Concerns and Challenges in Including SIB Patients in Registrational Trials

ISCTM

February 19, 2019

Washington, DC

Thomas Laughren, M.D.

Laughren Psychopharm Consulting, LLC

Active Consulting Relationships with Pharmaceutical Companies and Employment Relationship with MGH CTNI

- Part time employee of MGH CTNI
- Consultant to Abide, Acadia, AeviGenomics, Alzheon, Antares, Astellas, Axovant, Axsome, AZ Therapeutics, Biohaven, CogRx, Concert, Cox Bioscience, Evecxia, Greenwich, Harmony, Janssen, Karuna, KemPharm, LB Pharm, Lilly, Lyndra, MAPS, Marinus, Merck, Minerva, MVK Pharm, Neurocrine, Neurolifesciences, Noven, Ovid, Purdue Pharma, Rhodes, Roche, Tonix, Vallon, Vanda

Including patients with suicidal ideation and behavior (SIB) in registrational trials

- Unmet need
- Establishing the conditions for making such trials acceptable
- Cautions about including SIB patients from a drug development perspective
- Characterizing and quantifying SIB patients
- Regulatory perspective on including SIB patients
- IRB perspective on including SIB patients
- How to think about SIB as a target for drug development
- Study design considerations

Establishing the conditions for making trials with SIB patients acceptable

- Inpatient vs outpatient?
- Modifying the environment in which study visits occur
- What to do with SIB patients who do not qualify for study
- How to handle positive screens for SIB during trial
- What to do with patients who drop out of an SIB study, and at study end
- Important study design considerations (see later)
- Linking trial enhancements to degree of SIB

Why drug developers might be reluctant to include patients with SIB in registrational trials

- False positive: false attribution of excess SIB events to investigational drug
  - Failure of randomization
  - Chance finding
- True positive: true signal of excess SIB events for investigational drug
  - Programs with even weak early signal of possible excess SIB risk could lose out to less risky programs
  - Programs that continue and end up with SIB warning may be commercially less viable

Problem of characterizing and quantifying SIB patients for consideration as participants in registrational trials

- Use of standard assessment instruments as tools for such determinations
- Criterion approach
- Importance of getting agreement on how to do this

Regulatory basis for clinical holds and requests for modifications (CFR 312.42)
(focus on safety reasons)

- CFR 312.42
  - Ph 1 study (2 of 5 relevant reasons--safety):
    - Unreasonable and significant risk of illness or injury
    - Insufficient information to assess risk
      - Note: focus is usually on toxicology for ph 1
  - Ph 2 or ph 3:
    - Any of ph 1 reasons
      - Here could be on basis of withholding an effective treatment

Regulatory basis for clinical holds and request for modifications (CFR 312.42)--Continued

- What authority does CFR 312.42 grant FDA regarding including SIB patients IN PH 2 & 3 trials?
  - Gives FDA authority to hold studies including SIB patients that withhold an effective treatment for SIB (i.e., safety concern)
    - But there would have to be effective treatments for SIB
    - I would argue that there are no such treatments
- Need clarity from current leadership in DPP regarding this issue
  - In any case, need clear rules and need to be consistently applied

IRB perspective on inclusion of SIB patients in registrational trials

- What has the experience been in acceptance or rejection by IRBs of trials including SIB patients?

Perspectives on SIB as a target for drug development

- SIB in the context of DSM entities (MDD, Schizophrenia, Others?)
- SIB as a broader construct independent of DSM diagnosis

Study design considerations

- Time to rescue as an endpoint
- Comparator arm
  - Placebo control
  - Active control (with or without placebo)
  - Standard of care/Treatment as usual?
- Monotherapy vs adjunctive