FDA Lactation Workshop

“What do we currently know?”

An Example from Industry

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Disclosures

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Background

Understanding the therapeutic environment and the scientific rationale

- One of UCB’s main focus is the immunology therapeutic area in particular chronic rheumatic diseases and Crohn’s Disease

- UCB’s Immunology women of childbearing age (WoCBA) program is focused on studies with certolizumab pegol and is driven by patients and physicians needs:
  - Disease onset tends to overlap with a woman’s peak reproductive years
  - Balancing disease control and family planning wishes
  - High disease activity in the post-partum period
    - Need for treatment → Many women are prescribed anti-TNFs post-partum to control for rebound/flare after delivery while breast feeding
  - Limited published data on transfer of biologics into breast milk → Uncertainty around whether to take treatment for flare management and whether to choose to breastfeed

- Immunology WoCBA Program Goal: Provide robust data to better inform treatment decisions for women with autoimmune conditions planning for pregnancy and/or breastfeeding
Identifying Data Gaps and Potential Hurdles

What data are available to inform decision making regarding lactation and use of biologics?

- **Limited information in Package Inserts**

- **Systematic literature review:**
  - Limited data, mostly from case reports
  - Variability in breast milk sampling protocols
  - Lack of information on validation of assays
  - Inconsistency of available breast milk transfer data

- **Potential hurdles faced by industry:**
  - Lack of experience in clinical studies on lactating women
  - Ethical and study design challenges

Conflicting Messages
Evidence Based Approach

What methodology could be used to fill the data gap?

- **Review of pre-clinical data**
  - Assess potential concerns linked to drug molecular structure
  - Limited data available in lactation

- **Assay requirements and challenges**
  - Aim for a high sensitivity in lower ranges to ensure an informative lower limit of quantification (LLOQ)
  - Validation in milk matrix, including drug stability in milk

- **FDA draft guidance – February 2005**
Data Collection and Evaluation (1/3)

Study design considerations

- **Colostrum vs. mature milk study**
  - Breast feeding should be well-established (mature breast milk)
  - Sampling should not take place before 6 weeks post-partum when maternal physiology has largely returned to pre-pregnant state

- **Mother-infant pair vs. lactating mother only (milk only vs. milk and plasma)**
  - Milk only study can provide information regarding: (1) Timing of maternal dose relative to breast feeding, (2) Duration recommended to discard milk and (3) When to resume breast feeding relative to dose/exposure
    - If concentration of drug in breast milk is exceedingly low, this could preclude the need for further studies

- **Exclusive breastfeeding vs. supplemental**
  - Inclusion criteria allowed for exclusive and supplemental breastfeeding in order to provide closer to real life data
Data Collection and Evaluation (2/3)
Study design and Data collection consideration

- **Providing investigational drug vs. enrolling patients already on treatment**
- **Milk Sampling period**
  - Sampling should occur when drug is at steady-state
  - Sampling should cover the complete dosing interval
- **Study sample size**
  - Phase I – Clinical Pharmacology Study
  - FDA feedback
- **Balance between burden of data collection on mother vs. the need for enough information for data evaluation**
  - In order to account for high sampling frequency required, limit clinical data collection from mothers
  - The study should support continued breast milk feeding and to avoid disruption of breast feeding routine
Data Collection and Evaluation (3/3)

Data evaluation

- Mothers and baby demographics
- Pregnancy outcome information
- Concomitant medications
- Breastfeeding information
- AEs of interest
- Drug concentration in milk
- Calculation of Average Daily Infant Dose (ADID)
  - Dose ingested ≠ dose absorbed
## Study Overview

### Clinical Study Objectives

**Primary**
Determine the concentrations of CZP in human breast milk and to calculate the daily infant dose of maternal CZP

### Clinical Study Design

**Population**
Lactating women who were already prescribed commercial CZP for an approved indication in accordance with the current approved prescribing information

**Methods**
8–9 milk samples from lactating mothers across a single dosing period via use of in-home nursing visits

**Sample size**
17 lactating mothers taking CZP

**Assay**
UCB developed assay - validated in milk - LLOQ=0.032µg/mL
Transferred to CRO
Factors contributing to success and the need for continued evidence generation

Dedicated multi-functional team: Clinical, Bioanalytics, Medical, Epidemiology, Regulatory, Legal & Compliance

External expert advisors (paediatrician, OBs, lactation specialist, MFM)

Unique operational model

Patients & physicians needs

Generation of robust data

Scientific & Therapeutic Landscape → Data Gaps & Hurdles → Evidence Based Approach → Data Collection & Evaluation → Evidence Generation

The more relevant, high quality data available, the more we empower physicians and their patients