CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761128Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	110752
Request Receipt Date	29 October 2018
Product	Crizanlizumab (SEG101)
Indication	For the prevention of vaso-occlusive crises (VOC) in patients with sickle cell disease
Drug Class/Mechanism of Action	High affinity selective humanized monoclonal antibody that binds to P-selectin which effectively inhibits interactions between endothelial cells, platelets, red blood cells, sickled red blood cells, and leukocytes, thereby preventing vaso-occlusion.
Sponsor	(b) (4)
ODE/Division	OND/OCE/DHP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	28 December 2018

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** For the prevention of vasoocclusion (VOC) in patients with sickle cell disease (SCD).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Drug/Mechanism of Action: Crizanlizumab is high-affinity, selective, humanized monoclonal antibody which inhibits P-selectin whose interaction is unique to the vascular endothelial cells and platelets which contribute to the cell-to-cell and cell-to-endothelium interactions involved with vaso-occlusion and crises in sickle cell disease.
Indication/Disease: For the prevention of vasoocclusion (VOC) in patients with sickle cell disease
Available therapies:

- Hydroxyurea (Siklos®, Droxia®) is an oral capsule approved for the reduction of recurrent VOCs in patients ≥ 2 years old and older.
- L-glutamine (Endari™) is an oral powder administered as a twice-daily suspension approved for the reduction of acute complications of SCD in patients ≥5 years old and older.

Additional treatments that are also used for the patients with sickle cell disease include red blood cell transfusions, exchange transfusions and bone marrow transplants.

8. Information related to endpoints used in the available clinical data:

a. Endpoints accepted by the Division as a clinically significant endpoint (outcome measure) for patients with the disease:
   - Reduction in annualized rate of VOC leading to a healthcare visit
   - Time to 1st VOC leading to a healthcare visit (months)

b. Any other biomarkers the division would consider likely to predict a clinical benefit event if not yet a basis for accelerated approval.
   - No

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Table 9-1 Benefit over available therapies

	Crizanlizumab				Hydroxyurea			L-glutamine		
MOA	Blocks P-selectin (expressed on the endothelium and on platelets) and cell-to-cell and cell-to-endothelium interactions involved in the pathogenesis of vaso-occlusion, resulting in the prevention of VOCs Crizanlizumab MOA is unique compared to available therapies and may improve upon or complement the MOAs of available therapies or those in development				Not known, but known pharmacologic effects include increasing hemoglobin F levels in RBCs, decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.			Not fully understood. Pyridine nucleotides, NAD+ and its reduced form NADH, play roles in regulating & preventing oxidative damage in RBCs. L-glutamine improves the NAD redox potential through increasing the availability of reduced glutathione.		
Impact on VOCs	Criz§•	Pbo•	Change v. pbo	HL med diff v. pbo	HU'•	Pbo•	Change v. pbo	L-glut'•	Pbo•	Change v. pbo
	1.63	2.98	-45.3%	-1.01	2.5	4.5	-44%	3	4	-25%
Time to 1st crisis	Criz§&	Pbo&	HR^		HU&	Pbo&	HR	L-glut&	Pbo&	HR^
	4.07 mos	1.38 mos	0.50 (0.33, 0.74)		3 mos	1.5 mos	n/a	2.76 mos	1.77 mos	0.69 (0.52, 0.93)
Safety profile	Well-tolerated, no specific safety issue identified				• myelosuppression, • genotoxicity, • carcinogenicity, • impact on fertility • embryo-fetal toxicity. Not all patients can tolerate or are willing to take HU.			Safety in patients with renal and hepatic impairment is being further investigated (listed as a post-marketing commitment in the FDA approval letter). Many SCD patients have renal and hepatic dysfunction at baseline.		
Route of admin	30 min IV infusion on Day 1, Day 14 and then every 4 weeks;				Oral pill once daily			Oral powder mixed to form a suspension and taken twice daily		

