The Conundrum of Clinical Studies in Pregnant Women: Industry View

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- The views represented today are solely the speaker's, and do not represent any official position of Cytel
- MJF is a full-time employee of Cytel and provides consulting services to the pharmaceutical industry
- MJF owns stock in Trevena, Inc., a biopharmaceutical company
- Adjunct Professor in Pharmacometrics at UNTHSC – no disclosures

What is Pharma concerned about when contemplating studies during pregnancy?

- Safety considerations
  - Regulatory, as well as IRB/EC and investigator concerns
  - Legal Liability
- Recruitment
  - Perception of harm of therapeutic drugs during pregnancy
    - Data consistently show perceived risk to be much higher than actual risk (Widnes 2016)
    - Treating physicians show a similar trend
  - Can the study be recruited in a reasonable amount of time with a reasonable number of sites?
    - Oversight and maintenance of study sites is expensive, even if NO patients/subjects are recruited at that site
- Return on Investment

Can Clinical Studies in Pregnant Women be performed?

Treatment of spontaneous preterm labour with retosiban: a phase II pilot dose-ranging study

Steven Thornton[1], Guillermo Valenzuela[2], Charlotte Baidoo[3], Michael J. Fossler[3,4,†,‡], Timothy H. Montague[3,4], Linda Clayton[5], Marcy Powell[5], Jerry Snidow[6], Brendt Stier[6,*,‡] and David Soergel[6,†,‡]

- In parts A and B of a 3 part, double-blind, placebo-controlled multi-center trial, pregnant women with a diagnosis pf pret-term labor (34 $^{0/7}$ -35 $^{6/7}$ weeks gestation) were randomized 3:1 (Part A) or 2:1 (Part B) to either 12 hours of IV retosiban followed by oral placebo or 12 hours of placebo followed by oral retosiban

- Time from protocol initiation to FPFV: ~ two years
- Only Parts A and B were finished (n=19 evaluable) – Part C not conducted due to significant efficacy signal and *recruitment* concerns
- Subsequent Phase 3 trials stopped prematurely due to lack of recruitment

Return on Investment May Not be as High as it Seems at First Glance

- ***Does the potential knowledge gained represent a real treatment advance?***
  - Do the data to be obtained have the potential to significantly change prescribing during pregnancy?
    - Are there objective endpoints which could trigger increase/decrease in dose during pregnancy?
    - "Patient should be closely monitored during pregnancy, consider a dose increase" – probably does not rise to the level of needing a clinical trial
- ***Can the information gained be acted upon by prescribers?***
  - Sufficient dosage strengths available to alter dose during pregnancy?
  - If patient shows no objective change in clinical status as a result of pregnancy, should the dose be altered?
  - If the patient does show a change in clinical status, is PK the sole driver?

The Conundrum

- It is clear that pregnancy may result in a significant alteration in the disposition of many, if not all medicines, and we lack good quantitative data on these dispositional changes for most drugs
- It is equally clear that obtaining these data is a very difficult thing to do
  - Phase 1 – type studies: probably out of the question, due to IRB/EC and investigator concerns, study site concerns , and difficulty in recruiting
- Any studies in pregnant women need to offer potential benefit to the patient, and need to provide data that are actionable.
- Regulators must explicitly recognize the difficulty in recruiting this population as well as concerns of IRBs, study participants, and study sites