NOVARTIS

Quantitative Safety and Epidemiology

SEG101 (crizanlizumab)

Redacted Study Final Report

CSEG101A2404

Non-Interventional Study Final Report

Adakveo® (crizanlizumab) PRegnancy outcomes Intensive Monitoring (PRIM)

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Research question and objectives	The overall objective of this report is to collect data on pregnancy outcomes in patients treated with crizanlizumab during pregnancy or within 105 days before the last menstrual period (LMP) and about infant outcomes 12 months post-delivery.
Country(-ies) of study	Global

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Marketing authorization holder(s)	Novartis
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1 Abstract

Title

Adakveo® (crizanlizumab) PRegnancy outcomes Intensive Monitoring (PRIM)

Version and date

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Keywords

Crizanlizumab, Adakveo®, Sickle cell disease, Pregnancy Outcomes

Rationale and background

Compared with pregnant women in the general population, pregnant women with sickle cell disease (SCD) have increased risk of pregnancy complications and adverse pregnancy outcomes. It is currently unknown whether crizanlizumab therapy can affect the risk of pregnancy complications or adverse pregnancy outcomes in pregnant women with SCD. In preclinical study in cynomolgus monkeys, pregnant animals received intravenous doses of crizanlizumab at 10 and 50 mg/kg once every 2 weeks during the period of onset of organogenesis through delivery. Compared to control, there was an increase in the proportion of fetal loss (spontaneous abortions or stillbirths) at both crizanlizumab doses. This was higher in the third trimester. The cause for the increased losses is unknown but it is believed to be the development of anti-drug antibodies (ADA) in monkeys against crizanlizumab, a humanized monoclonal antibody. There were no teratological findings in the aborted fetuses, infant deaths or those otherwise born alive. There were no effects on infant growth and development at 6-months postpartum that were attributable to crizanlizumab.

In view of the increased risk of pregnancy complications and adverse outcomes in women with SCD, the animal data as mentioned above, lack of clinical studies in pregnant women on crizanlizumab, and potential use of crizanlizumab in women of childbearing potential, Novartis established the PRIM study for crizanlizumab. A limit of up to 105 days before last menstrual period (LMP) for crizanlizumab exposure, based on half-life and PK variability in SCD patients, was used, consistent with the overall crizanlizumab development program.

Although it was intended to continue the study until 500 prospective patients with pregnancy outcomes were available or for a total study period of 10 years (whichever comes first), the study was terminated early on account of low number of patients accrued in the study (8 prospective pregnancy patients in over 4 years) and the low probability of further substantial increase in eligible patients, in light of the revocation of the marketing authorization of crizanlizumab in the EU and other regions/countries.

Research question and objectives

The overall aim of the SEG101 (crizanlizumab) PRIM program was to collect data on pregnancy outcomes in patients treated with crizanlizumab during pregnancy or within 105 days before the LMP.

Primary objective:

- To estimate the proportion of pregnancies resulting in fetal loss (intrauterine death resulting in stillbirth, spontaneous abortion, or induced termination), among pregnant women exposed to crizanlizumab within 105 days prior to LMP or at any time during pregnancy.

Secondary objectives:

- To estimate the proportion of major congenital malformations among pregnancies exposed to crizanlizumab up to 105 days before LMP and during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for fetal anomaly (TOPFA).
- To estimate the proportion of overall congenital malformations among pregnancies exposed to crizanlizumab up to 105 days before LMP and during pregnancy reported to Novartis with the outcome of total live births, and live birth plus still births and TOPFA.

Study design

The crizanlizumab PRIM study is a non-interventional study (NIS) based on secondary use of data from a set of targeted follow-up (TFU) checklists with structured follow-up on pregnancies reported to the Novartis global safety database. This study is single-arm, descriptive in nature and includes worldwide data coverage.

Setting and study population

All prospective and retrospective pregnancy cases exposed to crizanlizumab during pregnancy or 105 days before LMP reported to the Novartis global safety database were eligible for the PRIM program.

Data sources and data collection methods

The data source was the Novartis global safety database and included cases reported from clinical trials, spontaneous post-marketing reports, post-marketing observational studies and patient-oriented programs. Data was collected using the TFU checklists, following Novartis case processing guidelines and standard operating procedures.

Statistical methods

The primary crizanlizumab PRIM analysis cohort consisted of the prospectively reported pregnancies associated with maternal exposure during pregnancy or up to 105 days before LMP. Since retrospective cases may be subject to reporting biases but still be informative, these are reported separately.

