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SEG101

Adakveo (crizanlizumab) PRegnancy outcomes Intensive Monitoring (PRIM)

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Gender	Female patients
Age	≥ 16 years

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Abbreviations

ADA	Anti-drug antibodies
CO	Country Organizations
DS&A	Data Safety and Analytics
EDD	Estimated date of delivery
ESPs	External service providers
FU	Follow-up
HCP	Healthcare provider
HU/HC	Hydroxyurea/hydroxycarbamide
IV	Intravenous
IUGR	Intra-uterine growth restriction
LMP	Last menstrual period
MAP	Manual for Argus Processing
POPs	Patient Oriented Programs
PGD	Product Guidance Document
PRIM	PRegnancy outcomes Intensive Monitoring
SCD	Sickle cell disease
SOPs	Standard operating procedures
TOPFA	Termination of pregnancy for fetal anomaly
VOC	Vaso-occlusive crises

1 Product

Adakveo (crizanlizumab) 10 mg/mL concentrate for solution for infusion

In the EU, Adakveo is indicated for the prevention of recurrent vaso-occlusive crises (VOC) in sickle cell disease (SCD) patients aged 16 years and older. It can be given as an add-on therapy to hydroxyurea (HU/HC) or as monotherapy in patients for which HU/HC is inappropriate or inadequate.

The recommended dose of Adakveo is 5 mg/kg administered over a period of 30 minutes by intravenous (IV) infusion at Week 0, Week 2, and every 4 weeks thereafter.

2 Rationale

Compared with pregnant women in the general population, pregnant women with SCD have increased risk of pregnancy complications and adverse pregnancy outcomes, including maternal complications such as pre-eclampsia, eclampsia, infection, and maternal mortality, as well as fetal complications such as intrauterine growth restriction (IUGR), preterm delivery, low birth weight, and perinatal mortality (Boafor et al 2016, Kuo and Caughey 2016).

The most precise estimates of the frequency of pregnancy complications and adverse pregnancy outcomes in SCD are available from the meta-analysis published by Boafor et al (2016) (Table 2-1). The adverse event frequencies range from approximately 3% for endpoints such as maternal or neonatal mortality to approximately 25% for common adverse

events such as bacterial infection. The frequencies of spontaneous abortions and malformations were not examined in this meta-analysis, but are known to be around 28% and 14%, respectively from other studies in SCD (Kuo et al 2016, Silva et al 2018).

Table 2-1 Frequencies of adverse pregnancy outcomes in SCD patients from a meta-analysis (Boafor et al, 2016)

Outcome	Number of studies reporting the outcome	Outcome frequency in SCD patients	%	Number of SCD patients (sample size)
IUGR	10	290	12.3	2367
Perinatal mortality	6	85	8.3	1025
Prematurity	11	437	21.1	2076
Low birthweight	9	322	16.5	1947
Stillbirth	10	131	8.1	1615
Neonatal mortality	6	24	2.5	954
Pre-eclampsia	12	229	10.3	2222
Eclampsia	9	245	7.3	3376
Postpartum hemorrhage	5	75	4.3	1752
Bacterial infection	8	690	25.8	2675
Maternal mortality	9	46	3.0	1523

IUGR = intrauterine growth restriction; SCD = sickle cell disease

It is currently unknown whether crizanlizumab therapy can affect the risk of pregnancy complications or adverse pregnancy outcomes in pregnant women with SCD. In an enhanced pre- and postnatal development study in cynomolgus monkeys, pregnant animals received intravenous doses of crizanlizumab at10 and 50 mg/kg once every 2 weeks during the period of onset of organogenesis through delivery. Maternal exposures at doses of 10 and 50 mg/kg were between 2.8 and 16 times higher, respectively, than the human clinical exposure based on area under the curve (AUC) in patients with SCD at 5 mg/kg/dose once every 4 weeks.

Findings of this study were:

- Measurable crizanlizumab serum concentrations were observed in the infant monkeys at postnatal Day 28, confirming that crizanlizumab crosses the placental barrier.
- No maternal toxicity was observed.
- Compared to control, there was an increase in the proportion of fetal loss (spontaneous abortions or still births) at both crizanlizumab doses which was higher in the third trimester. The cause for the –increased losses is unknown but is believed to be the development of anti-drug antibodies (ADA) in monkeys against crizanlizumab, a humanized monoclonal antibody. In most instances, the fetal losses occurred in mothers testing positive for ADAs, several having dose reactions.
- There were no teratological findings (external or visceral) 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.

