpoints**

Since no statistically significant difference was observed for the primary endpoint between 2.5 mg/kg SelG1 arm and the placebo arm, according to the sponsor pre-specified sequential testing procedure, no alpha was left for testing any of the key secondary endpoints except the annual rate of days hospitalized. FDA statistical reviewer’s findings are provided in 5 below.

**Table 17 Treatment Comparisons of Annual Rates of Days Hospitalized**

ITT	Placebo, N=65	SelG1, 5 mg/kg, N=67	SelG1, 2.5 mg/kg, N=66
Standard median	6.87	4.00	6.87
<sup>1</sup> Median difference, (95% CI)	---	0.00, (-4.36, 0.00)	0.00, (-3.90, 2.61)

<sup>1</sup>Median differences, and CIs were estimated using Hodges-Lehmann method. The Hodges-Lehmann median is a non-parametric estimator of the location parameter.

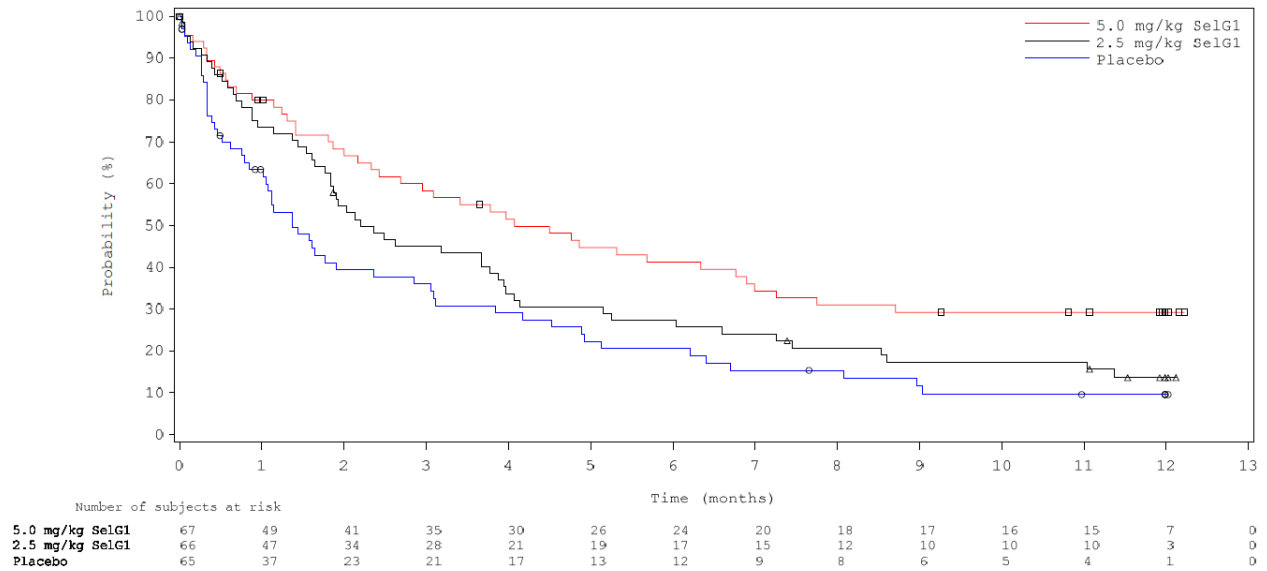
Source: FDA reviewer analysis.

The median annual rate of days hospitalized was numerically reduced in the 5 mg/kg arm versus the placebo arm (4.00 versus 6.87, respectively) but not in the 2.5 mg/kg arm versus the placebo arm (6.87 versus 6.87, respectively).

The Kaplan-Meier plots of time to first and second VOC are provided in Figure 8 and Figure 9 below.

**Figure 8 Kaplan-Meier Estimates of Time to First VOC – ITT Population**

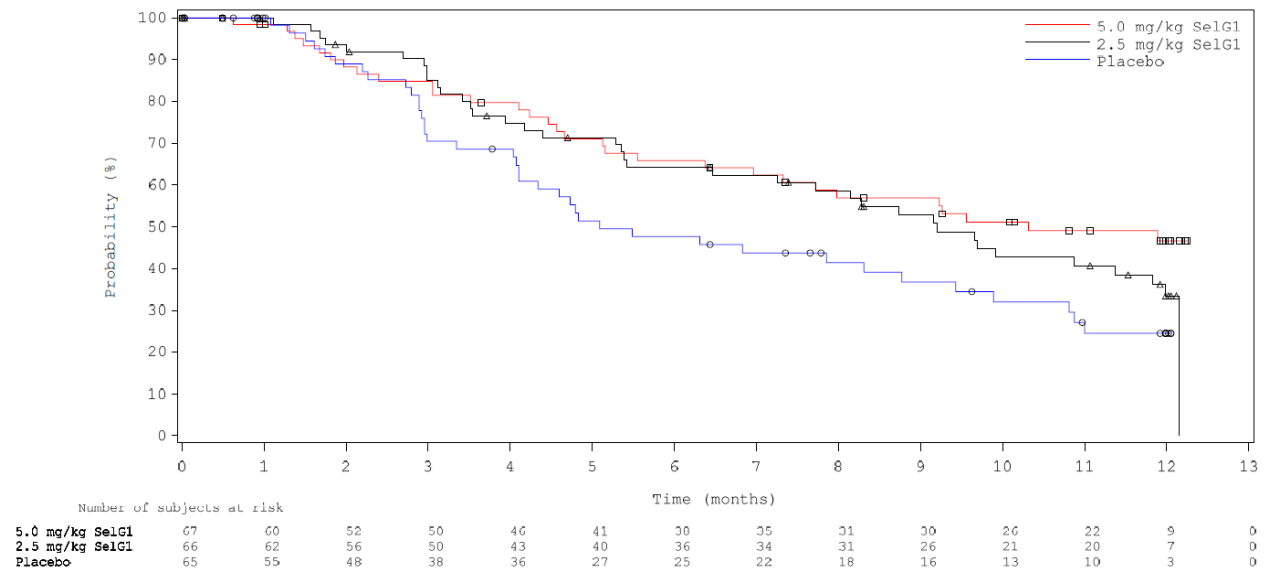
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Source: applicant's CSR.

The Kaplan-Meier estimate of the median time from randomization to first VOC was longer for the 5 mg/kg SelG1 arm (4.07 months) compared with the placebo arm (1.38 months). The median time to first VOC for the 2.5 mg/kg SelG1 arm (2.2 months) was also increased over that of placebo.

**Figure 9 Kaplan-Meier Estimates of Time to Second VOC – ITT Population**



Source: Applicant's CSR.

The Kaplan-Meier estimate of the median time from randomization to second VOC was also

longer for the 5 mg/kg SelG1 arm (10.32 months) compared with the placebo arm (5.09 months). The median time to second VOC for the 2.5 mg/kg SelG1 arm (9.20 months) was also increased over that of placebo. We noted that the 2.5 mg/kg SelG1 arm performed better than 5 mg/kg SelG1 arm and placebo before 3 months and the two drug arms performed similarly till 8 months, and the 5 mg/kg SelG1 had performed persistently better than 2.5 mg/kg SelG1 and also placebo.

### **Dose/Dose Response**

As shown in figures above, for the primary efficacy analysis there seemed to be a trend towards a dose response effect observed with the median annual rate of VOC events leading to a healthcare visit: 1.63 in the crizanlizumab 5 mg/kg treatment arm, 2.01 in the crizanlizumab 2.5 mg/kg treatment arm and highest (2.98) in the placebo group. However, the median difference between the crizanlizumab 2.5 mg/kg and the placebo group was not statistically significant [-0.69, (-1.84, 0.02)].

### **Durability of Response**

Study A2201 was conducted over a 12 month treatment period. Therefore, there is no information on the durability of efficacy beyond one year of treatment.

### **Persistence of Effect**

There is no information on persistence of efficacy beyond one year of treatment.

### **Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

There were no treatment difference ( $p < 0.05$ ) observed comparing the 5 mg/kg cohort or the 2.5 mg/kg cohort with placebo in the LS mean ( $\pm$  SE) change from Baseline to Week 52 or the Week 58 Follow-up visit in any of the SF-36 Questionnaires scales or domains.

There were no treatment differences ( $p < 0.05$ ) observed comparing the 5 mg/kg cohort or the 2.5 mg/kg cohort with placebo in the proportion of responders based on the body pain scale from the SF-36 Questionnaire at any time point assessed.

*Reviewer Comments: These were exploratory endpoints and were not included in the USPI.*

### **Additional Analyses Conducted on the Individual Trial**

#### **8.1.3 No additional analyses were conducted on the individual trial. Integrated Review of Effectiveness**

Efficacy was assessed based on data from one clinical trial.

### **8.1.4 Integrated Assessment of Effectiveness**

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. There is substantial evidence for the conclusion of effectiveness for ADAKVEO in patients with sickle cell disease.

## **8.2 Review of Safety**

### **8.2.1 Safety Review Approach**

The overall safety profile of crizanlizumab is based on data from 175 patients with sickle cell disease from two clinical studies (i.e. Study A2201 and Study A2202) who received at least one infusion of crizanlizumab at doses of 2.5 mg/kg ( $n = 64$ ) or 5 mg/kg ( $n = 111$ ), the recommended dose. Safety endpoints listed below were used to evaluate the safety and tolerability of crizanlizumab in patients with sickle cell disease.

(b) (4)

Analyses included:

- Incidence of Treatment Emergent Adverse Events (TEAEs) by severity or by relationship,
- Related TEAEs,
- TEAEs leading to treatment discontinuation,
- Serious TEAEs,
- Frequently reported TEAEs,
- Incidence of adverse drug reactions (ADRs),
- Incidence of discontinuation, dose interruptions and dose delays,
- Assessment of thrombocytopenia, hemostasis and thrombosis,
- Clinical laboratory values (hematology, serum chemistry, urinalysis and coagulation studies, vital signs and ECGs results),
- Plasma P-selection concentration, and
- Analysis of deaths.

### **8.2.2 Review of the Safety Database**

#### **Overall Exposure**

The overall evaluation of the safety of crizanlizumab is based on data from randomized, double-blind, placebo-controlled Study A2201 and open-label Study A2202 in SCD patients with a history of VOC. A pooled analysis (i.e. "safety pool") of the safety data from the 5 mg/kg treatment arms of Studies A2201 and A2202 allows for the indirect comparison of the safety

profiles of the Reprixys-manufactured crizanlizumab (SelG1) and the Novartis-manufactured crizanlizumab (SEG101) in SCD patients.

The safety pool consists of 175 patients with sickle cell disease from two clinical studies (i.e. Study A2201 and Study A2202) who received at least one infusion of crizanlizumab at doses of 2.5 mg/kg (n = 64), 5 mg/kg (n=66) and 5 mg/kg (n =45), respectively. This safety group includes 111 patients who received the proposed dose of 5mg/kg(Study A2202: 5mg/kg(n=45) group and Study A2201:5mg/kg dose (n=66). The groups who were administered the recommended dose of 5 mg/kg (n = 111), were also pooled for some safety analyses. The primary safety population for inclusion in the labeling is based on the 5mg/kg treatment arm from Study A2201 (n=66).

**Table 18: Demographics of the Safety Population at Randomization**

<b>Safety Population Demographic Parameters</b>	<b>2.5 mg/kg SelG1 n=64 n(%)</b>	<b>5 mg/kg SelG1 n=66 n(%)</b>	<b>Placebo n=62 n(%)</b>	<b>5 mg/kg SELG101 n=45 n(%)</b>
<b>Age</b>				
Mean and Std.Dev.	30.38 [9.82]	30.89 [10.97]	29.52 [10.52]	32.31 [12.71]
Median	29	29	27	29
Range	17-57	16-63	16-56	17-65
<b>Age Category - Subjects and %</b>				
>25 years	40 (62.5%)	46 (69.7%)	39 (62.9%)	27 (60%)
16 to 25 years, inclusive	24 (37.5%)	20 (30.3%)	23 (37.1%)	18 (40%)
<b>Sex - Subjects and %</b>				
Female	34 (53.1%)	34 (51.5%)	36 (58.1%)	25 (56%)
Male	30 (46.9%)	32 (48.5%)	26 (41.9%)	20 (44%)
<b>Race - Subjects and %</b>				
Black or African American	61 (95.3%)	59 (89.4%)	57 (91.9%)	44 (97.8%)
White	1 (1.6%)	4 (6.1%)	3 (4.8%)	0
Other	2 (3.1%)	3 (4.5%)	2 (3.2%)	1 (2.22%)
<b>Ethnicity - Subjects and %</b>				
Not Hispanic or Latino	51 (79.7%)	44 (66.7%)	51 (82.3%)	33 (73.3%)
Hispanic or Latino	11 (17.2%)	20 (30.3%)	10 (16.1%)	3 (6.67%)
Unknown	1 (1.6%)	2 (3.0%)	1 (1.6%)	9 (20%)
Not Reported	1 (1.6%)	0 (0.0%)	0 (0.0%)	0
<b>Country - Subjects and %</b>				
USA	51 (79.7%)	45 (68.2%)	51 (82.3%)	45 (100%)
BRA	11 (17.2%)	17 (25.8%)	10 (16.1%)	0
JAM	2 (3.1%)	4 (6.1%)	1 (1.6%)	0
<b>Weight Category - Subjects and %</b>				
> 64 kgs	43 (67.2%)	39 (59.1%)	33 (53.2%)	33 (73.3%)
<= 64 kgs	21 (32.8%)	27 (40.9%)	29 (46.8%)	11 (24.4%)
<b>Baseline Height (cm)</b>				

<b>Safety Population Demographic Parameters</b>	<b>2.5 mg/kg SelG1 n=64 n(%)</b>	<b>5 mg/kg SelG1 n=66 n(%)</b>	<b>Placebo n=62 n(%)</b>	<b>5 mg/kg SELG101 n=45 n(%)</b>
Mean and Std.Dev.	168.86 [9.27]	168.06 [8.88]	169.16 [10.85]	154.09 [1.47]
Median	168	167	166.25	168.8
Range	150-189	152.2-190.5	152-193	152.4-187.96
<b>Baseline Weight (kg)</b>				
Mean and Std.Dev.	71.05 [15.88]	69.46 [17.10]	68.02 [13.99]	58.5
Median	68.05	66.85	65.85	58.5
Range	44-117.3	39.4-123.8	42.4-112.1	48.9-134
<b>Baseline BMI (kg/m2)</b>				
Mean And Std.Dev.	24.99 [5.82]	24.32 [5.45]	23.81 [4.88]	26.81 [6.66]
Median	23.95	23	23.20	25.53
Range	18-49.4	14.5-36	17-37.9	18.1-47.7
<b>Hydroxyurea Usage - Subjects and %</b>				
Yes	39 (60.9%)	41 (62.1%)	39 (62.9%)	35 (77.8%)
No	25 (39.1%)	25 (37.9%)	23 (37.1%)	10 (22.2%)
<b>Crises Rate - Subjects and %</b>				
2-4	39 (60.9%)	41 (62.1%)	39 (62.9%)	26 (57.8%)
5-10	25 (39.1%)	25 (37.9%)	23 (37.1%)	19 (42.2%)
<b>Sickle Cell Disease Type - Subjects and %</b>				
HbSS	45 (70.3%)	46 (69.7%)	44 (71.0%)	26 (57.8%)
HbSC	15 (23.4%)	9 (13.6%)	8 (12.9%)	10 (22.2%)
HbSB <sup>0</sup> -thalassemia	2 (3.1%)	3 (4.5%)	7 (11.3%)	3 (6.6%)
HbSB <sup>+</sup> -thalassemia	2 (3.1%)	7 (10.6%)	1 (1.6%)	3 (6.6%)
Other	0 (0.0%)	1 (1.5%)	2 (3.2%)	3 (6.6%)
<b>Duration of Treatment (days)</b>				
Mean and Std.Dev.	311.38 [102.30]	293.77 [119.04]	293.26 [124.19]	247.8 [86.03]
Median	363	364	365	240
Range	15-386	15-385	15-396	42-406

In the pooled safety data there no notable differences between the pooled population at 5mg/kg(n=111) versus the smaller 5mg/kg group(n=45).