Data analysis included the number of cases of fetal loss, malformations, and specific pregnancy outcomes. Further analyses and estimation of 95% CI as proposed in the protocol were not performed on account of the low number of patients in the study.

Results

As of the data lock point of 30-Jun-2025, there were a total of 13 patients (8 prospective and 5 retrospective pregnancy cases) in the crizanlizumab PRIM study. Among the 8 prospective cases, the pregnancy outcome was known in 5 cases and unknown in 3 cases. Most patients in the prospective pregnancy cohort (7 of 8) had been exposed to crizanlizumab at least in the first trimester (this includes patients who may have been exposed in the pre-LMP period or other trimesters in addition to exposure in the first trimester).

Among the 8 prospective cases in the crizanlizumab PRIM study, 3 resulted in live births (2 full-term and 1 preterm). Among the 5 retrospective pregnancy cases, there were 2 live births (1 full-term and 1 preterm).

Pertaining to the primary objective of fetal loss, there were 2 spontaneous abortions among the prospective pregnancy cases and 1 spontaneous abortion among the retrospective pregnancy cases. No still births were reported. There was no induced termination among the prospective pregnancies and 2 induced terminations in the retrospective pregnancy cohort.

Related to the secondary objectives, no major or overall congenital malformations were noted.

CCI [redacted]

Discussion

The crizanlizumab PRIM study was terminated prematurely on account of the low number of patients in the study.

Specific to the primary endpoint of fetal loss, no stillbirths were reported in this study. The frequency of spontaneous abortion was generally in line with the frequency of spontaneous abortion reported in patients with SCD.

Pertaining to the secondary endpoints (major and overall congenital malformations) of this study, no congenital malformations were reported in this study.

CCI [redacted]

The very low number of cases, limited information on the cases, and the possibility of selection bias in reporting with multiple cases lost to follow-up are potential limitations of this study.

Conclusion

The crizanlizumab PRIM study was terminated prematurely on account of the low number of patients in the study. No safety concerns were identified in this study and there is no change in the benefit-risk balance of the product based on the results of this study.

Marketing Authorization Holder(s)

Novartis Pharmaceutical Corporation

Name(s) and Affiliation(s) of Principal Investigator(s)

Not applicable.

2 List of abbreviations

ADA	Anti-Drug Antibodies
EU	European Union
FU	Follow Up
HC	Hydroxycarbamide
HCP	Health Care Provider
HU	Hydroxyurea
CCI	[redacted]
LMP	Last Menstrual Period
MAH	Marketing Authorization Holder
MAP	Managed Access Program
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PK	Pharmacokinetics
PRIM	PRegnancy outcomes Intensive Monitoring
PT	Preferred Terms
SCD	Sickle Cell Disease
CCI	[redacted]
SMQ	Standardized MedDRA Queries
SOP	Standard Operating Procedure
TE	Tracheoesophageal
TFU	Targeted Follow-Up
TOPFA	Termination Of Pregnancy for Fetal Anomaly

3 Investigators

Not applicable

4 Other responsible parties

Not applicable.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date
Final protocol	**10-Jul-2020**	**10-Jul-2020**
Start of data collection	15-Nov-2020	15-Nov-2020
End of data collection (Last date of data collection)	14-Nov-2030*	30-Jun-2025
Final Study Report	14-Nov-2031^	30-Oct-2025

*or earlier once 500 prospectively reported pregnancy cases with known pregnancy outcome are enrolled, ^ or 12-months post-end of data collection, whichever comes first

6 Rationale and background

Adakveo® (crizanlizumab) is a p-selectin inhibitor indicated to reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease (SCD) (ADAKVEO USPI 2024).SCD is a genetic blood disorder that is present at birth and early on, progresses into a systemic disease resulting in complications such as vaso-occlusion, multi-organ damage, and early death (Rees et al 2010, Habara and Steinberg 2016, CDC 2025).

Compared with pregnant women in the general population, pregnant women with SCD have increased risk of pregnancy complications and adverse pregnancy outcomes, including both maternal as well as fetal complications, with frequencies ranging from approximately 3% for endpoints such as maternal or neonatal mortality, 8% for stillbirths, 21% for prematurity, to 26% for bacterial infection (Boafor et al 2016). The frequencies of spontaneous abortions and malformations have been reported to be around 28-38% and 14%, respectively in patients with SCD (Kuo et al 2016, Silva et al 2018).