Female patients with SCD are typically in the age of childbearing potential; therefore frequent use of crizanlizumab in this patient group can be expected. No clinical studies have been conducted in pregnant or lactating women, and data on crizanlizumab exposure during pregnancy in the clinical program is very limited. Until 04-Oct-2019, in crizanlizumab clinical studies, 5 cases of pregnancy were reported among subjects receiving crizanlizumab; 2 in the 5 mg/kg arm and 1 each in the 2.5 mg/kg and placebo arms of Study A2201, and 1 case in Study A2202. In two cases the pregnancy outcome was unknown (1 self-induced abortion, 1 follow-up missing). The three other cases were premature deliveries due to pre-eclampsia with two normal newborns and one with low birth weight. With this small number of cases and the high background risk of pregnancy complications and adverse pregnancy outcomes in women with SCD (Table 2-1), a causal association of these outcomes with crizanlizumab cannot be estabished.

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, Novartis is establishing the PRIM program 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 crizanlizumab), is used in the crizanlizumab development program.

3 Type of Program

A PRegnancy outcomes **I**ntensive **M**onitoring **(PRIM)** program (Geissbühler, Rezaallah, and Moore 2020), based on enhanced pharmacovigilance of the Novartis spontaneous reporting system to collect information about pregnancy outcomes in patients exposed to crizanlizumab during pregnancy and up to 105 days before last menstrual period (LMP) and about infant outcomes 12 months post-delivery will be initiated. All prospective and retrospective pregnancy cases reported to Novartis (as defined in Table 5-1) will be monitored using enhanced follow-up (FU) mechanisms. Retrospective cases will be analyzed separately due to the high risk of reporting bias.

4 Objectives

The overall objective of the crizanlizumab PRIM program is to collect data on pregnancy outcomes in patients treated with crizanlizumab during pregnancy or within 105 days before the last menstrual period (LMP).

Data on infant outcomes at 3 and 12 months post-delivery will also be collected. The findings from this program will be used to evaluate the missing information ‘Use in pregnancy’, according to the Risk Management Plan.

4.1 Primary objective

Considering the preclinical safety findings of fetal loss (without congenital malformations, maternal toxicity, or adverse effects on infant growth and development), the primary objective of this analysis was defined as follows:

- 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.

4.2 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.

5 Methodology

This program is based on pregnancy case reporting in the Novartis global safety database (Argus). All "prospective" and "retrospective" pregnancy cases reported to the Novartis global safety database (Table 5-1, Figure 5-1) via spontaneous reports, other post-marketing sources (including post-marketing observational studies, patient-oriented programs, literature) and clinical trials are included. Data from PRIM checklists are entered into the Novartis global safety database per Novartis standard operating procedures (SOPs) governing pharmacovigilance safety procedures and Manual for Argus Processing (MAP). As per the MAP, individual cases of mother and fetus/infant are linked with each other in Argus and can be identified for data extraction.

The primary outcome of interest is fetal loss (intrauterine death resulting in stillbirth, spontanous abortion, or induced termination). Pregnancy and fetal/infant outcomes are defined in Table 5-2 and Table 5-3 below.

All prospective and retrospective pregnancy cases exposed to crizanlizumab during pregnancy or 105 days before LMP reported to the Novartis global safety database will be eligible for the PRIM program. A limit of up to 105 days before last menstrual period (LMP) for crizanlizumab exposure will be used, as it accounts for 5 half-lives of crizanlizumab. This is based on PK data in SCD patients from Study A2202 (4-Oct-2019 cut-off), which showed that individual elimination half-life ranged up to 1.94 fold the mean elimination half-life of 10.6 days. Based on this, 5 half-lives are calculated as 103 days (mean half-life of 10.6 days x 1.94 x 5). This is consistent with a washout period of approximately 105 days (5 half-lives of crizanlizumab), which is used in the crizanlizumab development program.