- Hydroxyurea (Siklos®, Droxia®) is an oral capsule approved for the reduction of recurrent VOCs in patients ≥ 2 years old and older.
- L-glutamine (Endari™) is an oral powder administered as a twice-daily suspension approved for the reduction of acute complications of SCD in patients ≥5 years old and older.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

None

11. Information related to the preliminary clinical evidence:

The SUSTAIN Study (Study A2201) is a Phase 2, randomized, multicenter, placebo-controlled, double-blinded study of 198 patiens with Hgb SS, SC, S/Beta^0 Thalassemia and S/Beta$^+$ Thalassemia between 16 to 63 years of age with a history of 2-10 vasooclusive crises in the previous twelve months. These 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. Randomization was stratified by hydroxyurea (HU) usuage and number of crises (2-4 or 5-10). The primary efficacy endpoint is the annualized rate of VOCs leading to a healthcare visit. Crizanlizumab was administered intravenously on Week 0, 2 and every four weeks thereafter. Sixty-two (62%) of patients were on hydroxyurea while 65% of patients had a baseline history of 2-4 VOCs.

The preliminary results have shown that among those patients who received crizanlizumab 5 mg/kg was a 45.3% lower median annual rate of VOC leading to a healthcare visit (Median rate = 1.63) compared to placebo (Median rage = 2.98); 95% CI (-2.00,0.00); p = 0.010. In addition, the results did show a delay in the time to the first VOC (3-fold) and second VOC (2-fold) leading to a healthcare visit **(see Table 7.1)** The time to 1st VOC leading to healthcare visit (months) was higher compared to placebo over the current standard of care treatments (HU and L-glutamine) for the management of SCD.

Table 7-1 Main efficacy results

Event	Crizanlizumab 5 mg/kg (n= 67)	Placebo (n= 65)	% difference between medians	Treatment difference estimate	p-value
Annual rate of VOC leading to a healthcare visit*	1.63	2.98	-45.3%	HL= -1.01 (-2.00, 0.00)	p = 0.010
Number of patients with no VOC leading to a healthcare visit#	24 (35.8%)	11 (16.9%)			p = 0.013

Event	Crizanlizumab 5 mg/kg (n= 67)	Placebo (n= 65)	% difference between medians	Treatment difference estimate	p-value
Annual rate of days hospitalized*	4.00	6.87	-41.8%	HL= 0.00 (-4.36, 0.00)	p = 0.450
Time to 1st VOC leading to a healthcare visit (months)^	4.07	1.38		HR= 0.495 (0.331, 0.741)	p = 0.001
Time to 2nd VOC leading to a healthcare visit (months)^	10.32	5.09		HR= 0.534 (0.329, 0.866)	p = 0.022
Annual rate of uncomplicated VOC leading to a healthcare visit*	1.08	2.91	-62.9%	HL= -1.00 (-1.98, 0.00)	p = 0.015

* Standard median, HL = Hodges-Lehmann median difference (95% CI), Wilcoxon Rank Sum test
# n(%), Cochran Mantel-Haenszel test
^ Estimated Kaplan-Meier median, HR = Hazard-ratio (95% CI), Log Rank test

Crizanlizumab has a well-tolerated safety profile demonstrating efficacy in HU users and nonHU users, patients with frequent pain crises and patients with less frequent pain crises and among all SCD genotypes. It can address an unmet medical need in managingVOCs in SCD patients who are either refractory to HU, all SCD genotypes or as an additive effect of concomitant HU.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

- Sickle cell disease is a serious condition where the available therapy may not be beneficial or effective in all patients afflicted with this disease.
- The efficacy data has met its primary endpoint, showing a statistically significant and clinically relevant reduction in the median annual rate of VOC leading to a healthcare visit with crizanlizumab 5 mg/kg vs. placebo.
- Time to 1st VOC leading to healthcare visit (months) was higher compared to standard of care treatments (HU and L-glutamine).
- The safety profile has shown no significant safety concerns.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

- The Sponsor intends to submit a BLA for review in 2019 based on randomized Phase 2 data.
- (b) (4)
-

14. List references, if any:

1. Droxia (Hydroxyurea)-FDA product information. Retrieved from https://packageinserts.bms.com/pi/pi_droxia.pdf.
2. Silkos (Hydroxyurea)-FDA product information. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208843s000lbl.pdf.
3. Endari (L-glutamine oral powder) – FDA product information. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208587s000lbl.pdf.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation	☒
Deny Breakthrough Therapy Designation	☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/3/18/M. Raggio

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

/s/

PATRICIA A ONEAL
12/20/2018

TANYA M WROBLEWSKI
12/20/2018

ANN T FARRELL
12/20/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110752

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Amanda Bright, PharmD
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Bright:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SEG101 (crizanlizumab).