Data on the pregnancy and infant outcomes in patients with SCD treated with crizanlizumab are limited. No clinical studies have been conducted in pregnant or lactating women with SCD on crizanlizumab.

In a preclinical enhanced pre- and postnatal development study in cynomolgus monkeys, pregnant animals received intravenous doses of crizanlizumab at 10 and 50 mg/kg once every 2 weeks during the period of onset of organogenesis through delivery (Study number 20124482). Compared to control, there was an increase in the proportion of fetal loss (spontaneous abortions or stillbirths) at both crizanlizumab doses. This was higher in the third trimester. The cause for the increased losses is unknown but it is believed to be the development

of anti-drug antibodies (ADA) in monkeys against crizanlizumab, a humanized monoclonal antibody. In most instances, fetal losses occurred in mothers testing positive for ADAs, several having dose reactions.

There were no teratological findings (external or visceral or skeletal) in the aborted fetuses, infant deaths or those otherwise born alive. There were no effects on infant growth and development at 6-months postpartum (approximately equal to a 2 year old human) that were attributable to crizanlizumab. In view of the increased risk of pregnancy complications and adverse outcomes in women with SCD, the animal data as mentioned above, and potential use of crizanlizumab in women of childbearing potential with SCD, Novartis initiated the crizanlizumab PRIM study for crizanlizumab. A limit of up to 105 days before last menstrual period (LMP) for crizanlizumab exposure, based on half-life and PK variability in SCD patients, is used in the crizanlizumab development program. [Appendix 15.1.1-Section 2]

Although the study initiated in 2020, the marketing authorizations for Adakveo® were revoked or suspended in several countries, including the EU in Aug-2023, following the study results of CSEG101A2301. As of 30-Jun-2025, there were fewer than 15 pregnancies in the crizanlizumab PRIM study. Given the very low number of patients in the study and the low probability of substantial increase in the sample size, the crizanlizumab PRIM study was terminated prematurely and an abbreviated study report is prepared.

7 Research question and objectives

The overall objective of the crizanlizumab PRIM study was to collect data on pregnancy outcomes in patients treated with crizanlizumab during pregnancy or within 105 days before the LMP. Data on infant outcomes at 3 and 12 months post-delivery were also collected. The findings from this program were used to evaluate the missing information 'Use in pregnancy', according to the Risk Management Plan.

Primary objective:

- To estimate the proportion of pregnancies resulting in fetal loss (intrauterine death resulting in stillbirth, spontaneous abortion, or induced termination), among pregnant women exposed to crizanlizumab within 105 days prior to LMP or at any time during pregnancy.

Secondary objectives:

- To estimate the proportion of major congenital malformations among pregnancies exposed to crizanlizumab up to 105 days before LMP and during pregnancy reported to Novartis amongst (i) live births and (ii) live births plus still births plus termination of pregnancy for fetal anomaly (TOPFA).
- To estimate the proportion of overall congenital malformations among pregnancies exposed to crizanlizumab up to 105 days before LMP and during pregnancy reported to Novartis with the outcome of total live births, and live birth plus still births and TOPFA.

CCI

[redacted]

CCI

[redacted]

8 Amendments and updates to the protocol

None

9 Research methods

9.1 Study design

The crizanlizumab PRIM study is a secondary use of data, non-interventional study (NIS) based on the data collected via a set of targeted follow-up (TFU) checklists with structured follow-up on pregnancies spontaneously reported to the Novartis global safety database. This study is single-arm, descriptive in nature and includes worldwide data coverage.

9.2 Study population and data source

The study utilizes data collected on pregnancies reported to the Novartis global safety database and followed up via the PRIM process. The data source for this study is the Novartis global safety database.

All prospective and retrospective pregnancy cases exposed to crizanlizumab during pregnancy or up to 105 days before LMP reported to the Novartis global safety database were eligible for the PRIM program. Data corresponding to TFU checklists were entered into the Novartis safety database per Novartis SOPs governing pharmacovigilance safety procedures. See Table 9-1 and Table 9-2 for additional information on outcomes.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome (i.e., pregnancy outcome [live birth, stillbirth, spontaneous abortion, induced termination]) or known abnormal findings obtained from a prenatal test at the time of initial reporting to Novartis. In acknowledgement of the high risk of bias resulting from retrospective reports, retrospective pregnancy cases were analyzed and presented separately from prospective cases.

