

The Conundrum of Clinical Studies in Pregnant Women: Industry View

Michael J. Fossler, Pharm. D., Ph, D., F.C.P.

Executive Consultant and Vice-President, Strategic Consulting

Cytel

Adjunct Professor, Pharmacometrics

University of North Texas Health Sciences Center

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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 Thornton¹ , Guillermo Valenzuela², Charlotte Baidoo³, Michael J. Fossler^{3,4,†,‡}, Timothy H. Montague^{3,4}, Linda Clayton⁵, Marcy Powell⁵, Jerry Snidow⁶, Brendt Stier^{6,*†,‡}, and David Soergel^{6,†,‡}

- 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
- In parts A and B of a 3 part, double-blind, placebo-controlled multi-center trial, pregnant women with a diagnosis of preterm 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

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