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2018. The purpose of the meeting was to discuss (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Gwathmey, Regulatory Project Manager at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

32 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

NICOLE J GORMLEY
11/19/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110752

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Amanda Bright, PharmD
Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Bright:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SEG101 (crizanlizumab).

We also refer to the meeting between representatives of your firm and the FDA on August 9, 2018. The purpose of the meeting was to discuss the overall strategy, content and format for your planned submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Vishal Bhatnagar, MD
Acting Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	August 9, 2018, 2:00 PM – 3:00 PM ET
Meeting Location:	White Oak Building 22, Conference Room: 1419
Application Number:	IND 110752
Product Name:	SEG101 (crizanlizumab)
Indication:	Sickle Cell Disease
Sponsor/Applicant Name:	Novartis Pharmaceuticals Corporation
Meeting Chair:	Vishal Bhatnagar, MD
Meeting Recorder:	Natasha Kormanik, MSN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Associate Deputy Director
Vishal Bhatnagar, MD, Acting Clinical Team Leader
Rachel Ershler, MD, Clinical Reviewer
Natasha Kormanik, MSN, RN, OCN®, Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V
Olanrewaju Okusanya, PharmD, Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics V
Yuan-Li Shen, DrPH, Team Leader
Qing Xu, PhD, Mathematical Statistician

Office of Pharamceutical Quality (OB), Division of Biotechnology and Research II
Cyrus Agarabi, PhD, Team Leader
David Powers, PhD, Reviewer

SPONSOR ATTENDEES

Novartis Pharmaceuticals Corporation
Andrew Cavey, MD, Global Program Head, Benign Hematology
Shanthi Ganeshan, PhD, North American Region Head, Regulatory Affairs Oncology
Brian Elliott, MD, Clinical Development Medical Director
Savita Nandal, MD, Head Benign Hematology, US Oncology-Medical
Chiaki Tanaka, PhD, Director, Pharmacokinetics Sciences
Amanda Bright, PharmD, Global Program Regulatory Manager, Regulatory Affairs
Christoph Schoenlein, PhD, Region Europe Head, Regulatory Affairs Oncology
Nathalie Lauper von Raumer, PhD, Global Program Regulatory Director, Regulatory Affairs
Pascal Edrich, Global Program Biostatistics Head
Uwe Schuehly, MD, Senior Brand Safety Leader
Katja Baer, Technical Project Leader
Nancy Landzert, Franchise Head, Biologics, Regulatory Chemistry Manufacturing and Controls Biologics 2

(b) (4)

1.0 BACKGROUND

The purpose of this meeting was to discuss the overall strategy for the planned BLA submission of crizanlizumab in support the proposed indication of the prevention of vaso-occlusive crises in SCD patients aged 16 years and over, and to align on the overall content and format of the planned BLA.

FDA sent Preliminary Comments to Novartis Pharmaceuticals Corporation on August 3, 2018.

2.0 DISCUSSION

Question 1: *Novartis believes the results from the pivotal study A2201 (SUSTAIN), complemented by data from healthy subjects in Study A2101 and comparability Study A2102, and interim data from SCD patients A2202 are adequate to support the filing of a BLA for crizanlizumab for the proposed indication. Does the Agency agree?*

FDA Response to Question 1: Whether or not the results of the SUSTAIN study, complemented by data from Study A2101, A2102 and A2202, are adequate to support filing will be a review issue at the time of application submission. We have the following additional comments:

- We note that 34.8% of the patients discontinued treatment before the end of the evaluation year from the pivotal study A2201. Too much missing data could undermine the reliability and confidence of the estimates and cause difficulty in result interpretation. You proposed several sensitivity analyses to address the missing data issues. However,

without reviewing the data, it is challenging to identify which method could be appropriate to address the impact of early dropouts. Missing data will be a review issue.