Retrospective pregnancy cases are defined as pregnancy cases with known pregnancy outcome at the time of initial reporting to Novartis [i.e. pregnancy outcome (live birth, still birth, spontaneous abortion, induced termination)] or abnormal findings from a prenatal test is known (Table 5-1). Retrospective pregnancy cases will be analyzed and presented separately from the prospective cases in acknowledgement of the high risk of bias resulting from retrospective reporting. Necessary follow-up information will be collected for such cases.

Information on reporter types will be collected from HCPs and non-HCPs.

Cases with the following exclusion criteria will be excluded from PRIM:

- 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 will continue to be processed as per MAP.
- Cases lacking reporter contact details (e.g. cases from social media) or incomplete cases – cases in which data is missing to allow classification of pregnancy or infant outcomes.

Table 5-1 Prospective case definition[a], Adakveo PRIM

Timing and results of prenatal testing	PRIM
Pregnancy outcome has not occurred and prenatal tests have not been performed at the time of reporting or entry[b]	Prospective
Prenatal testing was performed at the time of entry, results have not been received by provider/patient/Novartis	Prospective
Prenatal test results were available, and were known to be normal or results were not specified at the time of entry	Prospective
Prenatal test results were available and were known to be abnormal at the time of entry	Retrospective

a) Definitions of retrospective and prospective cases is as per EMA guidance
b) 'Entry' is considered the date of initial report received by Novartis for PRIM cases

Table 5-2 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

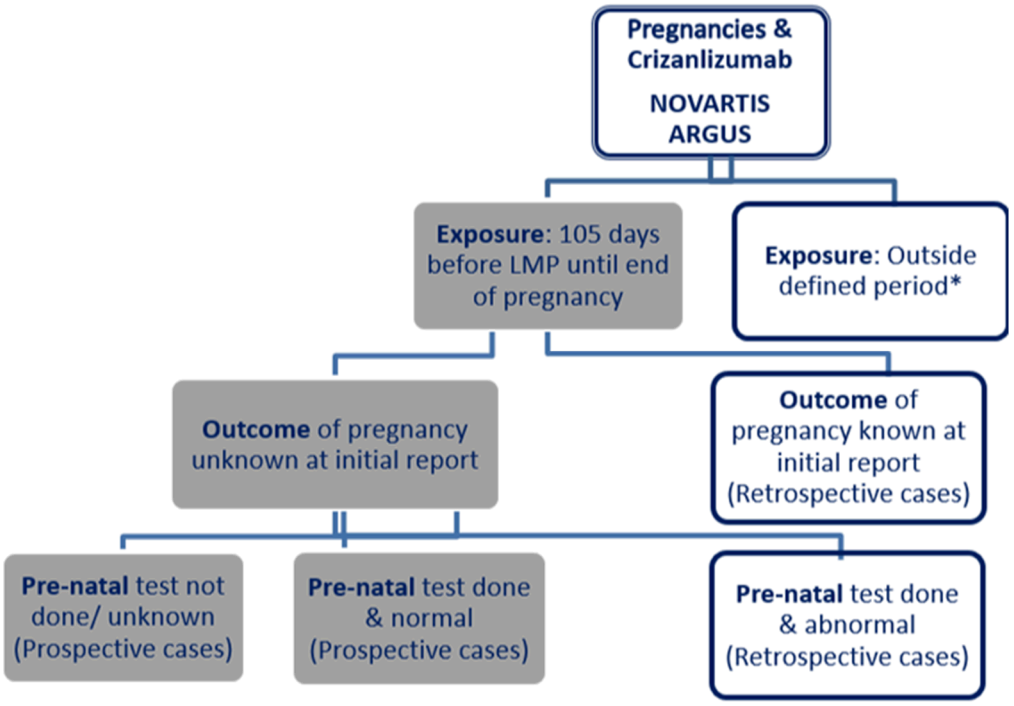
Table 5-3 Definition of fetal/infant outcomes

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

Outcome	Definition
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

Figure 5-1 Schematic representation of PRIM retrospective/prospective case in patients on crizanlizumab treatment reported to ARGUS



5.1 Follow up schedule

All follow-ups will be collected using crizanlizumab PRIM FU checklists, as per the following schedule:

Table 5-4 Follow Up schedule using PRIM FU checklists*

FU number	Checklist name	Type of information collected	Date of collection	Attempts cycle (in case of no response)
FU 1	Crizanlizumab Pregnancy Checklist Baseline	Baseline characteristics and demographics of the mother	As soon as possible after initial report, or at initial report if possible	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart, unless EDD is reached (in such case merge FUs 1 and
FU 2	Crizanlizumab Pregnancy Checklist – Pregnancy Outcome	Information related to the delivery and neonate details (including risk factors)	Between EDD and EDD+30 days	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.