The data source was the Novartis global safety database and included cases reported from clinical trials, spontaneous post-marketing reports, post-marketing observational studies and patient-oriented programs.

Inclusion criteria

All prospective and retrospective pregnancy cases exposed to crizanlizumab during pregnancy or 105 days before LMP reported to the Novartis global safety database were eligible for the PRIM program.

Exclusion criteria

Cases with the following exclusion criteria were excluded from the crizanlizumab PRIM study:

- Patients who upon initial case report refuse to be contacted to obtain any FU information. In such cases necessary information using PRIM follow-up checklists cannot be obtained.
- Indirect cases (reported by someone other than the patient or the healthcare provider (HCP)) for which the reporter refuses to provide FU information and the patient or HCP cannot be identified based on the information provided.
- Pregnancies of female partners of male patients taking crizanlizumab. Such cases were to be processed as per MAP.
- Cases lacking reporter contact details (e.g., cases from social media) or incomplete cases in which data was missing to allow classification of pregnancy or infant outcomes.

Table 9-1 Definition of pregnancy outcomes

Outcome	Definition
Full-term live birth	The patient gives birth to live neonate between 37 and 42 weeks of gestation
Premature live birth	The patient gives birth to a live neonate before 37 completed weeks of gestation.
Postmature Delivery	Delivery after 42 weeks of gestation
Elective termination	Termination of pregnancy due to choice of mother of an otherwise normal fetus.
Therapeutic abortion	If an abortion procedure occurs due to abnormal fetus, fetal death or risk to the mother, select 'therapeutic abortion'. Risk to the mother: When therapeutic abortion is due to maternal complications Fetal anomaly: If therapeutic abortion is due to fetal anomalies
Spontaneous abortion	The fetus is spontaneously aborted (prior to 22 weeks gestation); prior fetal status via prenatal testing may or may not be known.
Stillbirth	The patient gives birth to a still born (no signs of life) at or after 22 weeks of gestation is completed
Outcome pending	The outcome of the pregnancy is not known (outcome/due date is pending, or queries are outstanding)
Lost to follow-up (LTFU)	No further information is received regarding pregnancy outcome even after pursuing appropriate number of follow-ups for a case

Source: Manual for Argus processing

Table 9-2 Definition of fetal/infant outcomes

Outcome	Definition
Normal baby/normal infant	Live birth where there is no mention of fetal abnormalities or perinatal complications (regardless of gestational age).

Outcome	Definition
Congenital anomaly major	A congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact.
Congenital anomaly minor	A congenital abnormality that does not require medical or surgical treatment, does not seriously affect health and development, and does not have significant cosmetic impact.
Congenital/other (structural) abnormality, NOS	Reported congenital anomaly without diagnostic information or other structural anomalies not well described.
Perinatal complication (non-structural)	Non-structural perinatal complication of fetus: from 22 weeks of gestation (154 days) to 7 days after birth.
Post-perinatal complication	Non-structural post-perinatal complications of fetus: following 7 days after birth.
Abnormality, other (non-structural),	Non-structural abnormalities not related to delivery, other non-structural anomalies not well described or anomalies reported as normal variant
Fetal death / intrauterine death	Fetal death confirmed by pre-natal tests, followed by a spontaneous abortion or requiring a therapeutic abortion, or stillbirth.
Blighted ovum	Absence of an embryo in a normal-appearing gestational sac visible on ultrasound.
Ectopic pregnancy	Implantation of the embryo outside the uterine cavity
Hydatidiform mole	Gestational trophoblastic disease where a non-viable fertilized egg or embryo implants in the utero and grows into a mass (instead of a fetus).
Infant status unknown	Information regarding the fetus is not known
Outcome pending	Select when queries are pending, or if this is a future date of delivery
Lost to follow up	When all query attempts per SOP have been exhausted, or there is no consent to contact reporter

Source: Manual for Argus processing

9.3 Data collection methods

Data on pregnancies and infants was collected using crizanlizumab PRIM TFU checklists at baseline after the initial report of the case was received in the Novartis global safety database, then after the delivery, and again at 3 months and 12 months following birth. At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart were made at each timepoint. The full data collection methodology was described in the CSEG101A2404 protocol.

9.4 Bias

Given the low sample size available in the study, the data from this study may not be clinically meaningful, estimates may not be precise, and the results may not be representative of the SCD population on crizanlizumab therapy. Several patients did not respond to the TFU checklists despite multiple follow-up attempts and were lost to follow-up, leading to possible selection bias in the study.