- Note that the results from your PK comparability Study A2102 which showed higher 28% higher AUC for SEG101 compared to SelG1 will be a review issue.

Discussion: **No discussion.**

Question 2: *Novartis believes the proposed content of the clinical pharmacology package is adequate to support the filing. Does the Agency agree?*

FDA Response to Question 2: Yes, your proposed clinical pharmacology package appears adequate to support filing. In addition to your proposed exposure-response analyses for efficacy, you should also submit exposure-response analysis for safety based on pooled data to support the proposed dose regimen.

Discussion: **No discussion.**

Question 3: *Patients aged 16 to < 18 years with SCD have an unmet need and face specific challenges that can impact the quality of care provided. Given the similar physiology of 16-18 year olds and consistent pathophysiology of the disease, which are comparable to patients 18 and above, Novartis believes that crizanlizumab is appropriate for patients aged 16 years and over. Does the Agency agree?*

FDA Response to Question 3: No. Because only 3 patients aged 16 to 18 years have received crizanlizumab, there is insufficient data available for patients in this age range to fully assess safety. However, the Agency encourages further evaluation of crizanlizumab in the pediatric patient population.

Discussion: **The Sponsor requested clarification regarding the population 16-18 years of age. The Agency reiterated that the Sponsor should provide all available data from this population as well as a justification for why this population has a similar scientific pathophysiology as adults. The Sponsor will provide data that becomes available from an ongoing PK/PD study as well as possible data from the planned B2201 during the BLA review timeline.** (b) (4)

Question 4: *The initial* (b) (4) *formulation of SEG101 containing* (b) (4) *was replaced with a* (b) (4) *citrate* (b) (4) *based on the outcome of a formulation development study. Novartis believes comparability of the initial SEG101* (b) (4) *formulation to the commercial formulation of SEG101* (b) (4) *citrate* (b) (4) *has been demonstrated by the data obtained during in vitro physical, chemical, and bioanalytical experiments as well as by the additional characterization. Novartis believes no additional in-vivo comparability studies are required. Does the Agency agree?*

FDA Response to Question 4: Yes, in general the FDA agrees that the proposed (b) (4) drug product formulation (containing (b) (4) citrate) of SEG101 was

demonstrated to be comparable from the data obtained during *in vitro* physical, chemical, bioanalytical experiments and additional characterization assays. However, a final determination will be made when the BLA is submitted and the methods and results are reviewed.

The Agency agrees that no additional in-vivo comparability studies are required at this time.

Discussion: No discussion.

Question 5: *Novartis plans to provide up to 9 months of real time registration stability data from three representative drug product batches with the commercial formulation at the time of the planned submission. Does the Agency agree that additional time points of drug product stability data could be submitted during the review period in support of the initial commercial shelf life without the need for an extension of the initial review period?*

FDA Response to Question 5: Yes. FDA will permit submission of the 12-month real time stability data for SEG101 drug product in support of the initial commercial shelf life during the BLA review cycle. Final product expiration dating will be based upon real time data from the final commercial process and supporting data from clinical and development lots in accordance with ICH Q5C *Stability Testing of Biotechnological/Biological Products.*

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf

Discussion: No discussion.

Question 6: *Does the Agency agree with the proposed additional analyses of the primary efficacy endpoint of Study A2201 (SUSTAIN) as a way to evaluate the impact of early dropouts?*

FDA Response to Question 6: Please refer to the Agency's response to Question 1.

Discussion: No discussion.

Question 7: *Novartis believes that the proposed content and format of the Summary of Clinical Efficacy (SCE), Summary of Clinical Safety (SCS), Summary of Biopharmaceutics (SBP) and the Summary of Clinical Pharmacology (SCP) are appropriate. Does the Agency agree?*

FDA Response to Question 7: Yes, however refer to additional clinical pharmacology comments regarding our general expectations for your BLA submission.