FU 3	Crizanlizumab Pregnancy Checklist – Infant Status	Information related to infant health status and development	EDD + 3 months	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.
FU4	Crizanlizumab Pregnancy Checklist – Infant Status	Information related to infant health status and development	EDD + 12 months	At least 4 attempts, at a minimum of 1 week and maximum of 1 month apart.

**FU schedule and requirements to be included in crizanlizumab pharmacovigilance guidance document (PGD).*
EDD – estimated date of delivery

5.2 Follow up scheme

The follow up (FU) is composed of two main activities:

1. Intensive FU activities:
   a. Additional FU attempts before a patient is considered "lost to FU": Instead of the minimum 3 attempts at outcome as per the current SOP, Country Organizations (COs) will routinely make at least 4 FU attempts at each FU time point before a patient is considered "lost to FU". Such attempts should, when possible, be made simultaneously with the initial reporter and one or more HCPs (when such information is provided), and by all available means of contact (phone, e-mail, letter, fax, etc.).
   b. For specific Patient Oriented Programs (POPs) with continuous interactions with patients, external service providers (ESPs) will be requested to collect the necessary FU information (when allowable by local regulations and program design). If not feasible for ESPs to implement, the responsibility to ensure FU activities remains with the COs.
   c. Automated check for overdue FUs: Data Safety and Analytics (DS&A) will generate a listing of overdue FUs. This listing will be distributed to the countries, which will then perform the FU using the applicable targeted FU checklist (according to the intensive FU scheme).
   d. Global Medical Safety Function will contact directly COs with long overdue FU (>30 days). When necessary, assigned pharmacovigilance leader will liaise with global medical affairs and/or clinical development teams to request their support in obtaining the necessary FU (using the system in place for enhanced FU of events of special interest).
2. PRIM FU checklists: a specific set of targeted FU checklists will enable the collection of all necessary information to evaluate safety data on crizanlizumab exposure upto 105 days before LMP and during pregnancy and associated pregnancy, fetal and infant outcomes. In case of no response, further attempts will be made by COs as per schedule in table 5-4. Development, approval and distribution of these FU checklists will follow the applicable Novartis safety processesing standards.

PRIM FU Checklists are the minimum information necessary. Additional FU may be requested in case of congenital anomaly and/or concurrent adverse events. Additional FU will be done according to applicable SOP.

5.3 Sample size and power

Based on the present analysis of expected precision and power (Table 5-5 to Table 5-7), a sample of at least 500 prospective pregnancy cases with known pregnancy outcome may be acceptable, especially if the control sample size will exceed the size of the PRIM cohort at least by a factor of 3 (R=3). The latter is a reasonable expectation, considering the SCD cohort sizes shown in Table 2-1. For additional details on power and sample size estimation, please see Section 10.1 (Appendix).

For the primary endpoint of fetal loss, the event frequency is anticipated to be at least equal to 25%. For example, in one study of 89 SCD pregnancies, spontaneous abortion occurred in 25 pregnancies (28%) (Silva et al 2018). Stillbirth, which is another type of fetal loss has a reported frequency of approximately 8% in SCD (Boafor et al 2016).

For adverse events with background risk of 25% or greater, including the primary endpoint of fetal loss, superiority and non-inferiority power with N=500 treated patients is above 90% for all settings with R=3 shown in Table 5-7. Precision of estimation of the absolute and relative risk parameters is also reasonable at N=500 patients with R=3 (Table 5-5, Table 5-6).

For adverse events with background incidence around 10%, superiority power given an odds ratio of 2.0 (i.e., risk difference 0.082) is close to 100%, and non-inferiority power with a non-inferiority margin of 2.0 (risk difference 0.082) is well over 90%. With an odds ratio of 1.5, the null hypothesis of no increased risk is much more likely than not to be rejected (75% power) when at least 500 treated patients are enrolled with R=3, although this is slightly below the conventional threshold of 80% for this smaller effect size, which is equivalent to an absolute risk increase of about 0.043 (given the background risk of 0.10).

