Nonclinical Guidances Pertinent to Developmental Immunotoxicity

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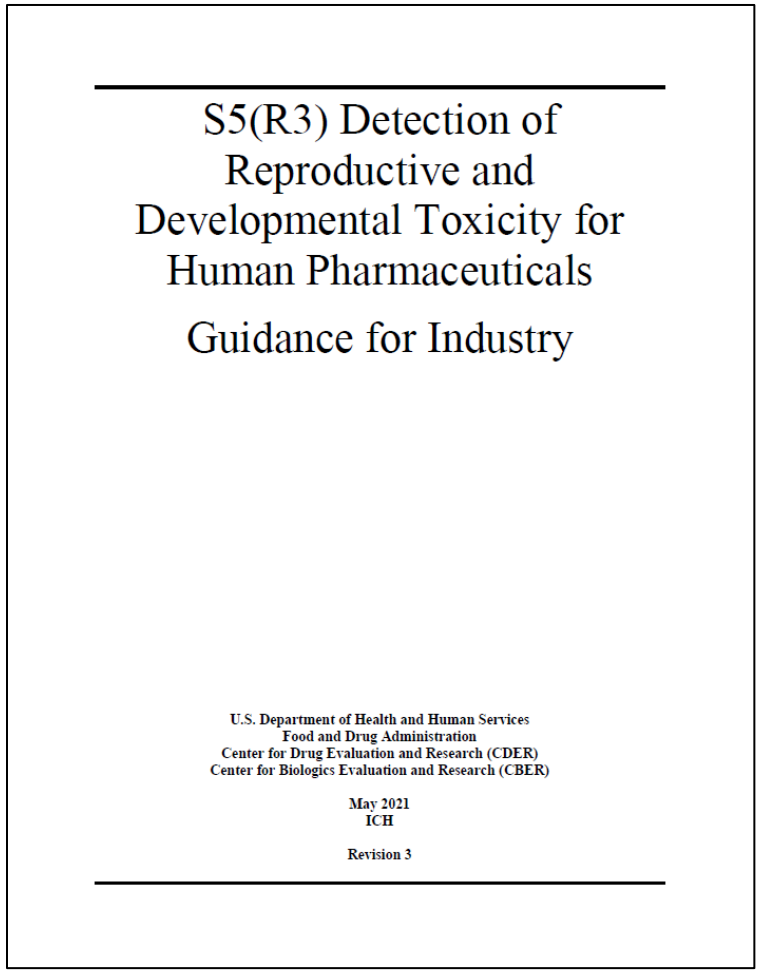
The opinions expressed by Dr. McMillan herein do not reflect official support or endorsement by the U.S. Food & Drug Administration

CDER Immunotoxicity Guidances

- ICH S8: Immunotoxicity Studies for Human Pharmaceuticals (April 2006)
- ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (May 2012)
- ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (January 2010)
- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals (March 2010)
- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals – Questions and Answers (June 2018)
- ICH S11: Nonclinical Safety Testing in Support of Development of Pediatric Medicines (May 2021)
- ICH S5(R3): Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals (May 2021)
- Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals (June 2023)