Discussion: No discussion.

Question 8: *Novartis believes the proposed Case Report Tabulations package (datasets and documentation) planned to be provided for the individual trials and data pooling appropriate to support the review of the proposed filing. Does the Agency agree?*

FDA Response to Question 8: Yes, your plan appears acceptable.

Discussion: **No discussion.**

Question 9: *Does the Agency agree with the content and timing of the proposed safety update?*

FDA Response to Question 9: The content appears acceptable. The timing of the proposed safety update will depend on the timing of your application submission.

Discussion: **No discussion.**

Question 10: *Novartis believes the proposed documentation to support potential FDA inspections of clinical sites meets the requirements for the FDA Office of Scientific Investigations' (OSI) Bioresearch Monitoring Program (BIMO). Does the Agency agree?*

FDA Response to Question 10: Your proposed documentation is acceptable.

Discussion: **No discussion.**

Question 11: *Novartis believes the proposed contents listed in the (eCTD) Table of Contents provided in Appendix 7 are acceptable to support this BLA. Does the Agency agree?*

FDA Response to Question 11: You should refer to the Guidance "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" regarding the proposed structure of your eCTD submission.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

Discussion: **No discussion.**

Question 12: *Novartis believes crizanlizumab meets the criteria for Breakthrough Therapy Designation. Does the Agency agree?*

FDA Response to Question 12: It is within your discretion to request preliminary Breakthrough Therapy Designation advice. However, the Agency reiterates that to qualify for breakthrough therapy designation, there must be preliminary clinical evidence to indicate that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint. Ultimately, the decision to grant Breakthrough Therapy Designation will be a review issue.

Discussion: **The Sponsor requested clarification regarding potential Breakthrough Therapy Designation. The Agency reiterated that the Sponsor should submit a dedicated preliminary Breakthrough Designation advice. The current meeting package cannot serve as a substitute to a preliminary Breakthrough Designation advice. The Agency requested ample evidence of improvement over available therapy. The Sponsor acknowledged and will submit a formal preliminary Breakthrough Designation in the future.**

Additional Comments

1. To facilitate timely review for the upcoming BLA submission, please provide an estimated submission time frame.

Clinical Pharmacology

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for dose selection in the following stages of drug development: first-in-human starting dose, dose range in phase 1 and phase 2 studies, the dose(s) in registration trials and the final proposed dose(s) to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
2. What are the exposure-response relationships for efficacy, safety, and biomarkers?
3. How do extrinsic (e.g., other drugs) and intrinsic factors (e.g., sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
4. What is the impact of immunogenicity on exposure, efficacy, and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

5. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
6. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
7. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
8. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line

- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

9. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation
   - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
   - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
10. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.
11. We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Statistical

1. The SAS programs that are used to create the ADaM data for the efficacy endpoints and the SAS programs that are used for efficacy data analysis for the primary and key secondary endpoints should be included in the submission. All programs should be thoroughly commented and should be executable formats that are compatible to the Agency's computation system.
2. Ensure the SAS dataset file name are consistent with those in the SAS programs that call them and include all SAS macros, if included in the SAS programs, so that the Agency can run the programs smoothly to verify the results/figures/tables reported in the submission.

3. Annotations for all efficacy and safety tables and figures should be included in the main text portion of the CSR. The annotations should indicate which analysis dataset variables and SAS program are used to produce the table or figure.

Discussion: The Sponsor explained that programs to produce ADaM files may not be fully executable. The agency acknowledged the explanation and will ask for more detailed information in the review process (using information requests). The Agency also encouraged the Sponsor to provide the data as detailed at possible so that the Agency can perform additional analysis.

The annotations and defined file proposed by the Sponsor are acceptable.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 8, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor plans to submit the BLA in its entirety around March 2019.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that REMS is not expected
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified.

5.0 ACTION ITEMS

No action items discussed.