For adverse events with background incidence of 3%, a sample size of 500 treated patients and R=3 will result in a power of approximately 81% to reject the null hypothesis of no increased risk, if the true odds ratio is equal to 2.0, which is equivalent to a risk difference of 0.028 (Table 4). On the other hand, under the causal null hypothesis (true odds ratio = 1, true risk difference = 0) with the same background risk and sample size settings, the power to rule out an odds ratio ≥ 2.0 (i.e., a risk difference ≥ 0.028) with 95% confidence would be somewhat lower, around 63% (Table 5-7), highlighting the important distinction between superiority and non-inferiority power.

Table 5-5 Precision of estimation of the absolute risk on treatment (SEG101), as a function of sample size

N for PRIM	Absolute Risk	E(LCL-Exact)	E(UCL-Exact)	Exact ME	E(LCL-Wald)	E(UCL-Wald)	Wald ME
100	0.03	0.008	0.084	0.038	0.000	0.063	0.033
300	0.03	0.014	0.056	0.021	0.011	0.049	0.019
500	0.03	0.017	0.049	0.016	0.015	0.045	0.015
100	0.05	0.018	0.112	0.047	0.007	0.093	0.043
300	0.05	0.028	0.081	0.026	0.025	0.075	0.025

500	0.05	0.033	0.073	0.020	0.031	0.069	0.019
100	0.10	0.050	0.175	0.063	0.041	0.159	0.059
300	0.10	0.069	0.140	0.035	0.066	0.134	0.034
500	0.10	0.075	0.130	0.027	0.074	0.126	0.026
100	0.15	0.087	0.235	0.074	0.080	0.220	0.070
300	0.15	0.112	0.195	0.042	0.110	0.190	0.040
500	0.15	0.120	0.184	0.032	0.119	0.181	0.031
100	0.20	0.127	0.291	0.082	0.122	0.278	0.078
300	0.20	0.156	0.250	0.047	0.155	0.245	0.045
500	0.20	0.166	0.238	0.036	0.165	0.235	0.035
100	0.25	0.169	0.346	0.088	0.165	0.335	0.085
300	0.25	0.202	0.303	0.050	0.201	0.299	0.049
500	0.25	0.213	0.290	0.039	0.212	0.288	0.038
100	0.50	0.399	0.601	0.101	0.402	0.598	0.098
300	0.50	0.442	0.558	0.058	0.443	0.557	0.057
500	0.50	0.455	0.545	0.045	0.456	0.544	0.044

N = PRIM sample size; E(LCL) = expected location of the 95% lower confidence limit; E(UCL) = expected location of the 95% upper confidence limit; ME = margin of error (one-half of the confidence interval length).

Technical note: Quantities denoted by E(LCL-Wald) and E(UCL-Wald) are means of normal distributions approximating the true finite sample distributions of the confidence limits. Thus, E(LCL) and E(UCL) are approximately equal to the true finite-sample expectations of the corresponding Wald confidence limits. Quantities denoted by E(LCL-Exact) and E(UCL-Exact) are the exact finite-sample expectations of the lower and upper exact binomial confidence limits, respectively (e.g., Scosyrev and Bancken 2017).

Table 5-6 Precision of estimation of the odds ratio, as a function of background (control) risk, sample size, and effect size