**Table 19: Duration of Exposure**

Weeks	Number of patients exposed to the study drug:		
	Study A2201 Crizanlizumab	Placebo (n= 62)	Study A2202 Crizanlizumab 5 mg/kg

	2.5 mg/kg (n=64)	5 mg/kg (n= 66)		(n=45)
Mean (SD)	44.5 (14.6)	42.0 (17.0)	41.9(17.8)	35.4 (12.3)
Median	51.9	52.0	52.1	34.3

]

**Reviewer’s Comments:** *Subject demographics were balanced between arms. Most patients were female (52% vs 49%), and 70% of the patients were greater than 65 years of age. Most patients were Black or African-American (89%). The locations from which most patients were enrolled were from the United States of American (68%). Only 6% were from Jamaica. The majority of patients carried the Hgb SS genotype (70%); other genotypes included Hgb SC (14%), Hgb SB+-thalassemia (11%), Hgb SB0-thalassemia (5%) and other (2%). The majority of patients were on hydroxyurea for the preceding six months prior to Day 1 of screening (62%) and have had experienced between 2-4 sickle cell pain crises within the preceding 12 months.*

*In the safety pool (n = 111), the mean exposure to crizanlizumab was approximately 42 weeks. The number of weeks patients were exposed to crizanlizumab in Study A2202 was 35.4 weeks. There were no notable differences between the treatment arms (crizanlizumab 2.5 mg/kg, crizanlizumab 5 mg/kg, and placebo) in mean exposure.*

**Adequacy of the safety database:**

The applicant submitted primary datasets containing data for each patient, including demographics, disease characteristics, drug exposure, concomitant medications, vital signs, pertinent physical findings, laboratory values, and adverse events. The demographics of the safety population are adequately consistent with those of the intended patient population and generalizable to the intended patient population.

**8.2.3 Adequacy of Applicant’s Clinical Safety Assessments**

**Issues Regarding Data Integrity and Submission Quality**

The submission was of adequate quality to enable clinical review. Overall, it was well organized with appropriate analyses and detailed reports and summaries. There are no concerns regarding the integrity of the submission. Adequate narratives were provided for subjects who experienced severe or serious adverse events.

### **Categorization of Adverse Events**

Adverse events (AE) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.0). Sick cell pain crises (SCPC) events (i.e. uncomplicated sickle cell-related pain crises, acute chest syndrome, hepatic and splenic sequestration and priapism requiring a medical facility visit) were not reported as an adverse event or serious adverse event (SAE). Treatment emergent events were defined as those events that occurred or worsened on, or after the first dose of study treatment up to the Follow-Up Evaluation Phase assessments at Week 56.

### **Routine Clinical Tests**

Safety assessments included physical examinations including vital signs, laboratory test measurements, ECGs, and documentation of the hemoglobin variant. The components and scheduling of safety monitoring was appropriate to capture the known AEs and SAEs that are associated with sickle cell disease which may occur throughout the duration of the study. Safety endpoints included incidence of AEs, SAEs and deaths, clinical laboratory tests, vital signs, ECG, immunogenicity (anti-P-selectin antibodies), coagulation laboratory tests as well as biomarkers of SelG1 activity. The schedules of monitoring for both trials are presented in Tables 17 and 18.

### 8.2.4 Safety Results

#### Deaths

There were seven deaths reported in this safety population. In study A2201, there were two patients who died in the 5mg/kg treatment arm; one patient due to sickle cell disease, one due to endocarditis and sepsis, and one patient died in the 2.5mg/kg treatment arm due to acute chest syndrome. Two patients died in the placebo treatment arm. The information from their narratives are shown in Table 20.

**Table 20: Deaths in the Safety Population**

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
A2201- (b) (6) /5 mg/kg/ (b) (6)	21/Male/Black or African American and Hispanic/Latino	26 days from last dose of SelG1 5 mg/kg	History of Hgb SS and history of acute chest syndrome (ACS) Admitted with acute abdominal pain related to VOC; developed pneumonia/acute chest syndrome DOD: (b) (6)
A2201- (b) (6) /5 mg/kg/ (b) (6)	40/Female/Black or African American and Hispanic/Latino	58 days from last dose of SelG1 5 mg/kg	History of Hgb SS, leg ulcer, iron overload and osteomyelitis endocarditis. Admitted for VOC and required intubation. Sepsis in the context of catheter/port contamination and endocarditis is the proposed cause of death DOD: (b) (6)
A2201 (b) (6) /2.5 mg/kg/ (b) (6)	33/Male/Black or African American	25 days from last dose of Sel G1 2.5 mg/kg	History of Hgb SS, ACS requiring intubation, priapism Admitted for respiratory failure and

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
			died on same day of admission DOD: (b) (6)
A2201- (b) (6) /Placebo (b) (6)	39/Female/Black or African American	20 days from last dose of Placebo	History of HgbSB <sup>0</sup> -thalassemia,pulmonary hypertension Had severe right valvular dilation and tricuspid regurgitation; EF of 55%; failure DOD: (b) (6)
A2201- (b) (6) Placebo (b) (6)	20/Male/ Black or African American and Hispanic/Latino	41 days from last dose of Placebo	History of Hgb SS, priapism and VOC; admitted on (b) (6) and diagnosed with hemophagocytic syndrome, ischemic stroke, coma, sepsis, and venous thrombosis of the right lower limb DOD: (b) (6)
A2202 (b) (6) Screen Failure/ (b) (6)	32/Female/Black or African American	Screen Failure/Did not receive any study medication	Unknown hemoglobinopathy; History of hemochromatosis and LVEF of 35% on Hydrea, deferasirox (Jadenu), gabapentin and morphine presenting with cardiorespiratory failure; developed pulmonary edema, died four days after hospitalization due to cardiopulmonary

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
			failure DOD: (b) (6)
A2202- (b) (6) /7.5 mg/kg/ (b) (6)	48/Female/Black or African American	40 days from last dose of SEG101 7.5 mg/kg	Unknown hemoglobinopathy; History of DM, HTN, Hyperlipidemia, CKD, reduced LVEF, EtOH hepatitis found unresponsive at home; in asystole in ED; CT of head suggestive of anoxia encephalopathy; not improving on maximum pressors; died two days after hospitalization due to cardiac arrest DOD: (b) (6)

***Reviewer's Comments: Four subjects (2%) in both the Novartis- and Reprixys- manufactured crizanlizumab arms had serious TEAEs with an outcome of death. Two subjects (1%) in the placebo arm had serious TEAEs with an outcome of death. Three of these deaths were the result of infections (i.e. acute chest syndrome/pneumonia and sepsis due to catheter port contamination) but were unlikely due to the administration of the crizanlizumab. The reviewer agrees with the Sponsor's assessment that none of the on-treatment deaths were considered by investigator to be related to crizanlizumab. In Study A2201, there were two deaths in the 5mg/kg arm, neither considered to be related to study drug.***

### Serious Adverse Events

In the safety pool, (22) 19.8% of patients had at least one SAE and the SAEs that were reported in more than a single patient were pneumonia (3 patients), pyrexia, endocarditis, and urinary tract infection (2 patients). The presentation of the SAEs take into events that are not considered related to sickle cell disease pain crisis (SCPC) events.

In Study A2201, there was no major difference in the incidences of SAEs 17(25.8%) compared to 17 (27.4%) in the 5mg/kg versus placebo arms, respectively. The only SAEs reported in more than a single patient in the 5mg/kg arm were pneumonia: 3(4.5%) vs 3(4.8%) and pyrexia 2(3%) vs 1(1.6%).The following table displays the TEAE by SOC and PT reported in one or more patients.

**Table 21 TEAE by SOC and PT reported in one or more patients in Study A2201.**

SOC PT	Crizanlizumab N=66 n(%)	Placebo N=62 n(%)
Patients with ≥ one serious TEAE	17(25.8)	17(27.4)
Congenital, Familial Genetic Disorders	1(1.5)	2(3.2)
Sickle Cell anemia with crisis	1(1.5)	2(3.2)
General Disorders and Administration Site Conditions	2(3.0)	1(1.6)
Pyrexia	2(3.0)	1(1.6)
Infections and Infestations	8(12.1)	10(16.1)
Pneumonia	3(4.5)	3(4.8)
Urinary Tract Infections	1(1.5)	3(4.8)

The following tables display the SAEs as reported by sickle cell pain crisis history (with and without).

**Table 22: Non-SCD–Related Serious Adverse Events Reported in ≥ 2 Subjects in Any Treatment Group (Safety Population- Study A2201)**

	2.5 mg/kg SelG1 n=64 n(%)	5 mg/kg SelG1 n=66 n(%)	Placebo n=62 n(%)	Total n=192 n(%)
	NON SCPC EVENTS	NON SCPC EVENTS	NON SCPC EVENTS	
<b>Subjects with at least 1 SAE - Subjects and %</b>	<b>21 (32.8%)</b>	<b>17 (25.8%)</b>	<b>17 (27.4%)</b>	<b>55 (28.6%)</b>
<b>INFECTIONS AND INFESTATIONS</b>	<b>11 (17.2%)</b>	<b>8 (12.1%)</b>	<b>10 (16.1%)</b>	<b>29 (15.1%)</b>
Pneumonia	2 (3.1%)	3 (4.5%)	3 (4.8%)	8 (4.2%)
Urinary Tract Infection	1 (1.6%)	1 (1.5%)	3 (4.8%)	5 (2.6%)
Tooth Infection	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Sepsis	0 (0.0%)	1 (1.5%)	1 (1.6%)	2 (1.0%)
Atypical Pneumonia	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Cellulitis	0 (0.0%)	1 (1.5%)	1 (1.6%)	2 (1.0%)
Endocarditis	1 (1.6%)	1 (1.5%)	0 (0.0%)	2 (1.0%)
Gastroenteritis Viral	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Lower Respiratory Tract Infection	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Viral Infection	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Influenza	3 (4.7%)	0 (0.0%)	0 (0.0%)	3 (1.6%)
Post Procedural Infection	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Osteomyelitis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Pyelonephritis Acute	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Pyelonephritis	1 (1.6%)	0 (0.0%)	1 (1.6%)	2 (1.0%)
Appendicitis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Sinusitis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Escherichia Sepsis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Arthritis Infective	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Bacterial Sepsis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Clostridium Difficile Colitis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>2 (3.1%)</b>	<b>2 (3.0%)</b>	<b>1 (1.6%)</b>	<b>5 (2.6%)</b>
Pyrexia	0 (0.0%)	2 (3.0%)	1 (1.6%)	3 (1.6%)
Systemic Inflammatory Response Syndrome	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)

	2.5 mg/kg SelG1 n=64 n(%)	5 mg/kg SelG1 n=66 n(%)	Placebo n=62 n(%)	Total n=192 n(%)
	NON SCPC EVENTS	NON SCPC EVENTS	NON SCPC EVENTS	
Non-Cardiac Chest Pain	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>VASCULAR DISORDERS</b>	<b>1 (1.6%)</b>	<b>2 (3.0%)</b>	<b>2 (3.2%)</b>	<b>5 (2.6%)</b>
Hypotension	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Deep Vein Thrombosis	0 (0.0%)	1 (1.5%)	1 (1.6%)	2 (1.0%)
Angiopathy	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Venous Thrombosis Limb	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>SURGICAL AND MEDICAL PROCEDURES</b>	<b>1 (1.6%)</b>	<b>2 (3.0%)</b>	<b>0 (0.0%)</b>	<b>3 (1.6%)</b>
Hysterectomy	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Abortion Induced	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Central Venous Catheterization	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>RENAL AND URINARY DISORDERS</b>	<b>0 (0.0%)</b>	<b>2 (3.0%)</b>	<b>0 (0.0%)</b>	<b>2 (1.0%)</b>
Renal Papillary Necrosis	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Urinary Retention	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
<b>CARDIAC DISORDERS</b>	<b>1 (1.6%)</b>	<b>1 (1.5%)</b>	<b>1 (1.6%)</b>	<b>3 (1.6%)</b>
Bradycardia	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Palpitations	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Right Ventricular Failure	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>CONGENITAL, FAMILIAL AND GENETIC DISORDERS</b>	<b>0 (0.0%)</b>	<b>1 (1.5%)</b>	<b>2 (3.2%)</b>	<b>3 (1.6%)</b>
Sickle Cell Anemia With Crisis	0 (0.0%)	1 (1.5%)	2 (3.2%)	3 (1.6%)
<b>ENDOCRINE DISORDERS</b>	<b>0 (0.0%)</b>	<b>1 (1.5%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Hyperparathyroidism Primary	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
<b>NERVOUS SYSTEM DISORDERS</b>	<b>2 (3.1%)</b>	<b>1 (1.5%)</b>	<b>1 (1.6%)</b>	<b>4 (2.1%)</b>
Syncope	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.5%)
Dizziness	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Hemorrhage Intracranial	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Coma	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Ischemic Stroke	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>HEPATOBIILIARY DISORDERS</b>	<b>2 (3.1%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>2 (1.0%)</b>
Bile Duct Stone	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Cholangitis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Cholecystitis Acute	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	<b>2 (3.1%)</b>	<b>0 (0.0%)</b>	<b>1 (1.6%)</b>	<b>3 (1.6%)</b>

	2.5 mg/kg SelG1 n=64 n(%)	5 mg/kg SelG1 n=66 n(%)	Placebo n=62 n(%)	Total n=192 n(%)
	NON SCPC EVENTS	NON SCPC EVENTS	NON SCPC EVENTS	
Cough	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Aspiration	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Acute Chest Syndrome	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Respiratory Failure	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Status Asthmaticus	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>	<b>2 (3.1%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>2 (1.0%)</b>
Acute Hemolytic Transfusion Reaction	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Infusion Related Reaction	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	<b>2 (3.1%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>2 (1.0%)</b>
Back Pain	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Osteonecrosis	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>	<b>1 (1.6%)</b>	<b>0 (0.0%)</b>	<b>1 (1.6%)</b>	<b>2 (1.0%)</b>
Anemia	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Leukocytosis	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS</b>	<b>1 (1.6%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Pre-Eclampsia	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	<b>1 (1.6%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Skin Ulcer	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>GASTROINTESTINAL DISORDERS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.6%)</b>	<b>1 (0.5%)</b>
Diarrhea	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Nausea	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Vomiting	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>PSYCHIATRIC DISORDERS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.6%)</b>	<b>1 (0.5%)</b>
Major Depression	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
Suicide Attempt	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)
<b>INVESTIGATIONS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.6%)</b>	<b>1 (0.5%)</b>
Neutrophil Count Decreased	0 (0.0%)	0 (0.0%)	1 (1.6%)	1 (0.5%)