6.0 ATTACHMENTS AND HANDOUTS

No handouts provided by Sponsor.

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

/s/

VISHAL BHATNAGAR
08/10/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 110752

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Sara Lorie, MBA
Senior Associate Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Lorie:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SEG101 (crizanlizumab).

We also refer to the meeting between representatives of your firm and the FDA on February 28, 2017. The purpose of the meeting was to discuss certain clinical, regulatory, pre-clinical safety, clinical pharmacology and multi-disciplinary aspects of SEG101 (crizanlizumab) development.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Gwathmey, Regulatory Project Manager at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: February 28, 2017, 11:00 AM – 12:00 PM ET
Meeting Location: White Oak Building 22, Room 1315

Application Number: IND 110752
Product Name: SEG101 (crizanlizumab)
Indication: Sickle Cell Disease
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Nicole Gormley, MD
Meeting Recorder: Michael Gwathmey, RN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Albert Deisseroth, MD, PhD, Associate Deputy Director
Nicole Gormley, MD, Clinical Team Leader
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Rachel Ershler, MD, Clinical Reviewer
Margaret Merino, MD, Clinical Reviewer
Patricia Oneal, MD, Clinical Reviewer
Michael Gwathmey, Regulatory Project Manager

Office of Biotechnology Products, Division of Biotechnology Review and Research II
Juhong Liu, PhD, Team Leader
Patrick Lynch, PhD, Product Quality Reviewer
Sarah Arden, PhD, Product Quality Reviewer

OHOP, Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Team Leader
Olanrewaju (Lanre) Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

Office of Biostatistics (OB), Division of Biometrics V
Yaping Wang, PhD, Mathematical Statistician

SPONSOR ATTENDEES

Anthony DeLise, PhD, Director Preclinical Safety
Robert Dobres, MBA, RAC Associate Director, Regulatory CMC
Brian Elliot, Global Clinical Lead
Marisa Gremigni, Msc, PhD, MBA Biologics Team Representative
Shanthi Ganeshan, PhD, NA Head, Regulatory Affairs
Adbullah Kutlar, MD, Director, Sickle Cell Center Augusta University
Sara Lorie, MBA, Senior Associate Director Regulatory Affairs
Krista McKerracher, VP Global Program Head SEG101
Chiaki Tanaka, Principal Fellow Clinical Pharmacology
Shantha Rao, PhD Director, Project Statistician
Michael Shi, MD, PhD, Global Clinical Head SEG101
Eric Slosberg, MD Head, US Clinical Strategy
Zewen Zhu, Associate Director, Biostatistics

1.0 BACKGROUND

Novartis Pharmaceuticals Corporation requested an End of Phase 2 meeting to seek the Agency's feedback on certain clinical, regulatory, pre-clinical safety, clinical pharmacology and multi-disciplinary aspects of SEG101 (crizanlizumab) development.

The proposed indication of SEG101 (crizanlizumab) is to decrease/reduce the frequency of painful crises in patients aged 16 years and over with Sickle Cell Disease. For this meeting, the Sponsor wanted to to discuss the efficacy results of their SUSTAIN study (involving crizanlizumab) and whether it can provide further support in the pursuance of SEG 101 for their proposed usage.

2.0 DISCUSSION

Question 1:

Adequacy of filing based on SUSTAIN Data

a. SUSTAIN Study Design to support the proposed indication

Does the Agency agree that the overall study design of the SUSTAIN trial is adequate to support a filing for full approval for reduction in frequency of painful crises in patients with sickle cell disease?

b. SUSTAIN efficacy data

Novartis believes the SUSTAIN data demonstrate robust efficacy, as assessed by the annualized rate of SCPC (a recommended endpoint in the "Overview of trial design and

regulatory considerations for clinical trials in sickle cell disease" FDA workshop), of crizanlizumab, and are therefore sufficient to support a filing. Does the Agency agree?

c. Safety

Novartis considers that the favorable safety profile and size of the safety database (based on clinical data and a comprehensive pre-clinical data package) of 198 SCD patients (130 of which were treated with crizanlizumab) followed in a double-blind, placebo controlled trial, and 20 healthy volunteers is adequate to assess the benefit/risk profile and sufficient to support an approval of crizanlizumab in this life-threatening orphan condition with a high unmet medical need. The data available to date demonstrate a favorable safety profile. Does the Agency agree?