			OR=1.0		OR=1.5		OR=2.0	
R	**Control Risk**	**N**	**E(LCL)**	**E(UCL)**	**E(LCL)**	**E(UCL)**	**E(LCL)**	**E(UCL)**
1	0.03	100	0.20	5.08	0.34	6.67	0.48	8.29
		300	0.39	2.56	0.63	3.55	0.88	4.54
		500	0.48	2.07	0.77	2.92	1.06	3.78
	0.10	100	0.40	2.52	0.63	3.55	0.87	4.58
		300	0.59	1.70	0.91	2.47	1.24	3.23
		500	0.66	1.51	1.02	2.20	1.38	2.90
	0.25	100	0.53	1.90	0.81	2.77	1.09	3.66
		300	0.69	1.45	1.05	2.14	1.41	2.83
		500	0.75	1.33	1.14	1.97	1.53	2.62
3	0.03	100	0.27	3.77	0.47	4.79	0.69	5.82
		300	0.46	2.15	0.77	2.93	1.08	3.70
		500	0.55	1.81	0.89	2.52	1.24	3.22
	0.10	100	0.47	2.13	0.76	2.95	1.06	3.77
		300	0.65	1.55	1.02	2.22	1.39	2.88
		500	0.71	1.40	1.11	2.03	1.51	2.65
	0.25	100	0.59	1.69	0.92	2.45	1.24	3.23
		300	0.74	1.35	1.13	1.99	1.52	2.64
		500	0.79	1.26	1.20	1.87	1.62	2.48

R = number of controls per treated patient (i.e., ratio of the control sample size to PRIM sample size); N = PRIM sample size; OR = true odds ratio; E(LCL) = expected location of the 95% lower confidence limit; E(UCL) = expected location of the 95% upper confidence limit.

Technical note: Mathematical expectation of a ratio of non-negative random variables does not exist if either infinite or indeterminate values of the ratio occur with positive probability. However, conditionally on occurrence of finite values, confidence limits have well-defined expectations closely approximated by the quantities denoted here by E(LCL) and E(UCL) (e.g., Scosyrev and Bancken 2017).

Table 5-7 Superiority and non-inferiority power, as a function of background (control) risk, sample size, and effect size or non-inferiority margin

					Superiority Power		Non-Inferiority Power	
R	**Control Risk**	**Risk Diff. if OR= 1.5**	**Risk Diff. if OR= 2.0**	**N**	**Pr(LCL_{OR}>1) if OR= 1.5**	**Pr(LCL_{OR}>1) if OR= 2.0**	**Pr(UCL_{OR}<1.5) if OR= 1.0**	**Pr(UCL_{OR}<2.0) if OR= 1.0**
1	0.03	0.014	0.028	100	0.08	0.16	0.07	0.13
				300	0.15	0.38	0.13	0.30
				500	0.22	0.57	0.19	0.46
	0.10	0.043	0.082	100	0.15	0.38	0.14	0.31
				300	0.36	0.81	0.32	0.72
				500	0.54	0.96	0.49	0.91
	0.25	0.083	0.150	100	0.25	0.61	0.24	0.56
				300	0.61	0.97	0.58	0.96
				500	0.82	1.00	0.79	1.00
3	0.03	0.014	0.028	100	0.10	0.25	0.09	0.17
				300	0.22	0.60	0.18	0.43
				500	0.33	0.81	0.27	0.63
	0.10	0.043	0.082	100	0.22	0.57	0.18	0.44
				300	0.53	0.96	0.45	0.88
				500	0.75	1.00	0.65	0.98
	0.25	0.083	0.150	100	0.37	0.81	0.33	0.74
				300	0.80	1.00	0.75	0.99
				500	0.95	1.00	0.93	1.00

R = number of controls per treated patient (i.e., ratio of the control sample size to PRIM sample size); Risk Diff. = risk difference corresponding to a given odds ratio (OR) and baseline (control) risk; N = PRIM sample size; LCL_{OR} = 95% lower confidence limit for OR; UCL_{OR} = 95% upper confidence limit for OR

5.4 Data analysis

Details of all pregnancy cases will be provided at subsequent crizanlizumab PSUR Data Lock Points (DLP). [redacted] Cases pending pregnancy outcome follow-up at the time of data lock will be excluded from the analysis.

Case details will be provided separately for all retrospective cases along with summary statistics. Statistical comparison with background SCD data will not be performed for retrospective cases in view of high risk of bias from retrospective reporting.

Descriptive analysis will be performed for all prospective pregnancy cases including case disposition (outcome known, pending, and lost to follow-up) and maternal characteristics (i.e.,

age, ethnicity, region) by providing the number and percentage of pregnancies in each category. Distributions of continuous variables will be summarized with means +/- standard deviations, medians, interquartile range and absolute range. Categorical variables will be summarized with proportions. Numbers and proportions for pregnancy outcomes will be reported. The 95% confidence intervals for proportions of pregnancy outcome endpoints will be constructed based on the exact (Clopper-Pearson) method.