**Reviewer’s Comments:** *The serious adverse events in the infections and infestations SOC occurred more commonly in the 2.5 mg/kg group compared to the 5 mg/kg group and the placebo group. Other serious events included general disorders and administration site conditions and vascular disorders. These events included influenza (3 subjects), pneumonia, urinary tract infection, appendicitis, endocarditis, osteomyelitis and pyelonephritis (1 subject each). Of note, the analysis did identify a few of the subjects with either pneumonia, acute chest syndrome and sickle cell anemia with crisis under non-SCPC events. Those events are represented in Table 21.*

**Table 23: SCD-Related Serious Adverse Events Reported in ≥ 2 Subjects in Any Treatment Group (Safety Population- Study A2201) by sickle cell pain crisis events**

	2.5 mg/kg SelG1 n=64 n(%)	5 mg/kg SelG1 n=66 n(%)	Placebo n=62 n(%)	Totals n=192 n(%)
	SCPC EVENTS	SCPC EVENTS	SCPC EVENTS	
<b>Subjects with at least 1 SAE - Subjects and %</b>	57 (89.1%)	50 (75.8%)	54 (87.1%)	161 (83.9%)
Uncomplicated Sickle Cell-Related Pain Crisis (SCPC)	55 (85.9%)	46 (69.7%)	52 (83.9%)	153 (79.7%)
Acute Chest Syndrome (ACS)	14 (21.9%)	15 (22.7%)	10 (16.1%)	39 (20.3%)
Priapism (Requiring A Visit To A Medical Facility)	1 (1.6%)	1 (1.5%)	1 (1.6%)	3 (1.6%)
Splenic Sequestration	2 (3.1%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Pneumonia	2 (3.1%)	3 (4.5%)	3 (4.8%)	8 (4.2%)
Sickle Cell Anemia With Crisis	0 (0.0%)	1 (1.5%)	2 (3.2%)	3 (1.6%)
Acute Chest Syndrome	1 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Not Available	3 (4.7%)	3 (4.5%)	3 (4.8%)	9 (4.7%)

**Reviewer’s Comments:** *Among the SCD-related serious adverse events reported, uncomplicated sickle cell related pain crises (SCPC) occurred evenly in the 2.5 mg/kg group and the placebo group. There was a slight reduction in SCPC events reported in the 5 mg/kg group. Other serious SCD-related serious adverse events included acute chest syndrome. The events listed as “non-available” could not be clearly assigned to any of the adverse events listed in Table 21.*

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***Reviewer's Comments: The serious adverse events by primary system organ class identified in Study A2202 were higher among the general disorders and administration site conditions (16 subjects; 53.3%) followed by infections and infestations (14 subjects (46.7%).***

**Table 24: Adverse Events and Treatment Related Serious Adverse Events by Studies A2201 and A2202**

	Study A2201 Crizanlizumab				Study A2202 Crizanlizumab N=45 n(%)		Pooled Crizanlizumab N=111 n(%)		Placebo N=62 n(%)	
	2.5mg/kg N=64 n(%)		5mg/kg N=66 n(%)		All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
	All Grades	Grade ≥ 3	All grades	Grade ≥ 3						
<b>Patients with at least one event</b>	56 (87.5)	13 (20.3)	57 (86.4)	12 (18.2)	29 (64.4)	9 (20.0)	86 (77.5)	21 (18.9)	55 (88.7)	12 (19.4)
<b>Treatment related SAEs</b>	5 (7.8)	3 (4.7)	6 (9.1)	3 (4.5)	0	0	6 (5.4)	3 (2.7)	2 (3.2)	1 (1.6)

**Reviewer's Comments:** *In the randomized Study A2201, overall AEs, SAEs and AEs leading to treatment discontinuation were reported with similar incidences (≤ 5% absolute differences) across treatment arms. AEs/SAEs considered treatment-related by investigators, and AEs requiring additional therapy tended to be more frequent in the crizanlizumab 5 mg/kg than the placebo arm.*

### Significant Adverse Events

**Dropouts and/or Discontinuations Due to Adverse Effects**

**Table 25: Table for Discontinuations due to Treatment Emergent Adverse Events**

<b>SOC PT</b>	<b>Crizanlizumab 5mg/kg N=66 n(%)</b>	<b>Placebo N=62 n(%)</b>
<b>Patients with ≥ 1 TEAE leading to study drug discontinuation</b>	2(3)	3(4.8)
<b>Blood and Lymphatic System</b>	0	1(1.6)
<b>Leukocytosis</b>	0	1(1.6)
<b>Cardiac Disorders</b>	1	0
<b>Bradycardia</b>	(1.5)	0
<b>Congenital, Familial and Genetic Disorders</b>	1(1.5)	0
<b>Sickle cell Anemia with crisis</b>	1(1.5)	0
<b>Hepatobiliary disorders</b>	0	1(1.6)
<b>Jaundice</b>	0	1(1.6)
<b>Infections and Infestations</b>	0	1(1.6)
<b>Arthritis infective</b>	0	1(1.6)
<b>Bacterial sepsis</b>	0	1(1.6)
<b>Clostridium difficile colitis</b>	0	1(1.6)
<b>Investigations</b>	0	2(3.2)
<b>GGT increase</b>	0	1(1.6)
<b>Neutrophil count decreased</b>	0	1(1.6)

*Reviewer's Comments: There were a substantial number of discontinuations in both arms of Study A2201. There were significant dropouts in both arms of Study A2201 and a number of dropouts and discontinuations in Study A2202. Approximately thirty-five percent (35%) of patients randomized in Study A2201 discontinued treatment before completion of the treatment study. The most frequent reason for discontinuations was the patient's decision or "other" (i.e., full-time employment, unblinding, going for bone marrow transplantation, incarceration and difficult venous access).*

***Over two percent (2.7%) of patients (n=3) in the pooled crizanlizumab arms discontinued treatment due to adverse events. Two patients in the 5mg/kg arm were discontinued with treatment due to VOC and bradycardia, respectively. The patient who died was not counted as a discontinuation due to an adverse event. The patient with bradycardia had a history of situs inversus, adrenal insufficiency and hypopituitarism. The one patient in the 2.5 mg/kg treatment arm was discontinued as a result of an intracranial hemorrhage which is believed to be a major complication of SCD. Three patients in the placebo arm were discontinued due to the following: Increased GGT, low neutrophil count and leukocytosis, jaundice, bacterial sepsis and Clostridium difficile colitis.***

***The concerns with the number of discontinuations only highlights the disparity in enrolling and sustaining participants in these clinical trials that may be due to limited or low resources of the study participants as well as the investigator's sites. The Agency agrees with the Sponsor's assessment that the majority of reasons for discontinuation was unrelated to crizanlizumab.***

***Reviewer's Comments: In the randomized Study A2201, overall AEs, SAEs and AEs leading to treatment discontinuation were reported with similar incidences ( $\leq 5\%$  absolute differences) across treatment arms. AEs/SAEs considered treatment-related by investigators, and AEs requiring additional therapy tended to be more frequent in the crizanlizumab 5 mg/kg than the placebo arm.***

**Table 26: Drug Withdrawal due to Adverse Events based on history of Sickle Cell Pain Crisis Events**

	2.5 mg/kg SelG1 N=64 n(%)		5 mg/kg SelG1 N=66 n(%)		Placebo N=62 n(%)		Totals N=192 n(%)
	NON SCPC EVENTS	SCPC EVENTS	NON SCPC EVENTS	SCPC EVENTS	NON SCPC EVENTS	SCPC EVENTS	
<b>Subjects with AE leading to drug withdrawal - Subjects and % with data</b>	<b>1 (1.6%)</b>	<b>1 (1.6%)</b>	<b>2 (3.0%)</b>	<b>5 (7.6%)</b>	<b>3 (4.8%)</b>	<b>3 (4.8%)</b>	<b>13 (6.8%)</b>
<b>CONGENITAL, FAMILIAL AND GENETIC DISORDERS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.5%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Sickle Cell Anemia with Crisis	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vaso-Occlusive Crisis	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>CARDIAC DISORDERS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (1.5%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Bradycardia	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Symptomatic Bradycardia	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
<b>NERVOUS SYSTEM DISORDERS</b>	<b>1 (1.6%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.5%)</b>
Hemorrhage Intracranial	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Intercranial Hemorrhage W/Sickle Cell Can Be From Moya Moya/Or Vascular Changes On MRA.	1 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Uncomplicated Sickle Cell-Related Pain Crisis (SCPC)	0 (0.0%)	1 (1.6%)	0 (0.0%)	3 (4.5%)	0 (0.0%)	2 (3.2%)	6 (3.1%)
Acute Chest Syndrome (ACS)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.0%)	0 (0.0%)	1 (1.6%)	3 (1.6%)
<b>INVESTIGATIONS</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>2 (3.2%)</b>	<b>0 (0.0%)</b>	<b>2 (1.0%)</b>
Neutrophil Count Decreased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Low Neutrophil Count	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)

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	2.5 mg/kg SelG1 N=64 n(%)		5 mg/kg SelG1 N=66 n(%)		Placebo N=62 n(%)		Totals N=192 n(%)
	NON SCPC EVENTS	SCPC EVENTS	NON SCPC EVENTS	SCPC EVENTS	NON SCPC EVENTS	SCPC EVENTS	
Gamma-Glutamyl transferase Increased	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Increased Gamma GT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>INFECTIONS AND INFESTATIONS</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
BACTERIAL SEPSIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Gram Negative Rod Sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>CLOSTRIDIUM DIFFICILE COLITIS</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Clostridium Difficile Colitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>ARTHRITIS INFECTIVE</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Bilateral Knee Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>HEPATOBIILIARY DISORDERS</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>JAUNDICE</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Jaundice	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>LEUKOCYTOSIS</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
Leukocytosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)	1 (0.5%)
<b>Not Available</b>	0 (0.0%)	1 (1.6%)	0 (0.0%)	5 (7.6%)	0 (0.0%)	3 (4.8%)	9 (4.7%)

*Reviewer's Comments: Among the adverse events associated with drug withdrawal, these events were mainly observed in the crizanlizumab 5 mg/kg arm compared with the placebo arm. These events appear to be associated with SCPC events such as*

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*uncomplicated sickle cell pain crises, decreased neutrophil count, gram negative sepsis, clostridium difficile colitis, bilateral knee infection, jaundice and leukocytosis. The events listed as “non-available” could not be clearly assigned to any of the adverse events listed in Table 26.*

*Reviewer’s Comments: The adverse events leading to drug withdrawal was highest in the crizanlizumab 5 mg/kg arm followed by the placebo arm. The most likely reason for drug withdrawal was due to sickle cell related pain crises. The events listed as “non-available” could not be clearly assigned to any of the adverse events listed in Table 28.*

*In Study A2201, there were no notable differences between the treatment arms in the frequency of AEs leading to treatment discontinuation:*

- Two (3.0%) patients in the 5 mg/kg treatment-arm: sickle cell anemia with VOC and bradycardia. The patient with sickle cell anemia with VOC died as a result. It was listed as discontinuation due to death. The patient with bradycardia had a medical history of a situs inversus (heterotaxia), adrenal insufficiency and hypopituitarism.*
- One (1.6%) patient in the 2.5 mg/kg treatment-arm: intracranial hemorrhage. The cerebrovascular accident is a major complication and leading cause of death in patients with SCD.*
- Three (4.8%) patients in the placebo treatment arm: increased GGT (reported in 1 patient), low neutrophil count (reported in 1 patient) and leukocytosis, jaundice, arthritis infective, bacterial sepsis, Clostridium difficile colitis (reported in 1 patient).*

#### Common Treatment Emergent Adverse Events

In the safety pool, no AE was reported in > 20% of patients. In Study A2201, only arthralgia was reported with an absolute difference greater than or equal to 10% compared to placebo arm.

**Table 27: Treatment Emergent Adverse Events and Adverse Reactions by Preferred Term**

	Study A2201		Study 2202 5mg/kg N=45 n(%)	Safety Pool 5mg/kg N=111 n(%)
	Placebo N=63 n(%)	Crizanlizumab 5mg/kg N=66 n(%)		
Patients with at least one event	55(88.7)	57(86.4)	29(64.4)	86(77.5)
Headache	10(16.1)	11(16.7)	7(15.6)	18(16.2)
Back Pain	7(11.3)	10(15.2)	5(11.1)	15(13.5)
Nausea	7(11.3)	12(18.2)	3(6.7)	15(13.5)
Pyrexia	4(6.5)	7(10.6)	8(17.8)	15(13.5)
Arthralgia	5(8.1)	12(18.2)	2(4.4)	14(12.6)
Pain in Extremity	10(16.1)	11(16.7)	2(4.4)	13(11.7)
Urinary Tract Infection	7(11.3)	9(13.6)	2(4.4)	11(9.9)
Diarrhea	2(3.2)	7(10.6)	2(4.4)	9(8.1)

	Study A2201		Study 2202	Safety Pool
	Placebo N=63 n(%)	Crizanlizumab 5mg/kg N=66 n(%)	5mg/kg N=45 n(%)	5mg/kg N=111 n(%)
Musculoskeletal Pain	6(9.7)	8(12.1)	1(2.2)	9(8.1)
Upper Respiratory Tract Infection	6(9.7)	7(10.6)	2(4.4)	9(8.1)
Hypokalemia	5(8.1)	1(1.15)	6(13.3)	7(6.3)
Fatigue	2(3.2)	5(7.6)	1(2.2)	6(5.4)
Pruritus	3(4.8)	5(7.6)	1(2.2)	6(5.4)

Most of the adverse events were mild in grade (grade 1 or 2).

*Reviewer's Comments: The treatment-emergent adverse events (TEAEs) were similarly distributed across all arms. When evaluating by SOC, the highest TEAEs (greater than ≥ 15%) were seen among infections and infestations (50%), musculoskeletal and connective tissue disorders (34.9%), gastrointestinal disorders (34.4%), general disorders and administration site conditions (33.9%), nervous system disorders (28.6%), investigations (22.9%), respiratory, thoracic and mediastinal disorders (22.9%), and skin and subcutaneous tissue disorders (18.8%).*

When evaluating treatment emergent adverse events by hydroxyurea use and sickle-cell related pain crisis history, there was no difference in TEAEs.