9.5 Study size

Based on the present analysis of expected precision and power, a sample of at least 500 prospective pregnancy cases with known pregnancy outcome was considered acceptable at the start of this study. However, at the time of the termination of the study, there are 8 prospective pregnancies and 5 retrospective pregnancies being evaluated in the study.

9.6 Data analysis

In view of the low number of patients in the study, only descriptive analysis was performed. Case counts for prospective and retrospective pregnancy cases, respectively, were presented for available variables, including case disposition (outcome known, pending, and lost to follow-up) and maternal characteristics (i.e., age, ethnicity, region). Estimation of 95% confidence intervals and further analyses were not performed.

10 Results

The Novartis global safety database was reviewed to identify pregnancy cases among patients exposed to crizanlizumab. The initial pool consisted of 71 cases identified using SMQ for Pregnancy and Lactation. From this, 2 incomplete cases and 25 cases with preferred terms (PT) related only to SCD or anemia (without pregnancy-related terms) were excluded, leaving 44 cases.

After applying all exclusion criteria, 13 cases were deemed eligible for inclusion in the crizanlizumab PRIM study. Table 10-1

Table 10-1 Review of pregnancy cases in the Novartis global safety database

Criteria used	Number of cases included	Cases excluded
Number of cases with SMQ – Pregnancy and Lactation	71	
Number of incomplete cases		2
Number of cases with PT of sickle cell disease/anemia (no pregnancy terms)		25
Number of cases after excluding incomplete cases and cases with PT of sickle cell disease or sickle cell anemia (no pregnancy-related terms)	44	
Baby case		5
Insufficient details/reported information/Did not want to be contacted		9

Criteria used	Number of cases included	Cases excluded
Lost to Follow-up		8
Paternal exposure		6
Exposure to crizanlizumab prior to 105 days before LMP		1
Reported prior to start of crizanlizumab PRIM study		1
Not pregnancy (repair of TE fistula in adult woman with SCD)		1
Number of cases for PRIM	13	

Source: Crizanlizumab pregnancy cases from Novartis safety database (28-Oct-2020 to 30-Jun-2025)

As of the data lock point of 30-Jun-2025, there were a total of 13 patients (8 prospective and 5 retrospective pregnancy cases) in the crizanlizumab PRIM study (Table 10-1). Among the 8 prospective cases, the pregnancy outcome was known in 5 cases and unknown (due to lost to follow-up) in 3 cases.

This indicates partial outcome data for prospective ones due to follow-up challenges. Most patients in the prospective pregnancy cohort (7 of 8) had been exposed to crizanlizumab at least in the first trimester (this includes patients who may have been exposed in the pre-LMP period or other trimesters in addition to exposure in the first trimester).

Information on the study outcomes is presented in Table 10-2.

Table 10-2 Pregnancy and maternal characteristics

Characteristic	Prospective cases (n=8)	Retrospective cases (n=5)
Number of pregnant women in PRIM	8	5
Number of pregnancies in PRIM	8	5
Maternal age (mean)		
Maternal ethnicity		
- Black	5	2
- Hispanic	2	0
- Arab	0	1
- Other/Not reported	1	2
CCI [redacted]		
Source of report		

Characteristic	Prospective cases (n=8)	Retrospective cases (n=5)
- Spontaneous report	1	1
- Clinical trial	3	1
- Managed access program	3	2
- Patient-oriented program	1	0
- Literature	0	0
- Non-Interventional Studies	0	1
Concomitant exposure to HU/HC		
- Yes	4	2
Case disposition		
- pregnancy outcome* known	5	5
- lost to follow-up	3	0
Exposure		
Trimester of exposure/timing of exposure category		
- Pre-LMP only (From 105 days before LMP to LMP)	0	0
- At least 1st trimester (This category may include cases with exposure also in other periods)	7	5
- After 1st trimester only	0	0
- Unknown timing of exposure during pregnancy	1	0
- Overall (any exposure between 105 days before LMP and end of the pregnancy)	8	5

Source: Crizanlizumab pregnancy cases from Novartis safety database (28-Oct-2020 to 30-Jun-2025)
***** Pregnancy outcomes - live birth, stillbirth, spontaneous abortion, induced termination

Among the 8 prospective cases in the crizanlizumab PRIM study, 3 resulted in live births (2 full-term and 1 preterm). Among the 5 retrospective pregnancy cases, there were 2 live births (1 full-term and 1 preterm).

