NOVARTIS

CSEG101A2404 Study Results Abstract for Public Disclosure

Title

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

Date

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NIS Type

NIS with Secondary Use of Data

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.

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.

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.

List of abbreviations

ADA	Anti-Drug Antibodies
EU	European Union
FU	Follow Up
HU	Hydroxyurea
LMP	Last Menstrual Period
NIS	Non-Interventional Study
PK	Pharmacokinetics
PRIM	PRegnancy outcomes Intensive Monitoring
PT	Preferred Terms
SCD	Sickle Cell Disease
TE	Tracheoesophageal
TFU	Targeted Follow-Up
TOPFA	Termination Of Pregnancy for Fetal Anomaly