ICH S5(R3): Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals


S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

Revision 3

https://www.fda.gov/media/148475/download

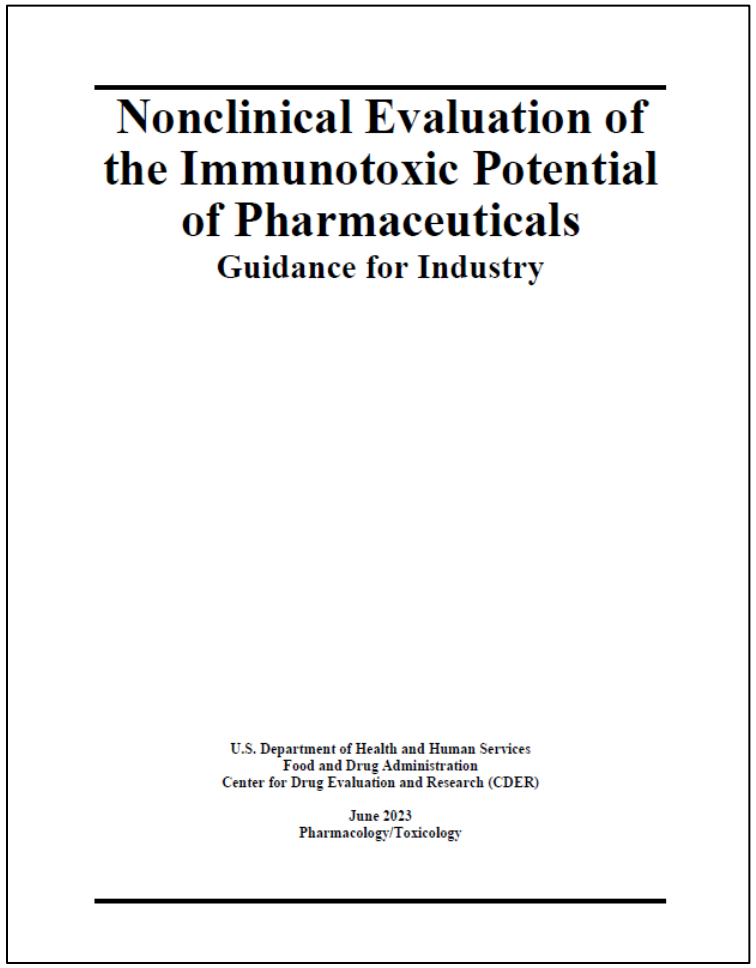
Scope of the guidance

- Primary guidance for the assessment of developmental and reproductive toxicity
- Applies to small molecules, biologics (including vaccines), and novel excipients

Relationship to Developmental Immunotoxicity

- Specific immune endpoints are not included by default
- If there is a concern about potential for immunotoxicity, then additional endpoints could be included in the study design as appropriate

Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals


Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

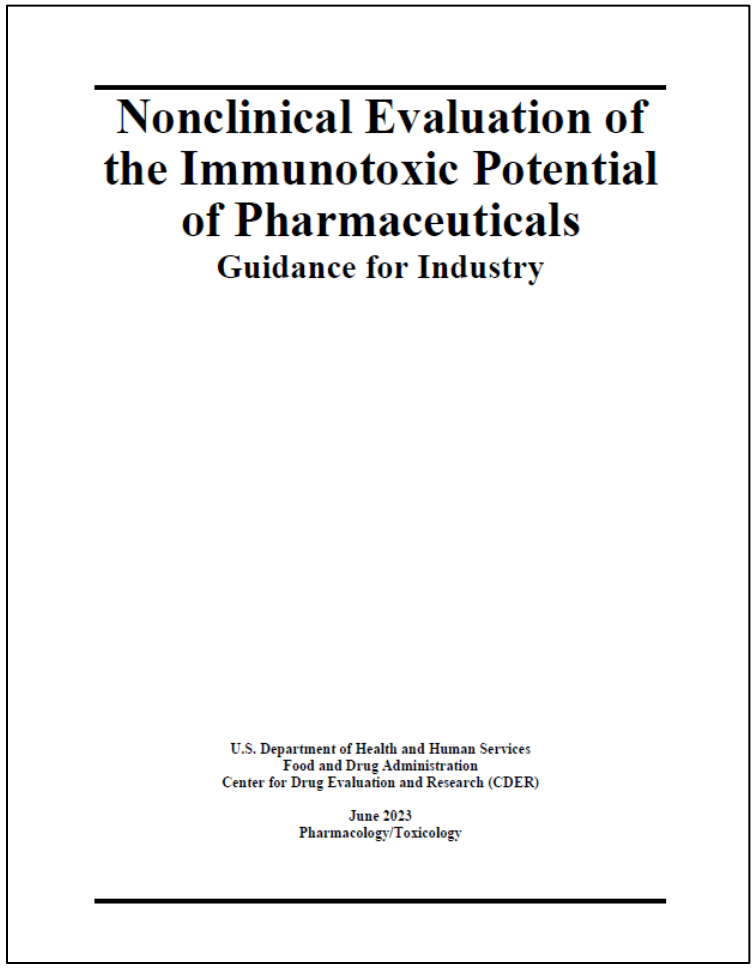
June 2023
Pharmacology/Toxicology

https://www.fda.gov/media/169117/download

Scope of the Guidance

- CDER guidance intended to supplement ICH S8 and S6(R1), and replace the 2002 CDER immunotoxicity guidance
- Applies to small molecules, oligonucleotides and CDER biologic products
- Provides expanded guidance on immunosuppression and immunostimulation assessment, dermal sensitization, and systemic hypersensitivity reactions
- Additional guidance on implantation and pregnancy:
  - The standard nonclinical fertility and embryo-fetal development studies (see ICH S5(R3)) are generally adequate to assess the risk of adverse effects on the maternal immune system that could adversely affect implantation and gestation.
  - However, if the mechanism is known to be incompatible with fertility or pregnancy, a weight-of-evidence (WoE) approach may be more appropriate to assess this risk.
  - Nonclinical fertility studies are generally not warranted for anti-cancer pharmaceuticals (see ICH S9).

Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals


Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals

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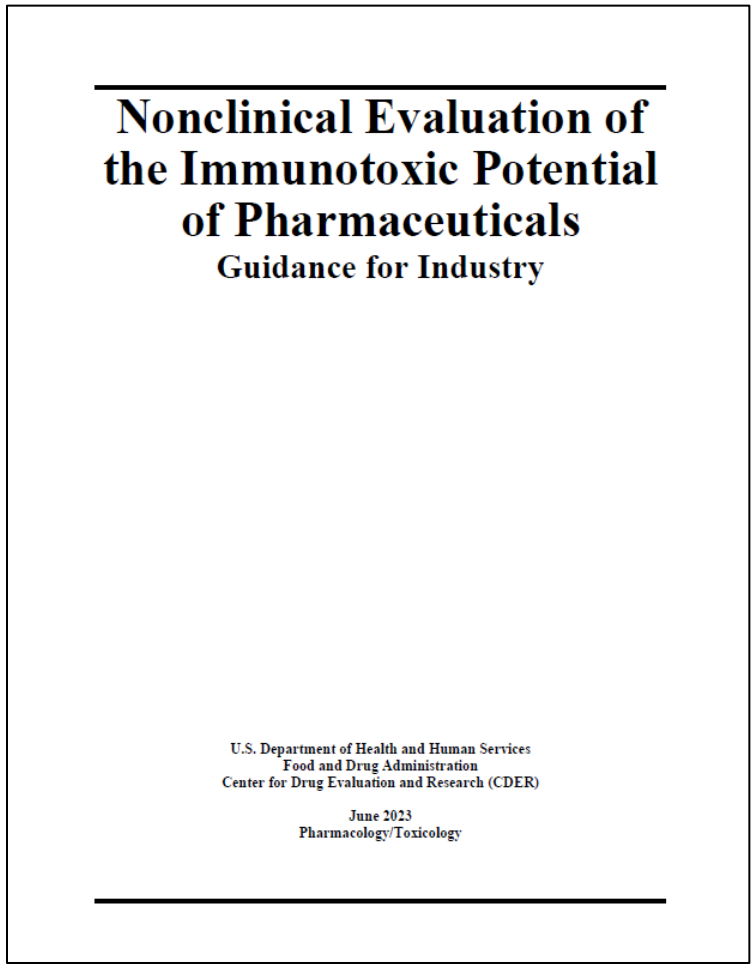
Relationship to Developmental Immunotoxicity

- An evaluation of the potential for developmental immunotoxicity relies on a WoE assessment of multiple factors.
- If a pharmaceutical may adversely affect immune development, and the existing data do not adequately characterize the clinical risk, then sponsors should further evaluate this risk.
  - Could evaluate immune endpoints in the offspring of treated pregnant females in an (enhanced) pre- and post-natal development (PPND/ePPND) study, if adequate exposure is demonstrated in the offspring.
  - If the PPND/ePPND study does not adequately characterize the risk, a juvenile animal study (JAS) in which juveniles are directly exposed to the pharmaceutical may be warranted.
  - JAS and PPND/ePPND studies are generally not warranted for anti-cancer pharmaceuticals (see ICH S9).