**Table 28 TEAEs by Hydroxyurea Use and Sickle Cell Related Pain Crisis(SCPC) History**

	<b>Crizanlizumab 5 mg/kg N=66 n(%)</b>	<b>Placebo N=62 n(%)</b>
<b>Patients with any TEAE (Overall Population)</b>	57(86.4)	55(88.7)
<b>Patients with any TEAE: HU use- YES</b>	35(85.4)	35(89.7)
<b>Patients with any TEAE: HU use-NO</b>	22(88)	20(87)
<b>Patients with any TEAE: SCPC history 2-4</b>	36(87.8)	34(87.2)
<b>Patients with any TEAE: SCPC history 5-10</b>	21(84)	21(91.3)

**SCPC-sickle cell pain crisis**

### Laboratory Findings

In the safety pool, almost all patients (98.2%) presented with some level of decreased hemoglobin. Out of the 45 (40.5%) patients with a grade abnormality post-baseline, 29 patients already had grade 3 abnormality at baseline and 18 patients had worsened from grade 2, and 3 patients had worsened from grade 1. Overall, there were no consistent significant changes from baseline in the mean or median hematological parameters.

In addition, the following high grades ( $\geq 3$ ) hematologic laboratory abnormalities were also reported in the safety pool:

- aPTT increase: 6 (3.1%) patients with grade 3, of which 3 worsened from baseline grade 0, and 1 from baseline grade 2. The etiology of the PTT increase was secondary to heparin contamination and seen to be higher in the 5 mg/kg crizanlizumab. Analysis of time-profiles for aPTT and INR in Study A2201 did not reveal any time-dependent effect during treatment or compared to Baseline, and no differences between the treatment arms and placebo. This finding, therefore, is not considered clinically significant.
- Leucocyte decrease: 1 (0.9%) patient with grade 3 worsening from baseline grade 2, and 2 (1.8%) patients with grade 4 of which one worsened from baseline grade 3 and the other from baseline grade 0 (no finding)
- Neutrophil (absolute) decrease: 4 (3.6%) patients with grade 3, of which 2 worsened from baseline grade 0, one from grade 2 and 1 was already grade 3 at baseline. Four (3.6%) patients with grade 4, of which 3 worsened from baseline grade 0 (including 1 due to incorrect entry of unit by the local laboratory, as the patient had normal value upon medical review) and 1 patient who was already grade 4 at baseline.
- Lymphocyte (absolute) decrease: 2 (1.8%) patients with grade 3, all worsened from baseline grade 0.
- Lymphocyte (absolute) increase: There were no Grade 3 or 4.
- INR increase: 1 (0.9%) patient worsening from baseline grade 0 to grade 3. There were no grade 4.
- PTT international normalized ratio: 1 (0.9%) patient with grade 3 worsened from grade 0 at baseline

Over the course of the study, there were no consistent significant changes from baseline in the mean or median blood chemistry parameters. The following were reported:

- Increased total bilirubin level was reported in 1 additional patient; the cumulative number (%) of patients with a grade 3/4 total bilirubin abnormality post-baseline increased from 32 patients (28.8%) to 33 patients (29.7%). Three additional patients were reported with grade 3 decreased potassium, one of whom entered the study with a grade 2 decrease. The cumulative number of patients with grade 3 decreased potassium increased from 1 patient (0.9%) to 4 patients (3.6%); there were no grade 4 abnormalities.
- Given that hemolysis is common in SCD patients and can lead to increase in TBILI and

AST independent of liver related toxicity, none of the patients who received crizanlizumab had a pattern of on-treatment laboratory parameters suggestive of potential DILI.

### **Vital Signs**

The following vital signs were summarized by treatment group at the scheduled times of Day - 30 to -1 (Screening Phase), Day 1, 15, Weeks 6,10,14,18,22,26,30,34,38,42,46,50,52 and Week 58. Systolic and diastolic blood pressure (mmHg), body temperature (°C), heart rate (beats per minute [bpm]), oxygen saturation (percent), respiratory rate (breaths per minute), and body weight (kg). The following differences between crizanlizumab arm and placebo arm were noted:

- Systolic blood pressure > 150mm HG reported for 7 patients (10.6%) in the 5 mg/kg arm, 10 patients (15.6%) in the 2.5mg/kg arm and 5 patients (8.1%) in the placebo arm.
- Diastolic blood pressure > 100mmhg reported for 3 patients(4.5%) in the 5 mg/kg arm, 5 patients (7.8%) in the 2.5mg/kg arm and 1(1.6%) patient in the placebo arm.

Overall, no clinically significant differences were found for mean or median changes in any vital sign parameters from baseline in the either crizanlizumab groups compared with those in the placebo group. There is slight trend for increased diastolic blood pressure in the crizanlizumab arm and this warrants additional follow-up safety data.

### **Electrocardiograms (ECGs)**

Electrocardiograms were collected during the screening period and on Days 1, 15, Weeks 6,10,14,18,22,26,30,34,38,42,46,50, and 52. Based on investigator assessment, no subject in either treatment group had a clinically significant abnormal ECG finding. There were no shifts from normal baseline ECG to an abnormal clinically significant post-baseline ECG.

### **QT**

In the safety pool, there were notable increases in QT, and QTcF. Nine patients had a QTcF shifting from  $\leq 450$  ms at baseline to  $> 450$  ms-  $\leq 480$  ms in the pooled study populations studied.

In Study A2201 (5 mg/kg arm), there was one patient had a QTcF prolongation to  $> 500$  ms,; however, this patient had already a QTcF  $> 480$  ms at baseline.

There were two AEs of increased QTcF reported in patients of Study A2202. Both were grade 1 QTcB prolongations and resolved without crizanlizumab interruption and without re-occurrence.

AE of ECG QTc prolonged were reported in 1 (1.5%) and 1 (1.6%) patients in the 5 mg/kg and placebo arm, respectively.

## Immunogenicity

(b) (4)

In Study A2102, one subject in the SelG1 (5 mg/kg) treatment group and another subject in the exploratory SEG101 7.5 mg/kg arm tested positive for ADA on Day 106. All other subjects in the SEG101 5 mg/kg and SelG1 5 mg/kg treatment groups tested negative throughout the study.

In Study A2201, twelve SCD patients tested positive for ADA, of which 9 patients had pre-existing ADAs. Three patients had treatment-induced ADAs, however, one of these 3 patients never received crizanlizumab being in the placebo group.

In Study A2202, there was no evidence of the development of ADAs in any patients.

A total of 5 (1.9%) patients developed treatment induced ADA in clinical studies, which indicates that the immunogenic potential of crizanlizumab is low. ADAs were transiently detected in 2 out of 175 (1.1%) SCD patients; one of these patients was among the 111 patients who received crizanlizumab at a dose of 5 mg/kg (0.9%). ADAs also developed in 3 out of 88 (3.4%) healthy volunteers.

### 8.2.5 Analysis of Submission-Specific Safety Issues

#### 8.2.5.1 Specific Safety Issues

#### Infusion-related Reactions (IRR)

Severe IRRs were observed in 2 (1.8%) patients treated with crizanlizumab 5 mg/kg did not require discontinuations. Both patients had Grade 1 and 2 infusion related reactions, respectively.

In Study A2201, the infusion related reactions were more frequent in the 5 mg/kg arm (23 patients; 34.8%) compared to the placebo arm (13 patients, 21.0%). The accompanying reaction was nausea with 10.6% compared to 1.6% patients in the 5mg/kg and placebo arms, respectively.

The first patient received only one infusion and the event reported was an “elevation in temperature during the infusion without additional details. The second patient reportedly had enuresis while sleeping during the infusion.

Reviewer Comment: None of the adverse events reported are suggestive of typical IRR, however recommend including IRRs in the warnings and precautions of the USPI.

#### Infections

In the safety pool, 48 (43.2%) patients reported Infections AEs. The individual events were typically reported in 1 or 2 patients only, except for urinary tract infection (11 patients, 9.9%), upper respiratory tract infection (9 patients, 8.1%), pneumonia and sinusitis (4 patients each, 3.6%). Seven (6.3%) patients had grade 3 events; no grade 4 events were reported and none of the Infection AEs led to treatment discontinuation. Three infection related AEs led to crizanlizumab interruption: arthritis infective, atypical pneumonia and sinusitis, reported in 1 patient each. Almost all patients (46/48) had recovered at data cutoff; the 2 events that were still ongoing were osteomyelitis and tooth infection.

In randomized Study A2201, there were no relevant differences between the crizanlizumab 5 mg/kg and the placebo arms in the nature, incidences, or severity of these Infection AEs. There were 35 (53.0%), vs. 33 (53.2%) patients who had at least 1 event and 4 (6.1%) vs. 2 (3.2%) who had grade 3 events in the 5 mg/kg vs. placebo arms, respectively. The most frequent infection events by PTs were urinary tract infection (13.6% vs. 11.3% patients) and upper respiratory tract infection (10.6% vs. 9.7% patients) in 5 mg/kg vs. placebo, respectively.

### **Hemorrhage**

In the safety pool, 13 (11.7%) patients had hemostasis or hemorrhage AEs. Except prolonged prothrombin time reported in 3 (2.7%) patients, these events were reported in 1 or 2 patients only. None were grade 4, or led to study withdrawal, and none were considered treatment related as per investigator assessment. The only grade 3 event was hemoglobin decreased which was related to the underlying disease. All patients had recovered without sequelae at data cutoff.

In Study A2201, hemostasis – hemorrhage AEs were reported in 11 (16.7%) patients in the 5 mg/kg and 8 (12.9%) patients in the placebo arm. All patients in 5 mg/kg arm had recovered (event resolved) at data cutoff. Of note, 1 event (intracranial hemorrhage) reported in the 2.5 mg/kg arm was considered serious (grade 4, hospitalization) and lead to study drug discontinuation.

### **Laboratory Test Interference**

Interference with automated platelet counts (platelet clumping) has been observed in patients treated with crizanlizumab in clinical studies, in particular when using tubes containing ethylenediaminetetraacetic acid (EDTA). This may lead to unevaluable or falsely decreased platelet counts. To mitigate the potential for laboratory test interference, it is recommended to run the test as soon as possible (within 4 hours) or use citrate tubes.

A search for potential AEs related to thrombosis (AESI hemostasis – thrombosis) did not identify any patients with AEs related to thrombosis the 5 mg/kg pooled data.

## **8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

Not Applicable

## 8.2.7 Safety Analyses by Demographic Subgroups

### Analysis by Gender

In the safety pool, the overview of AEs by gender (Female, N=59 vs. Male, N=52) did not reveal notable differences.

The AEs that were at least 5% more frequent (in absolute differences) in 1 gender were (female vs. male).

- Headache: 20.3% vs. 11.5%
- Urinary tract infection: 15.3% vs 3.8%

In Study A2201, there were notable difference in the incidence rates of AEs by gender between the treatment arms.

### Analysis by Ethnicity

In the safety pool, the overview of AEs by ethnicity did not reveal notable differences.

### Analysis by Age Category

Only 6 patients were pediatric (< 18 years at baseline), including 5 patients in Study A2201 (2 placebo, 1 crizanlizumab 2.5 mg/kg and 2 crizanlizumab 5 mg/kg) and 1 patient in Study A2202. Only 1 patient was geriatric ( $\geq$  65 years at baseline, in Study A2202). Therefore, no analysis by age category was done for this summary of safety.

### Analysis by HU/HC Use

In the safety pool, the overview of AEs by HU/HC use (No use of HU/HC, N=36 vs. Use of HU/HC, N=75) did not reveal notable differences.]

## 8.2.8 Specific Safety Studies/Clinical Trials

(b) (4)



Study A2102: A Phase I single dose, randomized, open-label, parallel group, single-center trial to assess the comparability of crizanlizumab pharmacokinetics and pharmacodynamics administered as SEG101 in comparison to SelG1 in healthy subjects

Based on the treatment with either Novartis- or Repixys-manufactured crizanlizumab, SEG101 or SelG1, the adverse events are listed below:

- At least 1 AE was reported in 10 subjects (35.7%) in the SEG101 5 mg/kg treatment group and in 12 subjects (36.4%) in the SelG1 5 mg/kg treatment group.
- AEs occurring in more than 1 subject were headache in 2 subjects (7.1%) in the SEG101 5 mg/kg group and 2 subjects (6.1%) in the SelG1 5 mg/kg group, viral upper respiratory tract infection in 3 subjects (10.7%) in the SEG101 5 mg/kg group, and paresthesia in 1 subject (3.6%) in the SEG101 5 mg/kg group and 1 subject (3.0%) in the SelG1 5 mg/kg group. No grade 3/4 AEs were reported.
- AEs with a suspected relationship to the study treatment were reported in 2 subjects (7.1%) in the SEG101 5 mg/kg group: 1 subject experienced grade 1 dizziness and grade 1 feeling abnormal on Day 3 that resolved on Day 4, and 1 subject reported grade 1 headache on Day 2 that resolved the same day. No AEs with a suspected relationship to the study treatment were reported in the SelG1 5 mg/kg group.
- In the SEG101 7.5 mg/kg treatment group, 3 of the 7 subjects (42.9%) had at least 1 AE and these were grade 1/2. In 1 subject, 2 AEs (dry throat, nasal congestion) were suspected to be related to study drug.
- There were no deaths or AEs grade 3/4 in any treatment group.

Study B2201: Multicenter, single-arm, open-label study is set to confirm and establish appropriate dosing and to collect safety data in pediatric patients aged 6 months to < 18 years receiving crizanlizumab for 2 years.

Crizanlizumab will be administered with or without HU/HC. Pediatric patients with SCD with history of VOC will be enrolled into the study. It is conducted in a sequential design in descending age groups, (b) (4)

## 8.2.9 Additional Safety Explorations

### Human Carcinogenicity or Tumor Development

Refer to the non-clinical review by Ramadevi Gudi, PhD.

### Human Reproduction and Pregnancy

The potential risk to pregnant or breast-feeding women is unknown. In these clinical studies, five cases of pregnancy were reported among patients receiving 2.5 mg/kg, 5 mg/kg and placebo treatment in Study A2201 and A2202.

In Study A2201, the following four women either were withdrawn from study or discontinued therapy due to pregnancy:

1. Patient (b) (6) in the Crizanlizumab 2.5 mg/kg arm: 22 year-old was withdrawn from the study due to pregnancy after receiving a total of eight doses; Delivered a male infant weighing 2 pounds 6 ounces (1.077 kg) by cesarean section. She did have pre-eclampsia.
2. Patient (b) (6) in the crizanlizumab 5 mg/kg arm: Discontinued due to pregnancy after receiving a total of two doses; Attempted self-abortion with “abortive teas” resulting in an incomplete abortion 48 hours later. A uterine curettage was performed.
3. Patient (b) (6) in the crizanlizumab 5 mg/kg arm: Discontinued treatment due to pregnancy after receiving a total of 11 doses; no information was available regarding the outcome of this case.
4. Patient (b) (6) in the placebo arm: Discontinued treatment due to pregnancy after receiving a total of 9 doses; patient delivered a male child at 38 weeks via spontaneous vaginal delivery. The patient’s child was 2.68 kg and had an Apgar score of 9 at 1 minute and Apgar score of 9 at 5 minutes.