The proportion of major malformations will be calculated using two denominators: denominator 1 = total number of live births and denominator 2 = total number of live births, still births and TOPFA. Proportions will be estimated overall and separately by timing of drug exposure in pregnancy (by trimester) and if possible also by previous exposure to HU.

The following information where available will be summarised:

- Country of origin and source of reports
- Concommitant exposure to HU/HC
- Exposure characteristics (trimester of exposure: "peri-LMP, 1st trimester, etc.)
- Type of congenital anomalies
- [redacted]
- [redacted]
- [redacted]

Adverse outcomes will be examined by trimester of exposure and concomitant hydroxyurea (HU/HC).

Based on the washout period of 105 days and timing of exposure to crizanlizumab before/during pregnancy, exposure windows are defined as follows:

a. Pre-LMP exposure: From 105 days before LMP to LMP

b. Exposure in 1st trimester: From first day of LMP and ending on the date of LMP + 84 days

c. Exposure in 2nd trimester: From LMP + 85 days and ending on the date of LMP + 182 days

d. Exposure in 3rd trimester: From LMP + 183 days to the end of the pregnancy

Considering the washout period and exposure windows, analyses will be performed using the following exposure categories:

- Overall (any exposure between 105 days before LMP and end of the pregnancy)
- Pre-LMP only (From 105 days before LMP to LMP)
- At least 1st trimester (This category may include cases with exposure also in other periods)
- After 1st trimester only

- Unknown

[redacted]

5.5 Limitations

The PRIM program is based on spontaneous reports received by the Novartis global safety database with the potential limitations of under-reporting, selective reporting of adverse outcomes, and loss to follow-up. To minimize these, information about the PRIM program will be included in the SmPC encouraging HCPs to report pregnancy cases. In addition, prospective cases (where pregnancy outcome is unknown at the time of reporting) and retrospective cases will be evaluated separately given the risk of selective reporting of adverse outcomes in retrsopective reporting. To reduce the potential for selection bias due to loss to follow-up, multiple follow-up attempts via various contact modalities will be systematically performed.

[redacted]

[redacted]

PRIM data cannot be used to determine incidence rates of adverse outcomes because of potential underreporting of the events and because of unknown number of patients exposed to the drug (lack of denominator or population at risk). Given the inability to compute an incidence rate, a proportion will be calculated (reporting proportion).

Despite these limitations, the PRIM approach allows for worldwide capture of cases providing a larger pool of patients than a than a traditional study or registry. Additionally, the uniform regulatory pharmacovigilance framework to collect data and the use of existing pharmacovigilance systems removes several operational barriers and hence cuts the time needed to accrue the required number of patients. Novartis considers the PRIM to be the most "time-effective' and scientifically and operationally feasible method to obtain data to identify safety signals related to the missing information on the use of crizanlizumab in pregnancy in SCD patients.

5.6 Timelines

The enhanced follow up (FU) process will apply until a sample of 500 prospective pregnancy cases with known pregnancy outcome is available or a maximum of 10 years from EU marketing authorization, whichever occurs first. Thereafter, this program will be terminated and the degree of follow-up reduced to conventional pharmacovigilance follow-up. In the case an earlier interim report would allow a conclusion on the potential risk of reproductive toxicity in crizanlizumab-treated patients, and such conclusion is endorsed by concerned health authorities (HAs), the program would be stopped earlier. After enhanced FU process stops, all subsequent new cases will be processed as per the MAP and applicable SOPs.

6 Plans of disseminating and communicating results

Data will be reported by Novartis, as mentioned in Section 5.4 , in subsequent crizanlizumab PSURs in alignment with the PSUR DLP

7 Databasing conventions

Specific databasing conventions and deviation to MAP for all information required in the PRIM FU checklists will be described in the crizanlizumab Pharmacovigilance guidance document (PGD).

8 Pharmacovigilance requirements

As per current applicable legal requirements and Novartis procedures, information on all cases of pregnancy associated with exposure to a medicinal product for which Novartis has a pharmacovigilance responsibility is collected and processed in order to fulfill the necessary pharmacovigilance obligations.