Nonclinical Evaluation of the Immunotoxic Potential of Pharmaceuticals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Relationship to Developmental Immunotoxicity, cont.

- Should a study be warranted to assess the risk of developmental immunotoxicity, the test species and endpoints should be appropriate and scientifically justified.
  - The endpoints could include enumeration of specific immune cell populations (immunophenotyping), measures of immune function (e.g., T cell-dependent antibody response [TDAR] assay), and/or assessments of immune anatomical integrity.
  - As there are species differences in the timing of immune development, the dosing interval should cover the intended developmental period.
- Sponsors should consult the appropriate review division before conducting JAS or ePPND studies to avoid unnecessary use of animals.

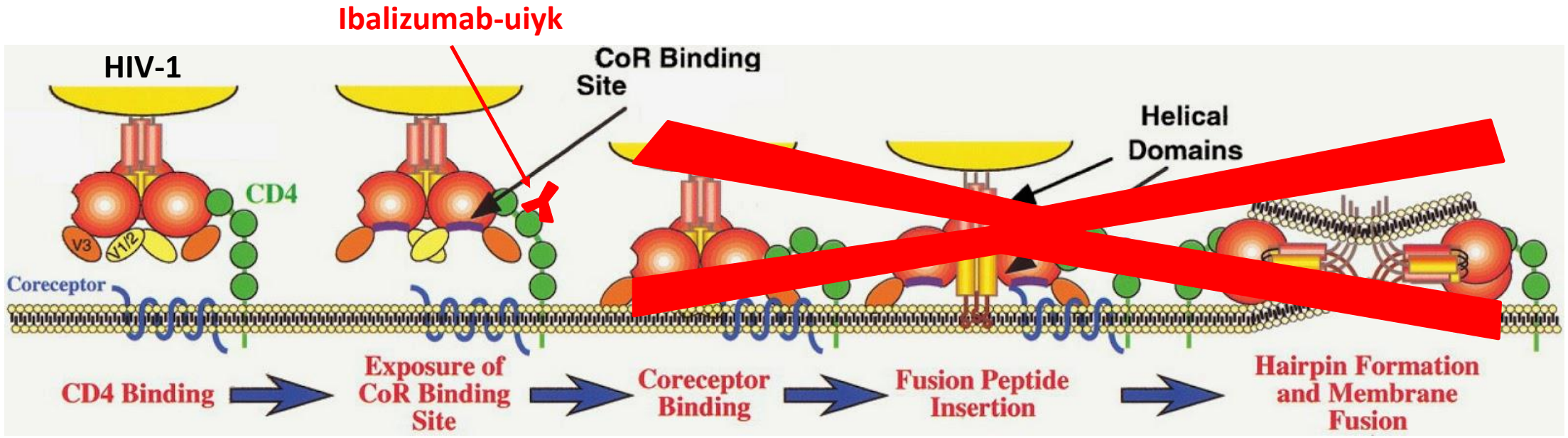
Ibalizumab-uiyk (Trogarzo®)*

- **Structure:** Humanized IgG4 kappa mAb against CD4 receptor domain 2
- **EPC:** CD4-directed post-attachment HIV-1 inhibitor
- **Indication:** Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen
- **Dosage:** 2000 mg IV loading dose w/ 800 mg IV maintenance dose every 2 weeks thereafter
- Licensure was issued in March 2018.
- Ibalizumab-uiyk recognizes human and monkey CD4 only – monkeys were considered the only pharmacologically relevant species.