In Study A2202, one female patient discontinued therapy due to pregnancy:

1. Patient (b) (6) in the crizanlizumab 5 mg/kg arm: Discontinued treatment due to pregnancy after receiving 3 doses of crizanlizumab 5 mg/kg by intravenous infusion; premature delivery by one month prior to estimated due date and diagnosis of pre-eclampsia. The baby was admitted to the NICU and then later discharged home; there is no evidence of developmental delay.

### Pediatrics and Assessment of Effects on Growth

The proposed indication is for patients aged 16 years and over. There are no formal assessments on the effects of growth.

### Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose were reported in clinical studies.

### **8.2.10 Safety in the Postmarket Setting**

#### **Safety Concerns Identified Through Postmarket Experience**

Crizanlizumab has not been marketed in any country.

#### **Expectations on Safety in the Postmarket Setting**

The safety of crizanlizumab in SCD patients with end-organ complications will be of interest. In addition, the long-term safety assessment of this product will be an important consideration as this drug may be given life-long.

### **8.2.11 Integrated Assessment of Safety**

The primary safety data provided by the Applicant in support of this application for crizanlizumab was derived from a single phase 2 randomized study (Study A2201/SUSTAIN) in adult and adolescent patients with SCD with the safety profile in adults supported by data from the open-label Phase 2a study, Study A2202. The demographics of the subjects enrolled in these studies were consistent with those for the general SCD population.

Across all clinical studies included in this BLA, crizanlizumab demonstrated an acceptable safety and tolerability profile. A total of 7 deaths overall and four on treatment deaths were reported in the pivotal phase 2 study (A2201) and the supportive Phase 2a study (A2202). None of the four on-treatment deaths of crizanlizumab-treated patients were considered related to the study treatment.

The safety profile of crizanlizumab is based on data from 175 patients with sickle cell disease (SCD) from 2 clinical studies (randomized Study A2201 and single arm Study A2202), who received at least 1 infusion of crizanlizumab at a dose of 2.5 mg/kg (N=64) or 5 mg/kg (N=111). Among the 111 patients exposed to the recommended dose of 5 mg/kg, the median (min-max) duration of exposure was 34 weeks (< 1 to 57 weeks), and 75 of the 111 patients (67.6%) were treated in combination with hydroxyurea/hydroxycarbamide (HU/HC). In addition, in Study A2201, 62 patients in the control arm received placebo.

Crizanlizumab (5 mg/kg) is associated with a favorable safety profile as demonstrated by:

- The overall frequency of TEAEs (86.4% vs. 88.7%), severe AEs (grade  $\geq$  3; 18.2% vs. 19.4%), SAEs (25.8% vs. 27.4%) and AEs leading to treatment discontinuation (3.0% vs. 4.8%) was similar between the crizanlizumab 5 mg/kg and placebo arms in Study A2201.
- In Study A2201, the two deaths that occurred in the crizanlizumab 5mg/kg treatment group were not considered to be related to the study drug.
- When considering the entire safety pool(n=175), the most frequent adverse drug

reactions reported in  $\geq 10\%$  of patients treated with crizanlizumab 5 mg/kg were back pain, nausea, pyrexia and arthralgia. The majority of these ADRs were mild or moderate (grade 1 to 2); severe events were pyrexia and arthralgia (1 case, 0.9%, each, both grade 3).

- Discontinuations due to adverse events (AEs) were rare and occurred in 2.7% of patients treated with crizanlizumab 5 mg/kg; no patient discontinued due to an ADR in the entire safety pool.
- As with other monoclonal antibodies, there is a potential for infusion-related reactions (IRRs) and immunogenicity:IRRs were observed in 2 (1.8%) patients treated with crizanlizumab 5 mg/kg, neither of which was serious or required discontinuation in safety pool.
- Treatment-induced anti-crizanlizumab antibodies were transiently detected in 1 (0.9%) patient receiving crizanlizumab 5 mg/kg. A total of 5 (1.9%) patients/subjects developed ADA. There was no impact of ADA development on the PK, efficacy or safety of crizanlizumab.
- No signs of drug-induced liver injury (DILI) were observed.
- Crizanlizumab given in combination with HU/HC did not result in any meaningful differences in the safety profile.
- There was no evidence that crizanlizumab confers an increased risk for infections, or had the potential to affect hemostasis/frequency of hemorrhage compared to placebo.
- ECG, hematology and clinical chemistry laboratory analyses were similar across treatment arms, with no clinically significant changes from baseline.

Across all clinical studies included in this BLA, crizanlizumab demonstrated an acceptable safety and tolerability profile that supports the proposed registration dose of 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter (10 mg/mL).

### 8.3 Statistical Issues

The median annual VOC rates in 5 mg/kg SelG1 treatment arm did not show a reduction compared with that of placebo arm, in both male patients and South America patients. The comparisons of these subgroups were not powered to achieve statistical significance.

A substantial number (35%) of the patients randomized in Study A2201 discontinued treatment before the end of the year of evaluation. The rates of discontinuation were 36.9%, 35.8%, and 31.8% for placebo, 5 mg/kg SelG1, and 2.5 mg/kg SelG1 arms, respectively.

Since no statistically significant difference was observed between 2.5 mg/kg SelG1 arm and the placebo arm, no alpha was left for all following secondary endpoints analyses.

## 8.4 Conclusions and Recommendations

The primary endpoint demonstrating a clinically relevant and statistically significant difference in the annual rate of VOCs leading to health care visit was shown with crizanlizumab 5 mg/kg compared to placebo. Crizanlizumab 5 mg/kg led to lower median annual rate of VOC leading to a healthcare visit compared to placebo (1.63 vs 2.98, respectively) (Hodges-Lehmann, median absolute difference of -1.01 VOC per year compared with placebo, 95%CI [-2.00, 0.00]), which was statistically significant ( $p=0.010$ ).

Crizanlizumab 5 mg/kg provided a clinical benefit over placebo in most relevant disease-related subgroups, independent of genotype, or of whether patients were receiving concomitant HU/HC. Additional supportive data include a delay in time to first and second VOC leading to a healthcare visit with a median time to first VOC of 4.07 versus 1.38 months and time to second VOC of 10.32 vs 5.09 months. The benefits of decrease in annual VOC rates is considered clinically meaningful given the morbidity and increase hospitalizations and emergency room visits in patients with VOCs.

The safety profile of crizanlizumab is based on data from 175 patients with sickle cell disease (SCD) from 2 clinical studies (randomized Study A2201 and single arm Study A2202), who received at least 1 infusion of crizanlizumab at a dose of 2.5 mg/kg (N=64) or 5 mg/kg (N=111). Among the 111 patients exposed to the recommended dose of 5 mg/kg, the median (min-max) duration of exposure was 34 weeks (< 1 to 57 weeks), and 75 of the 111 patients (67.6%) were treated in combination with hydroxyurea/hydroxycarbamide (HU/HC). The primary safety evaluation was based on the Study A2201 with recommended dose of 5mg/kg (N=66) compared to placebo(N=63).

The overall frequency of TEAEs (86.4% vs. 88.7%), severe AEs (grade  $\geq 3$ ; 18.2% vs. 19.4%), SAEs (25.8% vs. 27.4%) and AEs leading to treatment discontinuation (3.0% vs. 4.8%) was similar between the crizanlizumab 5 mg/kg and placebo arms in Study A2201.

Across all clinical studies included in this BLA, crizanlizumab demonstrated an acceptable safety and tolerability profile that supports the proposed registration dose of 5 mg/kg by intravenous (IV) infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter (10 mg/mL).

Overall, crizanlizumab 5 mg/kg demonstrated a decrease in the frequency of annualized VOCs and a delay in time to VOC compared to placebo. The potential long-term decrease in occurrence of VOCs may result in decreased organ damage and complications. The results showed a decrease in reduction of annual rate of VOCs leading to healthcare visit independent of concurrent HU/HC use.

The Applicant's proposed indication is for the prevention of vasoocclusive crises in sickle cell

disease patients aged 16 years and older. The Agency recommends that the indication be for the reduction in frequency of VOCs as the description of prevention of VOCs appears to overstate the efficacy of the product. Therefore, the recommend indication is to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

Given the potential long-term use of this product, the long term safety follow-up will be important considerations and will be addressed in postmarketing requirements.

#### Recommendations

In conclusion, sickle cell disease is a serious and life-threatening condition associated with recurrent vasoocclusive pain or crises episodes and chronic hemolytic anemia. The benefit-risk of crizanlizumab 5mg/kg administered over a 30 minute IV infusion at Week 0, Week2 and every 4 weeks thereafter provides meaningful clinical benefit with an acceptable risk profile for patients with sickle cell disease. Recommend approval of crizanlizumab to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease.

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X

Yaping Wang, PhD  
Primary Statistical Reviewer

X

Yeh-Fong Chen, PhD  
Statistical Team Leader

X

Patricia Oneal, MD  
Rosanna Setse, MD, PhD  
Primary Clinical Reviewers

X

Tanya Wroblewski, MD  
Clinical Team Leader

## **9 Advisory Committee Meeting and Other External Consultations**

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This application was not presented at an Advisory Committee or to any other external consultants. Presentation was not needed because the Division is familiar with the endpoints, trial design, and control arms.

## 10 Pediatrics

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SelG1 received Orphan Designation (#08-2597) for the treatment of vasoocclusive crisis in patients with sickle cell disease on July 22, 2008. With this designation, Novartis is exempted from the submission and approval of a Pediatric Study Plan as required under the Pediatric Research Equity Act (PREA).

(b) (4)



## 11 Labeling Recommendations

### 11.2 Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Indications and Usage	(b) (4) blocker indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease	Selectin blocker indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease
Dosage and Administration	Administer 5 mg/kg by intravenous infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter	Administer 5 mg/kg by intravenous infusion over a period of 30 minutes on Week 0, Week 2, and every 4 weeks thereafter
Warnings and Precautions	Infusion-related reactions and Laboratory Test Interference	In the SUSTAIN clinical trials, infusion-related reactions (defined as occurring within 24 hours of infusion) were observed in 2 (3%) patients treated with ADAKVEO 5 mg/kg. Monitor patients for signs and symptoms of infusion-related reactions, which may include fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath or wheezing. Discontinue ADAKVEO infusion for severe reactions and institute appropriate medical care.  Interference with automated platelet counts (platelet clumping) has been observed

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
		following administration of ADAKVEO, in particular, when blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA). Mitigation strategies are recommended.
Clinical Trials Experience	Percentage of serious adverse reactions were not included.	The percentage of serious adverse reactions were included.
Clinical Studies	Efficacy results included median time to first VOC from randomization in Table 3.	This information was removed from the table and placed in text.

The Applicant's submitted proposed Prescribing Information (PI) and Patient Labeling were reviewed for consistency with the labeling regulations and guidances; to ensure that the PI is a useful communication tool for healthcare providers; and uses clear, concise language. All disciplines contributed to the revisions of the PI. As labeling negotiations are ongoing, these recommendations should be considered preliminary and may not represent DHP's final recommendations for the ADAKVEO labeling.

## **12 Risk Evaluation and Mitigation Strategies (REMS)**

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A REMS is not necessary for this application. No new safety issues were identified that would require a REMS. Labeling is adequate to communicate the risks of ADAKVEO.

## 13 Postmarketing Requirements and Commitment

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The following are the draft proposed PMRs and PMCs for this application.

### **Post marketing Requirements under 505(O)**

**PMR 3741-1** Develop and validate a neutralizing antibody assay (NADA) to test confirmed anti-drug antibody positive samples from studies CSEG101 A2102, A2202 and A2301. The assay should be capable of detecting NADA responses in the presence of crizanlizumab levels that are expected to be present in the serum at time of subject sampling.

Final Report Submission: 12/2020

**PMR 3741-2** Assess neutralizing anti-drug antibody (NADA) responses with a validated NADA assay. NADA response will be evaluated in all confirmed ADA positive samples from studies CSEG101 A2102, A2202 and the primary analysis of A2301.

Study Completion: 12/2025  
Final Report Submission: 12/2025

Provide a final report and include information on the level of crizanlizumab in each sample at each sampling point.

**PMR 3741-3** Complete Study A2202: Phase 2 Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Sickle Cell Patients with Vaso-Occlusive Crisis (SOLACE-adults) and evaluate the serious risks of infusion related reactions, bleeding complications, and infections.

Interim Report (Primary Analysis Report): 12/2019  
Trial Completion: 06/2025  
Final Report Submission: 12/2025

In the primary analysis report include an updated evaluation of infusion related reactions, bleeding complications, and infection.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission or earlier if trial is completed earlier.

**PMR 3741-4** Complete Study B2201: Phase II, Multicenter, Open-label study to Access Appropriate Dosing and to Evaluate Safety of Crizanlizumab, with or without Hydroxyurea in Sequential, Descending Age Groups of Pediatric Sickle Cell Disease Patients with Vasoocclusive Crises and evaluate the serious risks of infusion related reactions, bleeding complications and infections.

Interim Report (Primary Analysis Report):	03/2023
Trial Completion:	06/2025
Final Report Submission:	12/2025

In the primary analysis report include an updated evaluation of infusion related reactions, bleeding complications, and infection, and any information on efficacy.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission.

**PMR 3741-5** Complete Study A2301 of Crizanlizumab in Adolescents and Adults ( $\geq 12$  years of age), a randomized, comparative dose study that compares 7.5 mg/kg dosing and 5.0 mg/kg dosing versus placebo. Assess the serious risks of infusion related reactions, bleeding complications, and infections.

Interim /Other (Primary Analysis Report):	12/2025
Trial Completion:	06/2029
Final Report Submission:	12/2029

In the primary analysis report include an updated evaluation of infusion related reactions, bleeding complications, and infection, and any information on efficacy.

In the final report submission, include full summary analysis (updated description of safety and efficacy data) and datasets at the time of the final report submission.

**PMR 3741-6** Assess immunogenicity of crizanlizumab, including anti-drug antibodies (ADA) and neutralizing anti-drug antibodies (NADA) in

all crizanlizumab-treated subjects in Study A2301. Evaluate the effect of immunogenicity on pharmacokinetics, pharmacodynamics, safety and efficacy of crizanlizumab.

Trial Completion: 12/2025  
Final Report Submission: 12/2025

In the primary analysis report include the complete immunogenicity data set, information on the drug product lots administered to each patient, the ADA status and titers, the NADA status and the level of drug in each patient's test sample at the specific sampling point.

**Postmarketing Commitments subject to reporting requirements under section 506B**

**PMC 3741-7** Demonstrate whether crizanlizumab induces myeloid cell-dependent effector functions using [REDACTED] (b) (4). If cell-dependent effector functions are identified as confirmed or potential activities for crizanlizumab, develop and implement an appropriate control strategy that monitors antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis.

Final Report Submission: 02/2020

**PMC 3741-8** Submit an Integrated Summary of Immunogenicity that describes the totality of the immunogenicity program, as recommended in Section VIII Documentation of the 2019 FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection.

Study Completion: 12/2025  
Final Report Submission: 12/2025

Submit the ISI report to eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study.

**Postmarketing Commitments not subject to the reporting requirements under section 506b**

**PMC 3741-9** Perform real-time shipping validation studies, per [REDACTED] (b) (4) [REDACTED] to support the stability of crizanlizumab drug product vials from the drug product manufacturing facility in Switzerland to the US.