FDA Response to Question 1:

a, b. It is not clear that you have the optimal dose for this population. We recommend that you pool clinical pharmacokinetic/ pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated exposure-response analyses for dose optimization. You should evaluate if there is a relationship between receptor occupancy and Ctrough concentrations and the probability of having a SCPC.

The overall study design of the SUSTAIN trial was previously discussed with the Agency and appears acceptable. However, the adequacy of the SUSTAIN trial to support a BLA will depend on the results of the planned PK/PD comparability study. Ultimately, the adequacy of the SUSTAIN trial data to support full approval and filing of a BLA will be a review issue.

c. In general, the Agency does not agree on the adequacy of the safety database in advance. The adequacy of the proposed safety database will be a review issue.

Discussion 1:

The Agency appreciates the exploratory PK/PD analysis that has been conducted thus far. The Agency advised to sponsor to conduct additional analysis in order to further optimize the dose.

The Agency also advised the sponsor to submit the PK/PD comparability protocol for review and comments. The Agency requested that the sponsor submit comparability results and have further discussion at that time regarding the submission process.

Question 2:

Use in patients 16-18 years of age

Based on clinical and pre-clinical evidence, Novartis believes that use of crizanlizumab is appropriate for patients aged 16 years or above. Does the Agency agree with proposed use of crizanlizumab in patients aged 16 years and over, particularly patients aged 16 to 18 years?

FDA Response to Question 2:

No. Because only 3 patients aged 16 to 18 years have received crizanlizumab, there is insufficient safety data available for patients in this age range. (b) (4)

Discussion 2:

No further discussion.

Question 3:

(b) (4)

FDA Response to Question 3:

(b) (4)

Discussion 3:

No further discussion.

Question 4:

Potential for Breakthrough Therapy designation

Novartis believes that crizanlizumab meets the criteria for Breakthrough Therapy Designation based on the criteria laid out in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA)-Section 902 (see FDA guidelines) as crizanlizumab addresses a Serious

Condition with Unmet Medical Need, in which Clinical Evidence of efficacy and safety has been shown. Does the Agency agree?

FDA Response to Question 4:

The decision to grant Breakthrough Therapy Designation requires that there is preliminary clinical evidence that indicates that the drug may demonstrate a substantial improvement on a clinically significant endpoint over available therapies. At this time, there is uncertainty about the comparability of SEG101 and SE1G. After this is resolved, the Agency would recommend that you request preliminary breakthrough therapy designation request advice from the review division prior to submitting a formal breakthrough therapy designation request.

Discussion 4:

No further discussion.

Question 5:

Carcinogenicity

Novartis believes that *in vivo* rodent carcinogenicity studies with crizanlizumab are not warranted based on guidance provided in ICH S6, the compound characteristics, and available data. Does the Agency agree?

FDA Response to Question 5:

The requirement for carcinogenicity studies may be waived pending the review of a formal waiver request with a fully developed rationale. Please also submit to the Electronic Document Room .pdfs of the nonclinical studies # 8220205 (Tissue Cross Reactivity), #SelG1-00002 (4-week monkey study), and #8259995 (26-week monkey study) with the request.

Discussion 5:

No further discussion.

Question 6:

Clinical Pharmacology package

Novartis obtained PK and PD data on crizanlizumab from a Phase I trial in healthy subjects and SUSTAIN trial in patients. In addition, a PK and PD comparability study using crizanlizumab monoclonal antibodies (mAbs) manufactured by Novartis and Selexys is planned in healthy subjects. Does the agency agree that the clinical pharmacology package that consists of these studies adequately supports an initial filing in patients aged 16 years and older?