*All information taken from the U.S. Prescribing Information (updated 12/12/2023) and the Action Package

Ibalizumab-uiyk Mechanism of Action

- Ibalizumab-uiyk binds to CD4 domain 2, which interferes with the post-attachment steps required for HIV-1 entry into host cells.
- By binding to domain 2 instead of domain 1, ibalizumab-uiyk is not anticipated to interfere with normal CD4-mediated immune functions.



http://stuarts-science.blogspot.com/2014/03/shutting-door-to-hiv.html

Ibalizumab-uiyk Nonclinical Safety Data

- Ibalizumab-uiyk is specific for human and monkey CD4, and no meaningful off-target binding was observed.
- No adverse, drug-related findings were observed in the GLP general toxicity studies up to the highest doses tested.
  - No changes in $CD4^+$ cell levels or other immune endpoints (immunophenotyping, TDAR assay).
- The nonclinical package was considered sufficient to support licensure.
- The final report of the ePPND study, ongoing at the time of licensure, was requested as a PMR.

Ibalizumab-uiyk ePPND Study

Study Design

Cynomolgus Monkeys

0 & 110 mg/kg/dose IV

20 pregnant females/group

Pregnant females were treated throughout pregnancy (starting GD 20-22 and once weekly thereafter until parturition on GD 160 ± 10).

Infant animals were not directly treated.

All animals (both mothers and infants) were monitored out to PND 180 ± 2.

GD = Gestation Day

PND = Postnatal Day

Results

No adverse findings in the pregnant adult animals.

Adverse findings in the offspring:

- Drug-related decreases in $CD4^+$ T cells (73-78%) and increases in $CD8^+$ T cells (2.2- to 2.3-fold) on PND 14 and 28. Also decreases in B cells (46%) on PND 14.
  - Correlated to ibalizumab-uiyk serum concentrations in the infants on the same days.
  - Recovered by PND 28-91 when only trace amounts of ibalizumab-uiyk were detected.
  - No meaningful drug-related immunosuppression was observed in a TDAR assay, conducted in the infants on PND 138 and 180 ± 2.
- One treated infant animal died on PND 24 of a systemic viral infection with secondary superficial bacterial infection, acquired during the postnatal period.
  - All lymphocyte subsets ($CD4^+$ T cells, $CD8^+$ T cells and B cells) were decreased 71-93% in this animal on PND 14.
  - Decreased cellularity was seen in the spleen, thymus and mandibular lymph node.
  - Body weight was decreased 17% between PND 14 and 24.

Maternal NOAEL = 110 mg/kg/dose

Offspring NOAEL = Not defined

Ibalizumab-uiyk Labeling Section 8.1

Risk Summary

Based on animal data, ibalizumab-uiyk use during pregnancy may cause reversible immunosuppression (CD4+ T cell and B cell lymphocytopenia) in infants exposed to ibalizumab-uiyk in utero. Immunoglobulin G (IgG) antibodies, such as ibalizumab-uiyk, are transported across the placenta in significant amounts, especially near term; therefore, ibalizumab-uiyk has the potential to be transferred from the mother to the developing fetus *(see Clinical Considerations)*. There are no available data on ibalizumab-uiyk use in pregnant women to evaluate for a drug- associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

In a reproductive study in monkeys, reversible decreases in CD4+ T cells and B cells and increases in CD8+ T cells were observed within the first 4 weeks after birth in infants born to pregnant monkeys receiving ibalizumab-uiyk intravenously (*see Data*). Lymphocyte counts returned to near normal levels by 3 months of age. One infant monkey died from a systemic viral infection that may be related to ibalizumab-uiyk-induced immunosuppression. No malformations or premature births were observed in this study.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761065s020lbl.pdf