Final Report Submission: 01/2020

**PMC 3741-10** Re-evaluate and, as applicable, revise the release and stability specifications for crizanlizumab drug substance (DS) and drug product (DP) based on the product quality attribute test results of clinical batches used in clinical studies.

Final Report Submission: 12/2025

**PMC 3741-11** Develop an endotoxin detection method capable of detecting endotoxin from crizanlizumab DP release samples.

Final report submission: 12/2020

## **14 Division Director (DHOT)**

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X

## **15 Division Director (OCP)**

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X

## **16 Division Director (OB) Comments**

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X

## 17 Division Director (Clinical) Comments

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(This review relies in part in the reviews of Drs. Tanya Wroblewski, Yaping Wang, Patricia O’Neal and Rosanna Setse.)

**Background:** Novartis submitted BLA 761128 for Crizanlizumab (ADAKVEO) as a rolling review on the following dates: February 19, 2019, March 15, 2019, March 29, 2019, April 30, 2019, and May 16, 2019. In this BLA, Novartis asked for approval of crizanlizumab, an IgG2 antibody to P-selectin, a glycoprotein on the surface membrane of activated endothelium and platelets. P-selectin contributes to the adhesive interactions between platelets, leukocytes and activated endothelial cells. Once tethered to the endothelial cell by P-selectin, the neutrophil is further activated, in a process called “priming” by interaction with Platelet Activating Factor. The interaction between P-selection and its ligand, P-selectin Glycoprotein Ligand 1 (PSGL-1) induces an enhancement of aggregation of platelets and thrombus formation. These processes can be blocked by the binding of P-selectin to crizanlizumab or by binding of an antibody to the PAF receptor on the neutrophil. These actions by crizanlizumab are predicted to lead to the reduction of vasoocclusive crises in patients with sickle cell disease (SCD). Accordingly, Novartis has requested approval of crizanlizumab for the following indication: to reduce the frequency of vasoocclusive crises (VOC) in adults and pediatric patients aged 16 years and older with sickle cell disease.

This requested indication relied on the SUSTAIN trial, a phase 2 trial of 198 patients with SCD of any genotype, who had a history of 2-10 vasoocclusive crises in the past year. These patients were randomized to one of 3 arms: placebo (N=65), crizanlizumab 2.5 mg/kg (N=66) or crizanlizumab at 5 mg/kg (N=67) and treated on day 0 and 14 and then monthly thereafter for a total of 52 weeks. The randomization was stratified by whether the patients were receiving concomitant hydroxyurea and by the number of VOCs in the previous year (2 to 4, 5 to 10). The primary endpoint was the annualized rate of VOC leading to a healthcare visit.

**Efficacy Results:** The patients on crizanlizumab at 5 mg/kg showed a lower median annual rate of VOC compared to patients on placebo (1.63 vs 2.98 respectively) (95% CI: -2.00, 0.00) that was statistically significant ( $p=0.010$ ). The annual rate of days hospitalized was 4 among those patients receiving 5 mg/kg of crizanlizumab as compared to 6.87 days among those patients receiving placebo. There was a three-fold increase in the median time to the first VOC (4.07 vs. 1.38 months, HR=0.495 (95%CI: 0.331, 0.741) and a two-fold increase in the time to second VOC (10.2 vs 5.09 months, HR=0.534 (95%CI: 0.329, 0.866) leading to a health care visit.

**Safety Results:** There were 4 on study deaths none of which were attributable to crizanlizumab. Back pain, nausea, pyrexia and arthralgia were the most commonly encountered adverse drug reaction in the safety population among those occurring at greater than 10%. Most of these

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were grade 1 or 2. There was one patient each with pyrexia and pain that had a grade 3 adverse drug reaction. There were no drug discontinuations due to an adverse drug reaction.

**Benefit Risk Discussion:** The benefit was significant in terms of reduction of the frequency of VOCs was not outweighed by the toxicity observed.

**Regulatory Action Recommended by A. Deisseroth, Supervisory Associate Division Director:**  
Approval.

X

## **18 Office Director (or designated signatory authority) Comments**

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X \_\_\_\_\_

## 19 Appendices

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### 19.2 References

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### 19.3 Financial Disclosure

The Applicant requested financial disclosures from all investigators participating in the clinical trials supporting this BLA.

#### Covered Clinical Study (Name and/or Number): Studies A2201 and A2202

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>83</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

## 19.4 Nonclinical Pharmacology/Toxicology

### 19.5 OCP Appendices (Technical documents supporting OCP recommendations)

#### 19.5.1 Summary of Bioanalytical Method Validation and Performance

**Table 29. Bioanalytical method performance summary: PK assay for Novartis-manufactured crizanlizumab (SEG101) and Reprixys-manufactured crizanlizumab (SelG1) in serum**

<b>Bioanalytical method validation report name, amendments, and hyperlinks</b>	Quantitative determination of crizanlizumab in human serum by ELISA [DMPK R1600631-pk] [DMPK R1600631-pk-01]
<b>Method description</b>	ELISA assay was used to quantify crizanlizumab in human serum samples. The method was based on the capture of SEG101/SelG1 in serum samples, calibration standards, and quality controls by human P-selectin. Human P-selectin then binds to a mouse anti-human P-selectin mAb, coated on the plate. The detection was done with a biotinylated goat anti-human IgG conjugated to streptavidin-HRP followed by the addition of a chromogenic substrate (TMB).
<b>Materials used for calibration curve &amp; concentration</b>	SEG101; Lot# 1010012967, 84.3 mg/mL
<b>Validated assay range</b>	150 to 5000 ng/mL SEG101 in human serum
<b>Material used for QCs &amp; concentration</b>	SEG101; Lot# 1010012967, 84.3 mg/mL
<b>Minimum required dilutions (MRDs)</b>	50

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<b>Source &amp; lot of reagents (LBA)</b>	<p>Mouse Anti Human P-Selectin Antibody Lot# W40-2016, 2.2 mg/mL, Supplier: Novartis</p> <p>Recombinant Human P-Selectin Lot# (b) (4) 5816071, 20 µg/mL, Supplier: (b) (4),</p> <p>Biotin Mouse Anti-Human IgG2 Lot# 6232634, 0.5 mg/mL, Supplier: (b) (4)</p>		
<b>Regression model &amp; weighting</b>	4-Parameter Logistic (4PL) fit (1/Y <sup>2</sup> weighting)		
<b>Validation parameters</b>	<b>Method validation summary</b>	<b>Acceptability</b>	
<b>Standard calibration curve performance during accuracy &amp; precision</b>	Number of standard calibrators from LLOQ to ULOQ	8 calibrators from 150 ng/mL (LLOQ) to 5000 ng/mL (ULOQ) and 2 anchoring points (100 and 7000 ng/mL)	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.3 to 4.0%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 9.9%	Acceptable
<b>QCs performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) in 5 QCs	-14.7% to 12.7%	Acceptable*
	Inter-batch %CV	9.1% to 19.6%	Acceptable*
	Total Error (TE)	≤ 20.6%	Acceptable*
<b>Selectivity &amp; matrix effect</b>	15 healthy human serum batches tested., All blank samples below LLOQ; 15 spiked samples with bias within ± 21.3%	Acceptable	
<b>Interference &amp; specificity</b>	Not assessed	N/A	
<b>Hemolysis effect</b>	5 lots tested, all blank samples below LLOQ, 5 spiked samples at LLOQ with bias within ± 18.7%	Acceptable	
<b>Lipemic effect</b>	5 lots tested, all blank samples below LLOQ, 5 spiked samples at LLOQ with bias within ± 21.3%	Acceptable	
<b>Dilution linearity &amp; hook effect</b>	<p>Dilution linearity was investigated by analysing 1 additional QC spiked with SEG101 at a concentration higher than the ULOQ to reach a concentration of 200, 500, 1000, 2000 and 4000 ng/mL (within the quantification range). Dilution factors of: 1: 250, 1: 500, 1: 1000, 1: 2000 and 1:5000 were tested. No apparent dilution effect was observed up to at least a 1: 5000 dilution as observed bias was below 6.5%</p> <p>Hook effect was investigated by analysing 1 QC spiked with SEG101 at 1.0 mg/mL which was serially diluted to reach a concentration above the upper range of the assay at 8000, 40000 and 200000 ng/mL. All hook effect samples exhibited signal response above the ULOQ, confirming the absence of hook effect</p>	Acceptable	

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<b>Bench-top/process stability</b>	At room temperature and refrigerated temperature: up to 24 h	Acceptable																																																																																																																																																																									
<b>Freeze-Thaw stability</b>	Stable after 6 freeze-thaw cycles in the deep freezer	Acceptable																																																																																																																																																																									
<b>Long-term storage</b>	Stable in human serum for up to 359 days in deep freezer. (Long term stability is still ongoing).	Acceptable																																																																																																																																																																									
<b>Parallelism</b>	6 human serum samples from study CSEG101A2102 were analyzed at different dilutions within quantification range. In all cases, precision was below 7.02 % meeting predefined acceptance criteria.	Acceptable																																																																																																																																																																									
<b>Carry over</b>	Not applicable	N/A																																																																																																																																																																									
<p>* In the "Special issues" section of report DMPK R1600631-pk, the sponsor stated that accuracy and precision assessments were performed over 7 runs. Six (6) out of the 7 runs demonstrated acceptable intra-assay precision and bias. Run 7 however showed outlier value at LQC, poor intraassay %bias for the MQC (22.7% bias) and poor intra assay% precision (39.0% CV) for the ULOQ.</p> <table border="1"> <thead> <tr> <th>Date of analysis</th> <th>Run ID</th> <th>Duplicate</th> <th>LLOQ (150 ng/mL)</th> <th>%Bias</th> <th>LQC (400 ng/mL)</th> <th>%Bias</th> <th>MQC (1500 ng/mL)</th> <th>%Bias</th> <th>HQC (3750 ng/mL)</th> <th>%Bias</th> <th>ULOQ (5000 ng/mL)</th> <th>%Bias</th> </tr> </thead> <tbody> <tr> <td colspan="13" style="text-align:center">Back-calculated SEG101 concentration in Human Serum (ng/mL)</td> </tr> <tr> <td>12-Sep-2017</td> <td>Run07</td> <td>1</td> <td>181</td> <td>7.3</td> <td>450</td> <td>12.5</td> <td><b>1920</b></td> <td>28.0</td> <td>4220</td> <td>12.5</td> <td><b>2900</b></td> <td>-42.0</td> </tr> <tr> <td></td> <td></td> <td>2</td> <td>169</td> <td>12.7</td> <td>406</td> <td>1.5</td> <td><b>1870</b></td> <td>24.7</td> <td>4380</td> <td>16.8</td> <td>5710</td> <td>14.2</td> </tr> <tr> <td></td> <td></td> <td>3</td> <td>153</td> <td>2.0</td> <td>448</td> <td>12.0</td> <td><b>1850</b></td> <td>23.3</td> <td>4280</td> <td>14.1</td> <td><b>3320</b></td> <td>-33.6</td> </tr> <tr> <td></td> <td></td> <td>4</td> <td>163</td> <td>8.7</td> <td>400</td> <td>0.0</td> <td>1700</td> <td>13.3</td> <td>4020</td> <td>7.2</td> <td>6010</td> <td>20.2</td> </tr> <tr> <td></td> <td></td> <td>5</td> <td>169</td> <td>12.7</td> <td><b>1200</b></td> <td>200.0</td> <td>1760</td> <td>17.3</td> <td><b>4880</b></td> <td>30.1</td> <td><b>6250</b></td> <td>25.0</td> </tr> <tr> <td></td> <td></td> <td>6</td> <td><b>272</b></td> <td>81.3</td> <td>414</td> <td>3.5</td> <td><b>1930</b></td> <td>28.7</td> <td>3680</td> <td>-1.9</td> <td><b>2430</b></td> <td>-51.4</td> </tr> <tr> <td colspan="3">Intra-assay Mean</td> <td>181</td> <td></td> <td><b>553</b></td> <td></td> <td><b>1840</b></td> <td></td> <td>4240</td> <td></td> <td><b>4440</b></td> <td></td> </tr> <tr> <td colspan="3">Intra-assay Stdev</td> <td>44.9</td> <td></td> <td>318</td> <td></td> <td>91.1</td> <td></td> <td>398</td> <td></td> <td>1730</td> <td></td> </tr> <tr> <td colspan="3">Intra-assay%CV</td> <td>24.8</td> <td></td> <td>57.4</td> <td></td> <td>5.0</td> <td></td> <td>9.4</td> <td></td> <td>39.0</td> <td></td> </tr> <tr> <td colspan="3">Intra-assay%Bias</td> <td>20.7</td> <td></td> <td>38.3</td> <td></td> <td>22.7</td> <td></td> <td>13.1</td> <td></td> <td>-11.2</td> <td></td> </tr> <tr> <td colspan="3">n</td> <td>6</td> <td></td> <td>6</td> <td></td> <td>6</td> <td></td> <td>6</td> <td></td> <td>6</td> <td></td> </tr> </tbody> </table> <p>Data source: Table 7.4 of report DMPK R1600631-pk</p> <p>As the poor intra-assay precision and bias observed in Run 7 was not seen in the other 6 runs, the sponsor thought it was an analytical issue related to that particular plate rather than inherent poor performance within the assay. The sponsor then decided to present data for accuracy and precision excluding this run (Table 7-5) and including this Run 07 (Table 7-4).</p> <p><b>Review comment:</b> Based on Applicant provided information, FDA agrees that the Run 7 data can be excluded when calculating accuracy and precision.</p>			Date of analysis	Run ID	Duplicate	LLOQ (150 ng/mL)	%Bias	LQC (400 ng/mL)	%Bias	MQC (1500 ng/mL)	%Bias	HQC (3750 ng/mL)	%Bias	ULOQ (5000 ng/mL)	%Bias	Back-calculated SEG101 concentration in Human Serum (ng/mL)													12-Sep-2017	Run07	1	181	7.3	450	12.5	<b>1920</b>	28.0	4220	12.5	<b>2900</b>	-42.0			2	169	12.7	406	1.5	<b>1870</b>	24.7	4380	16.8	5710	14.2			3	153	2.0	448	12.0	<b>1850</b>	23.3	4280	14.1	<b>3320</b>	-33.6			4	163	8.7	400	0.0	1700	13.3	4020	7.2	6010	20.2			5	169	12.7	<b>1200</b>	200.0	1760	17.3	<b>4880</b>	30.1	<b>6250</b>	25.0			6	<b>272</b>	81.3	414	3.5	<b>1930</b>	28.7	3680	-1.9	<b>2430</b>	-51.4	Intra-assay Mean			181		<b>553</b>		<b>1840</b>		4240		<b>4440</b>		Intra-assay Stdev			44.9		318		91.1		398		1730		Intra-assay%CV			24.8		57.4		5.0		9.4		39.0		Intra-assay%Bias			20.7		38.3		22.7		13.1		-11.2		n			6		6		6		6		6	
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<b>Method performance in Study SEG101A2102</b> A Phase I single dose, randomized, open-label, parallel group, single-center trial to assess the comparability of crizanlizumab pharmacokinetics and pharmacodynamics administered as SEG101 in comparison to SelG1 in healthy subjects Bioanalytical data report: [Determination of SEG101 in human serum DMPK RCSEG101A2102-pk]																																																																																																																																																																											
Assay passing rate	51 runs were accepted from the 60 runs performed for Sample analysis or ISR	Acceptable																																																																																																																																																																									
Standard curve performance	Bias from LLOQ to ULOQ within $\pm 3.0\%$ Precision from LLOQ to ULOQ $\leq 5.4\%$	Acceptable																																																																																																																																																																									
QC performance	Bias range from 3.7 to 6.0% Precision $\leq 19.2\%$ Total error not assessed during sample analysis	Acceptable																																																																																																																																																																									

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Method reproducibility	Incurred sample reanalysis was done in 111 samples out of 1203 (9.2%). 102 samples out of 111 (92%) met the pre-specified acceptance criteria	Acceptable
Study sample analysis/ stability	Sample analysis were performed within a maximum of 116 days after sample collection.	Acceptable
<b>Method performance in Study SEG101A2202</b>		
A phase 2, Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Adult Sickle Cell Patients with Vaso-Occlusive Crisis Interim bioanalytical data report: [Determination of SEG101 in human serum DMPK RCSEG101A2202-pk]		
Assay passing rate	34 runs were accepted from the 47 runs performed for sample analysis or ISR	Acceptable
Standard curve performance	Bias from LLOQ to ULOQ within $\pm 3.0\%$ Precision from LLOQ to ULOQ $\leq 5.4\%$	Acceptable
QC performance	Bias range from 4.7 to 9.8% Precision $\leq 9.9\%$	Acceptable
Method reproducibility	Incurred sample reanalysis was done in 56 samples out of 1282 ((4.3%). Note that A2202 study is still ongoing and additional ISR will be performed when additional samples will be available. 51 samples out of 56 (91%) met the pre-specified acceptance criteria	Acceptable
Study sample analysis/ stability	Sample analysis were performed within a maximum of 225 days after sample collection. Note that A2202 study is still ongoing, sample stability will be further assessed during the course of the study.	Acceptable.