FDA Response to Question 6:

It is not clear that you have adequately characterized the PK of your drug. We note the differences in clearance at the 5 mg/kg dose and 8 mg/kg dose in your healthy subject study and it appears that you may not have captured a sufficient portion of your elimination phase. We recommend that you develop a population PK model to adequately characterize the PK of your drug. Also see response to Question 1 and 3.

FDA has the following recommendations regarding the overall clinical pharmacology development program for Crizanlizumab:

1. Assess the following items to facilitate rational dose selection for efficacy and safety trials and dose adjustment for specific populations:
   - Optimal systemic exposure of your drug in general patient population
   - Effect of intrinsic factors (e.g. renal or hepatic impairment, disease, age, sex, body weight) and extrinsic factors (e.g., concomitant drugs) alter systemic exposure
   - Effect of your drug on the systemic exposure of other concomitant drugs

2. Conduct the following evaluations to support the proposed dose regimen(s) for further clinical development.
   - Validation of bioanalytical assays for the quantification of your drug
   - Characterization of single-dose/multiple-dose pharmacokinetics, dose proportionality, and time-dependence of pharmacokinetics
   - Assessment of the effect of body size (e.g., body weight and body surface area) on pharmacokinetics and pharmacodynamics of your drug to determine the appropriate dosing approach (e.g., body size-based or fixed dosing)
   - Characterization of the development of anti-drug antibodies (ADA) to your drug, including rate, titer, neutralizing capacity, duration, and effect on the pharmacokinetics, pharmacodynamics, efficacy and safety of your drug

3. Collect pharmacokinetic samples in all patients enrolled in trials intended to demonstrate safety and efficacy to perform population pharmacokinetic and exploratory exposure-response analyses.

4. Refer to the following FDA documents of "Guidance for Industry" for greater details regarding the above recommendations:
   - Bioanalytical Method Validation
   - Assay Development for Immunogenicity Testing of Therapeutic Proteins
   - Immunogenicity Assessment for Therapeutic Protein Products
   - Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications
   - Population Pharmacokinetics

Discussion 6:

No further discussion.

Question 7:

Suitability of bridging data package between Selexys and Novartis materials

Clinical and toxicological studies performed to date for crizanlizumab under IND 110,752 were conducted using Selexys material (i.e. SelG1 mAb) produced in [redacted] CHO [redacted] cells [redacted]. To ensure supply of future clinical studies as well as commercial demand, Novartis has optimized the production of crizanlizumab. The Novartis material (i.e. SEG101 mAb) is produced in the Novartis [redacted] cell line [redacted] and drug substance and drug product will be manufactured in Novartis sites. Novartis intends to demonstrate comparability between Selexys material (used in current Phase I and II studies) and Novartis material (to be used in future clinical/ toxicological studies and as commercial product) with a comparability package comprising analytical in-vitro-comparison in accordance with ICH Q5E, a study in the cynomolgus monkey and a study in human healthy subjects. [redacted] Does the Agency agree with this approach?

FDA Response to Question 7:

Based on the preliminary data provided in the meeting packages, the proposed commercial crizanlizumab product manufactured at Novartis differs from the Selexys material in [redacted] Your nonclinical study results with cynomolgus monkeys also indicated that these differences may potentially impact the PK of crizanlizumab. If such differences are confirmed through analyses of additional post-change lots, you will need to provide human PK/PD data to demonstrate that the differences have no impact on the safety and efficacy.

The Agency has concerns regarding your ability to demonstrate comparability of the pre- and post-change products based on the information provided. Given the above, your proposal to submit an application that relies on clinical data from studies which use the old product is risky. You should consider conducting a clinical trial using the new product to demonstrate safety and efficacy.

Discussion 7:

The Agency advised the sponsor to provide characterization studies to support the position of no expected impact on PK and effector function due to differences in [redacted] FDA agreed to work with the sponsor to provide additional feedback as needed.

3.0 OTHER INFROMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None at this time

5.0 ACTION ITEMS

None at this time

6.0 ATTACHMENTS AND HANDOUTS

Slide presentation provided by the sponsor is attached.

14 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NICOLE J GORMLEY
03/03/2017