Pertaining to the primary objective of fetal loss, there were 2 spontaneous abortions among the prospective pregnancy cases and 1 spontaneous abortion among the retrospective pregnancy cases. No still births were reported in either the prospective or retrospective pregnancy cases. There were no induced terminations among the prospective pregnancies, whereas 2 occurred in the retrospective pregnancy cohort (one therapeutic abortion due to severe anemia and other maternal complications, and one elective termination).

Related to the secondary objectives, no major or overall congenital malformations were noted.

PPD CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 10-3 Study Outcomes

Outcome	Prospective case (n = 8)	Retrospective case (n = 5)
For primary objective		
Fetal loss		
- Stillbirth	0	0
- Spontaneous abortion	2	1
- Induced termination		
- Therapeutic abortion	0	1
- Elective termination	0	1
Live birth	3	2
Lost to follow-up (pregnancy outcome unknown)	3	0
Gestational age at live birth		
- CCI [redacted]		
- Full-term	2	1
- CCI [redacted]		
-		
For secondary objectives		
Major congenital malformation	0	0
Minor congenital malformation	0 #	0
Overall congenital malformation*	0 #	0

Source: Crizanlizumab pregnancy cases from Novartis safety database (28-Oct-2020 to 30-Jun-2025)

*includes major, minor, not otherwise specified; PPD CCI [redacted]

11 Discussion

11.1 Key results and interpretation

The crizanlizumab PRIM study was terminated prematurely on account of the low number of patients in the study and the low probability of substantial increase in the sample size. Although at the time of the initiation of the study, it was planned to include a sample size of 500 prospective pregnancy cases with known outcome or continue the study up to a period of 10 years from the start of the study, only 8 prospective pregnancy cases were accrued in the study over an almost five-year period. Further substantial increase in patient numbers is considered unlikely with the recent changes in the regulatory status. Among the countries that have previously reported cases to the PRIM study, crizanlizumab is currently (as of June 2025)

commercially available only in the US, which accounted for just 3 of the 13 cases available in the PRIM study.

Due to the small number of patients available for evaluation and the fact that the pregnancy outcome was unknown in several of these cases, no definitive conclusions can be made from the data. Specific to the primary endpoint of fetal loss (intrauterine death resulting in stillbirth, spontaneous abortion, or induced termination), no stillbirths were reported in this study. Two of the 8 prospective pregnancies (25%) and 1 of 5 retrospective pregnancies (20%) ended in spontaneous abortion, which is in line with the frequency of spontaneous abortion (28% and 38% in patients with SCD genotypes Hemoglobin SS and Hemoglobin SC, respectively) reported in patients with SCD by Silva et al 2018. When considering only the cases where the outcomes were known, 2 of 5 prospective pregnancy cases (40%) resulted in spontaneous abortion. Although numerically higher than the frequency of spontaneous abortions among SCD patients with HbSS in the study by Silva et al 2018, considering the very low number of cases, limited information on the cases, and the possibility of selection bias in reporting with multiple cases lost to follow-up, these numbers are considered inconclusive. Pertaining to the secondary endpoints (major and overall congenital malformations) of this study, no congenital malformations were reported in this study.

CCI [redacted]

No safety concerns were raised in this study and the results of this study do not change the benefit-risk balance of crizanlizumab.

11.2 Limitations

The main limitation of this study was that only a very small sample of patients was available for analysis. The study included only 8 prospective pregnancies and 5 retrospective pregnancies. Furthermore, pregnancy outcomes were not available on all patients. Therefore, the estimates of the event frequencies are not considered precise and may not be representative of the entire population. CCI [redacted]

12 Conclusion

The crizanlizumab PRIM study was terminated prematurely on account of the low number of patients in the study.

No safety concerns were identified in this study and there was no change in the benefit-risk balance of the product based on the results of this study.

13 References

Available upon request.

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Appendices

Appendix 1 – List of stand-alone documents

Appendix	Appendix Title	Documents included
15.1.1	Protocol	Yes
15.1.2	Crizanlizumab (SEG101) Pregnancy Baseline FU checklist	Yes
15.1.3	Crizanlizumab (SEG101) Pregnancy Outcome FU checklist	Yes
15.1.4	Crizanlizumab (SEG101) Infant Health Status FU checklist	Yes
15.1.5	Signature page of final study report	Yes