**Table 30. Bioanalytical method performance summary: PD assay for Novartis-manufactured crizanlizumab (SEG101) and Reprixys-manufactured crizanlizumab (SelG1) in serum**

<b>Bioanalytical method validation report name, amendments, and hyperlinks</b>	Validation Report: Pharmacodynamic (PD) Assay for Analysis of SEG101 and SelG1 in Serum Using Pioneer Surface Plasmon Resonance (SPR) System [RPT-01398] Addendum to Validation Report RPT-01398 for Specimen Longevity [RPT-10019] Addendum to Validation Report RPT-01398: Biotinylated GSnP6 Qualification Report [RPT-10013]
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<p><b>Method description</b></p>	<p>The SPR-based PD assay is a label free system to measure the inhibition of P-Selectin-PSGL-1 interaction by SEG101 (test article) and SelG1 (reference article) in serum samples from human donors treated with these investigational agents. SEG101 and SelG1 blockage is measured as %inhibition of spiked PSEL-Ig (P-selectin fused to immunoglobulin) binding to Glycosulfopeptide 6 (GSP-6), a peptide analogue mimicking PSGL-1 binding domain. Initially, streptavidin is immobilized on two channels (FC-2 and FC-3) of the biosensor chip using standard amine coupling followed by injection of biotinylated GSP-6 to immobilize the peptide for analysis. A reference channel (FC-1) is prepared by biotin-blocking streptavidin. Sensor regeneration is performed to condition and stabilize the GSP-6 (or GSnP-6) sensor chip by injecting Regeneration Solutions 1 and 2 for at least three times. Each assay run should include a Negative Control (NC; 50% Pooled Normal Human Serum (PNHS) in dilution buffer), two sets of Positive Control (PC; 50% PNHS with 5 µg/mL PSEL-Ig in dilution buffer), and three QC samples (QCs) at three concentrations (10, 5, and 3 µg/mL) of SEG101 or SelG1. QCs are prepared in neat PNHS, being tested at the beginning and end of the run. The NC and PC are normalization controls used to calculate % inhibition of the SEG101 or SelG1 fortified/dosed samples. The NC represents baseline response of the immobilized SA-biotin-blocked surface of reference flow channel 1 (FC-1). The NC is mixed (1:1) with dilution buffer without PSEL-Ig prior to plating for analysis. The PC represents maximum PSEL-Ig binding response to the immobilized SA-biotinylated-GSP6 complex over FC-2 and FC-3. PCs and SEG101/SelG1 samples are mixed (1:1) with a solution of 5 µg/mL PSEL-Ig in dilution buffer. Samples are allowed to equilibrate after mixing for at least 1 hour before injection on to the biosensor for PD assessment. For testing of clinical serum samples treated with SEG101 or SelG1, the pre-dose sample will be used as the donor specific negative and positive controls. Thus, the pre-dose sample will be mixed (1:1) with dilution buffer without PSEL-Ig to represent the baseline response (i.e., NC) and also mixed (1:1) with 5 µg/mL PSEL-Ig in dilution buffer to represent maximum response (i.e, PC). Corresponding post-dose samples, similar to the PC sample, will be mixed (1:1) with a solution of 5 µg/mL PSEL-Ig in dilution buffer and % inhibition values calculated utilizing the formula: % inhibition of sample n: <math display="block">= 100\% - \% \text{ binding}</math><math display="block">= 100\% - \frac{RU_n - RU_{NC}}{(RU_{PC1} - RU_{NC}) - \frac{(RU_{PC1} - RU_{NC}) - (RU_{PC2} - RU_{NC})}{\text{Max cycle \#} - 2} \times n} \times 100\%</math>Each assay cycle will encompass injection of test serum sample over the reference FC-1 channel (biotin blocked channel) and over the biotinylated GSP-6 channels (FC-2 &amp; FC-3) for 3 minutes followed by biosensor regeneration as described above (2 minute injections each). All serial samples from a treated donor are tested on a single biosensor chip/analytical run in the following sequence for each subject/donor: negative control, positive control, post-dose samples and second replicate of positive control.</p>
<p><b>Materials used for inhibition curve &amp; concentration</b></p>	<p>SEG101 and SelG1 were used to generate the inhibition curve in pooled normal human serum at the following concentrations: 192, 96, 48, 24, 12,10, 6, 5, 3, 1.5, 0.75 µg/mL</p>

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<b>Validated assay range</b>	Inhibition range were established from 10.4% (LLOQ) to 100% (ULOQ) for SEG101 and from 20.8% to 100% for SelG1. LLOQ of the assay was adjusted to 9.2% for SEG101 following change of GSP6 reagent		
<b>Material used for QCs &amp; concentration</b>	Pooled normal human serum was used to prepare SEG101 QCs at concentrations of: 10 µg/mL, 5 µg/mL, 3 µg/mL, and 1.5 µg/mL The 1.5 µg/mL concentration was used only post qualification of new GSnP6-Biotin reagent.		
<b>Minimum required dilutions (MRDs)</b>	1:2		
<b>Source &amp; lot of reagents (LBA)</b>	P-selectin-T-IgG, Novartis Pharma AG, lot 110774 GSP6-Biotin, (b) (4), Lot 25-May-2017 GSnP6-biotin, (b) (4) Lot (b) (4)-8-093-F6		
<b>Regression model &amp; weighting</b>	4-PL curve fit used for determination of IC50.		
<b>Validation parameters</b>	<b>Method validation summary</b>	<b>Acceptability</b>	
<b>Inhibition curve performance during accuracy &amp; precision</b>	Number of inhibition curve points from LLOQ to ULOQ	11	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Not applicable	N/A
	Cumulative precision (%CV) from LLOQ to ULOQ	From 0.4 to 19.2% for SEG101 From 0.5 to 21.0% for SelG1	Acceptable
<b>QCs performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) in 5 QCs times 3	From 0.6 to 14.3% recovery for SEG101 From 1.2 to 18.4% recovery for SelG1	Acceptable
	Inter-batch %CV	≤ 21.9% for SEG101 ≤ 10.7% for SelG1	Acceptable
	Total Error (TE)	Not applicable as nominal inhibition values are not available	N/A
<b>Selectivity &amp; matrix effect</b>	Not applicable as the inhibition result is computed as function of the individual patients' pre-treatment sample.		N/A

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<b>Interference &amp; specificity</b>	Interference: equivalent inhibition values were observed in healthy volunteers and SCD patient sera. Specificity not tested as the intrinsic design of the assay method demonstrates assay specificity. Pooled normal human serum (blank) is tested with PSeI-Ig (Positive Control) and without PSeI-Ig (Negative Control). The value for blank serum sample without PSeI-Ig is subtracted from the PSeI-Ig spiked samples. Test samples are injected over a reference channel (coated with biotin only) and two channels coated with GSP6 biotin. The RU response from reference channel is subtracted from the GSP6 (GSnP6)-biotin RU response.	Acceptable
<b>Hemolysis effect</b>	Not assessed during method validation; No hemolysis effect was observed based on retrospective analysis of samples from patients enrolled in A2301 study (study ongoing, no report available).	N/A
<b>Lipemic effect</b>	Not tested	N/A
<b>Dilution linearity &amp; hook effect</b>	Highest concentration tested and number of dilution factors: 192 µg/mL followed by ten 2-fold dilutions down to 0.75 µg/mL Range of observed bias: Not applicable as nominal inhibition values are not available (no gold standard).	Acceptable
<b>Bench-top/process stability</b>	SEG101 and SelG1 stable on the bench-top for up to 5 hours	Acceptable
<b>Freeze-Thaw stability</b>	SEG101 and SelG1 stable up to three freeze-thaw cycles	Acceptable
<b>Long-term storage at -20°C and -80°C</b>	Long-term stability established up to 94 days at -20°C for SEG101 and SelG1. Long term stability established up to 375 days at -80°C for SEG101 and SelG1. Lon-term stability is ongoing up to 2 years.	Acceptable
<b>Parallelism</b>	In absence of a gold standard, parallelism was performed by comparing different concentrations of SEG101 and SelG1 in serum from SCD patients (n=5) and healthy volunteers (n=7). IC50 was comparable in both SCD and healthy volunteers as shown below.	Acceptable
<b>Carry over</b>	Not applicable	N/A
<p><b>Review comment:</b> <i>This PD assay was designed measure the % inhibition of spiked PSeI-Ig binding to GSP-6 by SEG101 (test article) and SelG1 (reference article) in serum samples from human donors treated with these investigational agents, which aimed to mimic the inhibition effect of SEG101 and SelG1 on P-Selectin-PSGL-1 interaction in vivo.</i></p> <p><i>At concentrations ≥ 12 µg/mL, both SEG101 (test article) and SelG1 (reference article) caused nearly complete inhibition of PSeI-Ig-GSP-6 binding. The (≥ 99%). Therefore, the PD assay may not differentiate any potential potency difference between SEG101 (test article) and SelG1 (reference article). At concentrations ≤ 10 µg/mL, both SEG101 (test article) and SelG1 (reference article) exhibited concentration dependent inhibition on PSeI-Ig-GSP-6 binding. The estimated IC<sub>50</sub> for SEG101 and SelG1 are 5.2 µg/mL and 5.6 µg/mL, respectively. Based on the % inhibition data of SEG101 and SelG1 at concentrations ≤ 10 µg/mL, the PD assay is acceptable.</i></p>		

<b>Method performance in Study SEG101A2102</b>						
A Phase I single dose, randomized, open-label, parallel group, single-center trial to assess the comparability of crizanlizumab pharmacokinetics and pharmacodynamics administered as SEG101 in comparison to SelG1 in healthy subjects						
Determination of SEG101 and SelG1 pharmacodynamics (P-selectin binding inhibitory effect) in human serum by Surface Plasmon Resonance analysis [RPT-01430]						
<b>Assay passing rate</b>	95% (18 out of 19 runs)					Acceptable
<b>Standard curve performance</b>	Not applicable					N/A
<b>QC performance</b>	QC Level	Cumulative %Inhibition	n	Cumulative %CV	Acceptance Range	Acceptable
	HQC	100.0%	36	0.0	73.9% to 100.0%	
	MQC	45.6%	36	12.3%	36.2% to 60.3%	
	LQC	21.8%	31	12.5%	17.0% to 28.3%	
<b>Method reproducibility</b>	Incurred sample reanalysis was not performed in SEG101A2102 study.					N/A
<b>Study sample analysis/stability</b>	Long term matrix stability is in progress up to 2 years at -80°C. Stability for SEG101 and SelG1 established up 375 days at -80°C which covers the duration of the sampling in the clinical study.					Acceptable
<b>Method performance in Study SEG101A2202</b>						
A phase 2, Multicenter, Open-Label Study to Assess PK/PD of SEG101 (crizanlizumab), with or without Hydroxyurea/Hydroxycarbamide, in Adult Sickle Cell Patients with Vaso-Occlusive Crisis						
Interim bioanalytical data report: DMPK RCSEG101A2202-pd [Bar-10001]						
<b>Assay passing rate</b>	100% (9 out of 9 runs)					Acceptable
<b>Standard curve performance</b>	Not applicable					N/A
<b>QC performance</b>	QC Level	Cumulative % Inhibition	n	Cumulative % CV	Acceptance Range	Acceptable.
	HQC	99.4	18	2.5%	75.0% to 100.0%	
	MQC	49.1	18	12.1%	39.8% to 66.4%	
	LQC	16.4	14	19.5%	12.8% to 21.4%	
<b>Method reproducibility</b>	Incurred sample reanalysis was performed in 8.6% of study samples and 98.2% of samples met the pre-defined ISR criteria.					Acceptable
<b>Study sample analysis/stability</b>	Long term matrix stability is in progress up to 2 years at -80°C. Stability for SE101 and SelG1 established up 375 days at -80°C which covers the duration of the sampling in the clinical study.					Acceptable

**Table 31. Bioanalytical method performance summary: PK assay for Reprixys-manufactured crizanlizumab (SelG1) in serum**

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<b>Bioanalytical method validation report name, amendments, and hyperlinks</b>	Qualification of SelG1 pK ELISA for Activity in Serum Samples [MVR-0062-00] [MVR-0062-00-W-1] [MVR-0062-01]		
<b>Method description</b>	A sandwich ELISA was used to detect SelG1 in serum. Mouse anti-human P-selectin antibody was coated on a 96-well high bind immunoplate and then blocked using a non-specific protein. The plate is then coated a second time using soluble human P-selectin. Quantified SelG1 used to prepare standards and QCs is then added to designated sample wells. The assay was visualized by the subsequent additions of biotinylated goat anti-human IgG, streptavidin-HRP and a chromogenic substrate (TMB). The concentration of SelG1 in samples is then back-calculated from a calibration curve		
<b>Materials used for calibration curve &amp; concentration</b>	SelG1, 0.10 mg/mL (lot and expiry date not provided in report)		
<b>Validated assay range</b>	0.625 to 10.0 ng/mL		
<b>Material used for QCs &amp; concentration</b>	SelG1, 0.10 mg/mL (lot and expiry date not provided in report)		
<b>Minimum required dilutions (MRDs)</b>	1000 and 10000 (cynomolgus) 100 (human)		
<b>Source &amp; lot of reagents (LBA)</b>	Mouse Anti Human P-Selectin Antibody (W40)	Supplier: (b) (4)	(lot not provided in report)
	Soluble Human P-Selectin	Supplier: (b) (4)	, catalog number #ADP3-200, Lot #ARL48090061, expiry date: Oct-2011
	Goat anti Human IgG Biotin conjugate	Supplier: (b) (4)	catalog number #190-065-088, Lot #70625, expiry date: 01-May-2012
<b>Regression model &amp; weighting</b>	4-Parameter Logistic (4PL) fit		
<b>Validation parameters</b>	<b>Method validation summary</b>		<b>Acceptability</b>
<b>Standard calibration curve</b>	Number of standard calibrators from LLOQ to ULOQ	5 calibrators from 0.625 ng/mL to 10.0 ng/mL and 3 anchoring points (20.0, 40.0 and 80.0 ng/mL)	Acceptable

