STUDY PROTOCOL

Title	An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) Exposed to UPLIZNA® (inebilizumab-cdon) During Pregnancy
Version	1.**4**
Date	**09 October 2024**
EU PAS register number	EU PAS 50808
Active substance	Inebilizumab
Medicinal product	UPLIZNA
Product reference	N/A
Procedure reference	EMEA/H/C5818/MEA/001
Marketing authorisation holder	Horizon Therapeutics **Ireland DAC now part of the Amgen Group** 70 St. Stephen's Green Dublin 2 Ireland, D02 E2X4
Joint PASS	No
Research questions and objectives	This study is conducted to better characterize how inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes. The primary objective is to assess pregnancy and birth outcomes in female patients with neuromyelitis optica spectrum disorder (NMOSD), exposed to UPLIZNA during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception.
Country(-ies) of study	Global
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ABSTRACT

Title:	An Observational Pregnancy Safety Study in Women with Neuromyelitis Optica Spectrum Disorder (NMOSD) Exposed to UPLIZNA® (inebilizumab-cdon) during Pregnancy
Rationale and background:	The data on pregnancy exposure from clinical studies of inebilizumab are insufficient to inform on drug-associated risk. Thus, a worldwide pregnancy registry is being conducted to evaluate how exposure to inebilizumab commercial product (UPLIZNA) may affect pregnancy and infant outcomes.
Research question and objectives:	• To assess pregnancy and birth outcomes in female patients with neuromyelitis optica spectrum disorder (NMOSD), exposed to UPLIZNA during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. • To describe major congenital malformations (MCMs), minor congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births, if they occur, in women with gestational exposure to UPLIZNA.
Study design and methodology:	This observational pregnancy safety study is a post-marketing commitment that aims to monitor female patients who were exposed to UPLIZNA during pregnancy, as defined by receipt of any dose during pregnancy or within 6 months preceding conception. Duration of study is 10 years, at minimum. This study is strictly observational; the schedule of office visits and all treatment regimens will be determined by the treating healthcare provider (HCP). This study requires voluntary reporting of pregnancies in patients exposed to UPLIZNA during pregnancy or within 6 months preceding conception. Pregnancy-related data, potential confounding factors (such as exposure to other medications), and information related to the outcome of the pregnancy will be collected. Women with NMOSD will be able to contribute with more than one pregnancy if they meet the eligibility criteria. Patients who participate in this study will be required to provide written informed consent **or written assent based on local regulations** for data collection. This observational study will be conducted globally in any country where Horizon Therapeutics (or Amgen) is a marketing authorization holder or sponsoring any program where UPLIZNA is administered.
Sample size:	Approximately 60 women with exposure to UPLIZNA 6 months prior to conception or during pregnancy are expected to be enrolled over a minimum 10-year period.
Eligibility criteria:	Patients will be eligible for the study if they: 1. Provide informed consent/**assent based on local regulations**. 2. Age ≥ 1**5** years. 3. Are a female of reproductive potential with a confirmed or suspected diagnosis of NMOSD. 4. Have been exposed to UPLIZNA during pregnancy as defined by receipt of any dose during pregnancy or within 6 months preceding conception. To evaluate the safety of UPLIZNA among pregnant women globally in real world practice and considering the rarity of pregnancies among patients with NMOSD, there are no exclusion criteria, to maximize the enrollment of this pregnancy study.

Data collection:	The data collection will be performed both prospectively (when the pregnancy outcome is still unknown) and retrospectively (after pregnancy outcome has been identified). Initial, follow-up, and final pregnancy exposure data will be collected by Amgen or its designee. Follow-up of exposed women will stop at up to 8 weeks post-delivery (or early termination/withdrawal or death, if they happen earlier). Follow-up of infants/live births (for outcome ascertainment only) will start at delivery and end at 12 months of age of the infant (or disenrollment or death if they happen earlier).
Data source:	Participants and/or HCPs will be requested to provide Amgen/designee with pregnancy exposure and outcome data.
Data analysis:	All data will be analyzed using the Statistical Analysis Software (SAS) Version 9.4 or later. Categorical data will be summarized by the number and percentage of participants in each category. Continuous variables will be summarized by descriptive statistics, including number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum. A detailed description of the statistical analyses used to analyze study data will be provided in the statistical analysis plan. Pregnancy outcomes include spontaneous abortion (pregnancy loss before 20 weeks' gestation), fetal deaths/stillbirths (loss at or after 20 weeks' gestation), elective/therapeutic abortions, and live births. The presence of congenital malformations or other abnormalities will be evaluated, if data allow. Pregnancy outcomes will be summarized by the trimester of exposure and by preconception exposure. Reports of multiple exposures during a pregnancy are classified by the earliest trimester of exposure. The number of infants with congenital malformations will be summarized descriptively. In addition, the risk of infants with congenital malformations, defined as the percentage of infants with congenital malformations among total number of infants and associated 1-sided exact 95% confidence interval, will be reported. Due to the rarity of NMOSD, the total enrollment is expected to be low, and all analyses will be conducted descriptively. Potential confounders and effect measure modifiers are considered and will be addressed, if feasible. If data permit, analyses will also be presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic pregnancy termination status, prospective cases vs. retrospective cases, and other important risk factors (such as concomitant medication, smoking or alcohol intake). All reported pregnancy outcomes will be included in the periodic summary reports of this study.
Limitations of the research methods:	The main challenge of this study is the anticipated small number of reported UPLIZNA-exposed pregnancies. Amgen will periodically monitor participants' count of UPLIZNA-exposed pregnancies in this study. If counts are substantially low, such that the study may be rendered uninformative, Amgen will raise the issue with the regulatory agencies and discuss next steps.