9 References

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10 Appendix

10.1 Sample size and power considerations

Target sample size for the PRIM analysis was calculated based on the following approach. First, we evaluated the expected precision of estimation of the absolute risks of specific adverse pregnancy outcomes as a function of sample size and the true values of the absolute risk parameters (e.g., Scosyrev and Bancken 2017). The precision of estimation was expressed as the expected location of the lower and upper 95% confidence limits based on the exact (Clopper-Pearson) and asymptotic (Wald) interval estimators, and as the 95% margin of error, defined as one-half of the expected length of the corresponding 95% confidence interval (Table 5-5). For the primary endpoint of fetal loss, the event frequency is anticipated to be at least equal to 25%. For example, in one study of 89 SCD pregnancies, spontaneous abortion occurred in 25 pregnancies (28%) (Silva et al 2018). Stillbirth, which is another type of fetal loss has a reported frequency of approximately 8% in SCD (Boafor et al 2016).

Next, we considered a two-sample inference problem where the event frequencies observed in this PRIM program (i.e., in patients treated with crizanlizumab) are compared to the event frequencies observed in external controls. Because the control group is not defined at the present time, we examined two scenarios with different treatment-to-control allocation ratios. It is expected that the size of the control group will be at least equal to the size of the PRIM cohort, but it is also plausible that the control sample size will be considerably larger than the size of the PRIM cohort. For sample size calculation, we examined scenarios with R=1 and R=3, where R is the number of controls per treated patient.

The effect size in the two-sample problem was defined as an odds ratio. The expected precision of estimation was quantified by the expected location of the lower and upper 95% confidence limits for the odds ratio based on the standard asymptotic (Wald) method (e.g., Scosyrev and Bancken 2017). Expected precision was expressed as a function of background (control) risk, sample size, and effect size (Table 5-6).

Power analysis for the two-sample problem included a joint assessment of superiority and non-inferiority power, following the approach described in Scosyrev and Bancken (2017). Unlike power analysis for efficacy endpoints, which is usually based on either superiority or non-inferiority framework, power analysis for a safety study can benefit from a joint assessment of superiority and non-inferiority power (Scosyrev and Bancken 2017). In a safety study, we want to reject the null hypothesis of no increased risk with high probability if there is modest or large increase in risk (superiority power, the causal null is false), but we also want to rule out modest or large increase in risk with high probability if there is truly no increase in risk (non-inferiority power, the cause null is true).

More formally, the superiority power was defined as probability of rejecting the null hypothesis of no increased risk based on location of the two-sided 95% confidence interval, expressed as a function of the true odds ratio, the background (control) risk and the treatment and control sample sizes. In other words, superiority power is the probability that the lower 95% confidence limit for the odds ratio will fall above the null value of 1, given some true non-null effect size (e.g., a true odds ratio of 1.5) and other initial conditions.

The non-inferiority power was defined as the probability of ruling out a risk increase of a certain magnitude based on location of the two-sided 95% confidence interval, given that there is no true increase in risk. This probability was expressed as a function of effect size that we aim to rule out with 95% confidence (i.e., the non-inferiority margin), the background (control) risk and the treatment and control sample sizes. In other words, non-inferiority power is the probability that the upper 95% confidence limit for the odds ratio will fall below some non-null value (e.g., non-inferiority margin = 1.5), given that the null hypothesis of no treatment effect is true (i.e., the true odds ratio is equal to 1) and other initial conditions are satisfied.

It is important to note that effect sizes and non-inferiority margins defined on the ratio scale (e.g., as an odds ratio) must be interpreted in the context of background risk, taking into consideration the corresponding magnitude of the absolute risk increase (risk difference). For example, non-inferiority margins of 1.5 or 2.0 on the odds ratio scale can be quite small on the risk difference scale, depending on the magnitude of the background (control) risk.

Superiority and non-inferiority power calculations are presented in Table 5-7. The range of background (control) risks for Table 5-6 and Table 5-7 was defined based on reported frequencies of key adverse pregnancy outcomes in patients with sickle cell disease (e.g., Boafor et al 2016, Kuo et al 2016).

10.2 Crizanlizumab (SEG101) Pregnancy Baseline FU checklist

10.3 Crizanlizumab (SEG101) Pregnancy Outcome FU checklist

10.4 Crizanlizumab (SEG101) Infant Health Status FU checklist