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<b>performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) from LLOQ to ULOQ	Not available	
	Cumulative precision (%CV) from LLOQ to ULOQ	From 1.8% to 3.9%	Acceptable
<b>QCs performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) in QCs: SelG1	from 98.1% to 113.7%	Acceptable
	Inter-assay %CV	From 1.8% to 3.9%.	Acceptable
	Total Error (TE) QCs	Not available	N/A
<b>Selectivity &amp; matrix effect</b>	Not assessed		N/A
<b>Interference &amp; specificity</b>	10 serum patients were analyzed, and corresponding signals were found to be below lower limit of quantification. It was therefore considered that specificity of the assay was acceptable.		Acceptable
<b>Hemolysis effect</b>	Not required at the time of the validation		N/A
<b>Lipemic effect</b>	Not required at the time of the validation		N/A
<b>Dilution linearity &amp; hook effect</b>	Dilution linearity was investigated by analyzing 2 QCs: High QC spiked with 15.0 ng/mL of SelG1 and Low QC spiked with 1.00 ng/mL. Dilution factor of 1:5000, 1:50000, 1:100000, 1:500000 were tested. No apparent dilution effect was observed up to at least 1:500000 dilution. Accuracy % at the highest dilution (1/500000): from 90% to 104%. Hook effect was not assessed.		Acceptable
<b>Bench-top/process stability</b>	SelG1 stability was demonstrated for up to 16 hours at room temperature and at 2-8°C at 2.5, 8 and 14 µg/mL		Acceptable
<b>Freeze-Thaw stability</b>	Stability to 10 freeze/thaw cycles was demonstrated at 2.5, 8 and 14 µg/mL SelG1.		Acceptable
<b>Long-term storage</b>	Long term stability at -20°C and -80°C was demonstrated for 261 days at 2.5, 8 and 14 µg/mL.		Acceptable
<b>Parallelism</b>	Parallelism was assessed with 10 patient sera spiked at 13 µg/mL SelG1 and then serially diluted. Correlation coefficient and slope results from linear regressions were acceptable for all 10 patients.		Acceptable
<b>Carry over</b>	Not applicable		N/A

(b) (4)



**Method performance in Study CSEG101A2201**

Serum SelG1 concentration determination for a Phase II, multicenter, placebo-controlled, 12-month study to assess safety and efficacy of SelG1 with or without hydroxyurea therapy in sickle cell disease patients with sickle cell-related pain crisis.

Report: [BP-0013 / BP-0013-A1]

<b>Assay passing rate</b>	79 runs out of 80 passed acceptance criteria	Acceptable.
<b>Standard curve performance</b>	Cumulative bias range: -1% to 5% Cumulative precision: ≤ 10% CV	
<b>QC performance</b>	Cumulative bias range: -4% to 0% Cumulative precision: ≤13%CV	
<b>Method reproducibility</b>	Incurred sample reanalysis was performed in 37 samples out 2482 from which 11 were within assay range. All 11 samples were within 30% of their original value.	
<b>Study sample analysis/stability</b>	Sample were collected between Aug 2013 and March 2016. Analysis were performed between Feb2016 and April 2016. Currently available long-term stability data (261 days for SelG1 and 359 for SEG101) doesn't allow to cover the longest storage period. Long term stability is still ongoing for SEG101 and should allow to cover the maximum length of storage of the present study samples	

<b>Bioanalytical method validation report name, amendments, and hyperlinks</b>	Addendum to report: SLP - Qualification of SelG1 pK ELISA for Activity in Serum Samples [MVR-0062-00-W-1-A1]	
<b>Changes in method</b>	Assay validated in Human serum	
<b>New validated assay range if any</b>	Same assay range as reported in MVR [MVR-0062-00], [MVR-0062-00-W-1], [MVR-0062-01] the only change is the MRD applied at 1/100	
<b>Validation parameters</b>	<b>Cross-validation performance</b>	<b>Acceptability</b>

<b>Standard calibration curve performance during accuracy &amp; precision</b>	Number of standard calibrators from LLOQ to ULOQ	5 calibrators from 0.625 ng/mL to 10.0 ng/mL and 4 anchoring points (0.313, 20.0, 40.0 and 80.0 ng/mL)	Acceptable
	Cumulative accuracy (%bias) from LLOQ to ULOQ	From 0.8% to 14.4%	Acceptable
	Cumulative precision (%CV) from LLOQ to ULOQ	From 0.01% to 0.14%	Acceptable
<b>QCs performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) in QCs	From 2.1% to 18.5%	Acceptable
	Inter-batch %CV	Not available	NA
	Percent total Error (TE)	Not available	NA
<b>Cross-validation</b>	successful assay qualification for analysis of SelG1 in human serum		Acceptable
<b>List of other parameters</b>	Not applicable		NA

**Table 32. Bioanalytical method performance summary: PD assay for Reprixys-manufactured crizanlizumab (SelG1) in serum**

<b>Bioanalytical method validation report name, amendments, and hyperlinks</b>	Final Report for the validation of CRP-0000, PD Assay for analysis of SelG1 inhibition in human serum CRP-VP-0000-FR
<b>Method description</b>	<p>SensiQ Pioneer, a SPR-based biosensor system was used with a sensor chip immobilized with GSP-6 (glycosulfopeptide 6, a peptide mimic of the PSGL-1 domain that binds P-selectin). The sensor was first immobilized with Streptavidin using standard amine coupling followed by injection of GSP-6-biotin to immobilize the peptide for analysis. A reference channel was also prepared by biotin-blocking Streptavidin. Sensor regeneration was then performed to condition and stabilize the GSP-6 sensor by injecting 10 mM EDTA in 2M NaCl followed by 0.2% SDS at least 3 times each. QC samples (SelG1 spiked into normal human serum) and patient samples were mixed with a blocking buffer containing Psel-Ig. Pre-dose patient serum was used to produce a negative control sample which was mixed with blocking buffer without Psel-Ig and a positive control sample which was mixed with blocking buffer with Psel-Ig. Samples were allowed to equilibrate after mixing at least 1 h before testing to allow full inhibition at lower analyte concentrations.</p> <p>Sample testing was performed in an assay cycle where sample is injected over a GSP-6 flow channel (FC) and a reference FC (biotin blocked Streptavidin) for 3 min followed by sensor regeneration as described above (2 min injects each). All patient samples were tested in a collective assay run where negative control was tested first, followed by positive control then each time point sample and the positive control was then retested.</p> <p>Multiple patient samples were tested in automated, sequential assay runs and QC samples were tested at the beginning, middle, and end of the full assay run.</p>

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<b>Materials used for calibration curve &amp; concentration</b>	SelG1 reference standard at 9.4 mg/mL (batch not provided in validation report)	
<b>Validated assay range</b>	6 to 12 µg/mL SelG1	
<b>Material used for QCs &amp; concentration</b>	SelG1 reference standard at 9.4 mg/mL (batch not provided in validation report) The LOQ QC, low QC, mid QC and high QC samples were prepared at 6, 8, 10, and 12 µg/mL, respectively.	
<b>Minimum required dilutions (MRDs)</b>	No MRD applied	
<b>Source &amp; lot of reagents (LBA)</b>	GSP6 Biotin at 1mg/mL, Selexys ( batch not provided in validation report) PSeI-Ig protein at 1.709 mg/mL provided to (b) (4) ( batch not provided in validation report)	
<b>Regression model &amp; weighting</b>	Not reported	
<b>Validation parameters</b>	Method validation summary	<b>Acceptability</b>
<b>Standard calibration curve performance during accuracy &amp; precision</b>	Number of standard calibrators from LLOQ to ULOQ	6
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Data not provided in method validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	Data not provided in method validation report
<b>QCs performance during accuracy &amp; precision</b>	Cumulative accuracy (%bias) in 3 QCs	Recovery between 81.14 and 121.47% for QCs from 8 to 12 µg/mL
	Inter-batch %CV	%CV between 0.81% and 15.42%
	Total Error (TE)	Not reported
<b>Selectivity &amp; matrix effect</b>	Not assessed	
<b>Interference &amp; specificity</b>	Not assessed	
<b>Hemolysis effect</b>	Not assessed	
<b>Lipemic effect</b>	Not assessed	

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<b>Dilution linearity &amp; hook effect</b>	Not assessed	
<b>Bench-top/process stability</b>	Not assessed	
<b>Freeze-Thaw stability</b>	Stability to 2 freeze/thaw cycles was tested at 8, 10 and 12 µg/mL but was outside of acceptance criteria. It was considered that freeze/thaw cycles should be avoided and such event noted for study samples	
<b>Long-term storage</b>	Not assessed	
<b>Parallelism</b>	Not assessed	
<b>Carry over</b>	Not applicable	

(b) (4)



**Method performance in Study SEG101A2201**

SPR Pharmacodynamics results for SelG1 inhibitory activity in Human patient serum from a Phase II, Multicenter, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises.

<b>Assay passing rate</b>	Data not reported	Not acceptable
<b>Standard curve performance</b>	Data not reported	
<b>QC performance</b>	Data not reported	
<b>Method reproducibility</b>	Data not reported	

<b>Study sample analysis/stability</b>	Sample were collected between Aug 2013 and March 2016 and corresponding analysis were performed on a period from 26Jan2016 to 29Apr2016. However, no long term stability data are currently available to cover storage of these samples.	
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### **19.6 Additional Clinical Outcome Assessment Analyses**

[ Add Text and Figures/Tables Here]


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### Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Ramadevi Gudi, PhD	OOD/DHOT	Sections: 5	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: <b>Ramadevi Gudi -S</b> <small>Digitally signed by Ramadevi Gudi -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ramadevi Gudi -S, 0.9.2342.19200300.100.1.1=2000462985                      Date: 2019.11.14 14:09:54 -05'00'</small>			
Nonclinical Team Leader	N/A		Sections:	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature:			
Nonclinical Team Division Director	John Leighton, PhD, DABT	OOD/DHOT	Sections: 5	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: <b>John K. Leighton -S</b> <small>Digitally signed by John K. Leighton -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S                      Date: 2019.11.14 14:14:37 -05'00'</small>			
Clinical Pharmacology Reviewer	N/A		Sections:	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
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Clinical Pharmacology Reviewer	Xiling Jiang, PhD	OCP/DCP I	Sections: 6	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
	Signature: <b>Xiling Jiang -S</b> <small>Digitally signed by Xiling Jiang -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xiling Jiang -S, 0.9.2342.19200300.100.1.1=2001167656                      Date: 2019.11.14 14:36:41 -05'00'</small>			
Clinical Pharmacology Team Leader	Olanrewaju Okusanya, PharmD, MS	OCP/DCP I	Sections: 6	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
	Signature: <b>Olanrewaju Okusanya -S</b> <small>Digitally signed by Olanrewaju Okusanya -S                      DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001410838, cn=Olanrewaju Okusanya -S                      Date: 2019.11.14 14:51:06 -05'00'</small>			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Division Director	Brian P Booth, PhD (Nam Rahman, PhD signed on his behalf)	OCP/DCP I	6 Sections:	<b>Select one:</b> <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				<b>Signature:</b> <b>Nam A. Rahman -S</b> <small>Digitally signed by Nam A. Rahman -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597            Date: 2019.11.14 15:37:08 -05'00'</small>
Pharmacometrics Reviewer	N/A		Sections:	<b>Select one:</b> <input type="checkbox"/> Authored <input type="checkbox"/> Approved
				<b>Signature:</b>
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				<b>Signature:</b>
Pharmacometrics Division Director	N/A		Sections:	<b>Select one:</b> <input type="checkbox"/> Authored <input type="checkbox"/> Approved
				<b>Signature:</b>
Clinical Reviewer	Patricia Oneal, MD (Tanya Wroblewski, MD signed on her behalf)	ODE I/DHP	2, 3, 4.1, Sections: 7,8	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				<b>Signature:</b> <b>Tanya M. Wroblewski -S3</b> <small>Digitally signed by Tanya M. Wroblewski -S3            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011605845, cn=Tanya M. Wroblewski -S3            Date: 2019.11.14 18:37:07 -05'00'</small>
Clinical Reviewer	Rosanna Setse, MD, PhD	ODE I/DHP	7,8, 13 Sections:	<b>Select one:</b> <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				<b>Signature:</b> <b>Rosanna W. Setse -S</b> <small>Digitally signed by Rosanna W. Setse -S            DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1000634340, cn=Rosanna W. Setse -S            Date: 2019.11.14 17:41:41 -05'00'</small>

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Tanya Wroblewski, MD	ODE 1/DHP	All Sections:	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Tanya M. Wroblewski -S3 <small>Digitally signed by Tanya M. Wroblewski -S3 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011605845, cn=Tanya M. Wroblewski -S3 Date: 2019.11.14 18:37:40 -05'00'</small>
Statistical Reviewer	Yaping Wang, PhD (Yeh Fong Chen signed on his behalf)	OB/DB IX	8 Sections:	Select one: <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
				Signature: Yeh Fong Chen -S <small>Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2019.11.14 16:03:04 -05'00'</small>
Statistical Team Leader	Yeh-Fong Chen, PhD	OB/DB IX	8 Sections:	Select one: <input checked="" type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
				Signature: Yeh Fong Chen -S <small>Digitally signed by Yeh Fong Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yeh Fong Chen -S, 0.9.2342.19200300.100.1.1=1300157970 Date: 2019.11.14 16:04:51 -05'00'</small>
Cross-Disciplinary Team Leader (CDTL)	Tanya Wroblewski, MD	ODE I/DHP	All Sections:	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
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Division Director (Clinical)	Albert Deisseroth, MD, PhD	ODE I/DHP	All Sections:	Select one: <input type="checkbox"/> Authored <input type="checkbox"/> Approved
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Division Director (OB)	Thomas E Gwise, PhD	OB/DB IX	8 Sections:	Select one: <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
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Labeling Reviewer	Virginia Kwitkowski, MS, ACNP-BC	ODE I/DHP	11 Sections:	<b>Select one:</b> <input type="checkbox"/> Authored <input type="checkbox"/> Approved
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11/15/2019 01:38:07 PM