Ibalizumab-uiyk Labeling Section 8.1

Animal Data

In an enhanced pre- and post-natal development (ePPND) study, pregnant cynomolgus monkeys were administered intravenous doses of either vehicle or 110 mg/kg ibalizumab-uiyk every week from Gestation Day 20-22 (GD 20-22) until parturition on GD 160 ± 10. Significant changes in infant monkey immune cell levels on Postnatal Day (PND) 14 (mean decreases of 78% in CD4+ T cells and 46% in B cells and increases of 2.3-fold in CD8+ T cells) and PND 28 (mean decreases of 73% in CD4+ T cells and increases of 2.2-fold in CD8+ T cells), attributed to in utero ibalizumab-uiyk exposure, were observed relative to concurrent controls. The lymphocyte changes correlated with infant ibalizumab-uiyk serum concentrations and appeared to return to near normal levels between PND 28-91, when ibalizumab-uiyk concentrations were nearly undetectable. Although ibalizumab-uiyk exposure in these infant monkeys may be significantly higher than in human infants following in utero exposure at the recommended human maintenance dose, the risk of ibalizumab-uiyk-induced immunosuppression in human infants is possible. No meaningful differences in infant monkey lymphocyte counts were observed on PND 180. Further, no differences in immune cell function were observed in a T cell-dependent response assay conducted on PND 138 to 180 ± 2 following immunization of the infant monkeys with keyhole limpet hemocyanin. One treatment-group infant monkey died on PND 24 from a systemic viral infection with secondary superficial bacterial infection which was acquired during the postnatal period. Despite the low incidence (1 of 20 infants), the death may be related to ibalizumab-uiyk-induced immunosuppression. Decreases in CD4+ T cells (93%), and B cells (92%) were observed in this infant on PND 14, and decreased cellularity was observed in the spleen, thymus and mandibular lymph node. Unlike the rest of the ibalizumab-exposed infant monkey population, this infant also exhibited a decrease in CD8+ T cells of 71% on PND 14. Body weight was also decreased in this infant between PND 14 and 24. No structural abnormalities were observed among the ibalizumab-uiyk-exposed infants. In addition, no maternal toxicities, including no changes in maternal lymphocyte subsets or effects on embryo-fetal survival, were observed.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761065s020lbl.pdf

Ibalizumab-uiyk Clinical Labeling

Section 5 – Warnings and Precautions

5.3 Embryo-Fetal Toxicity

Based on animal data, TROGARZO may cause reversible immunosuppression (CD4+ T cell and B cell lymphocytopenia) in infants born to mothers exposed to TROGARZO during pregnancy. Immune phenotyping of the peripheral blood and expert consultation are recommended to provide guidance regarding monitoring and management of exposed infants based on the degree of immunosuppression observed. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. *[see Use In Specific Populations (8.1)]*.

Section 8.1 – Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G (IgG) antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Administration of TROGARZO during pregnancy may affect immune responses in the in utero-exposed infant. For infants with perinatal exposure to TROGARZO, immune phenotyping of the peripheral blood, including CD4+ T cell and B cell counts, is recommended. Expert consultation is also recommended to provide guidance on monitoring and management (e.g., need for antibiotic or immunoprophylaxis) of exposed infants based on the degree of immunosuppression observed. The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

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Ibalizumab-uiyk Conclusions

- No ibalizumab-related adverse effects or immune changes were observed in adult animals.
- Ibalizumab-related changes in lymphocyte levels (↓ $CD4^+$ T cells and B cells and ↑ in $CD8^+$ T cells) were observed in infant monkeys following in utero exposure.
  - Lymphocyte changes resolved 1-3 months post-birth and no functional immune changes were observed by 4-6 months post-birth.
  - One treated infant died on PND 24 of a systemic infection acquired during the neonatal period. Lymphocyte levels were decreased up to 90% in this animal and body weight decreased between PND 14 and 24.
- Infants exposed to ibalizumab-uiyk in utero may be mildly immunocompromised and have increased susceptibility to infection within the first 3 months of life.
  - Ibalizumab-uiyk may interfere with lymphocyte development during late gestation and/or early in the neonatal period.
- Follow-up nonclinical safety studies have not been recommended. Because of immunogenicity issues, it is not thought to be possible to identify a lower dose without immune effects.
- Safety concerns from the ePPND study have been addressed in the label.


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