Sponsor-Investigator: Personal Experience with Cholic Acid Treatment of Bile Acid Synthetic Disorders

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NASPGHAN Annual Meeting
FDA Concurrent Session 1
October 9, 2015

Financial Disclosures

- Equity interest in Asklepion Pharma, LLC.
- Funding: NCATS, NIDDK, NICHD, and CFF
- Consultant to Nordmark, Retrophin
- Supported by grants from NCATS, NICHD, NIDDK, CFF
Metabolic Basis for Cholic Acid Therapy

- Transcription Factor: LXR, FXR
- Cholesterol: Downregulation of CYP7A1
- 7α-hydroxycholesterol
- Cholic acid
- Bile acids
- Atypical bile acids
- Orally administered Cholic acid

Δ⁴-3-oxosteroid-5β-reductase deficiency

- Initial description of monochorionic twins presenting with neonatal cholestasis
- Presented with jaundice and varying severity of liver dysfunction
- Rapidly progressive disease leading to cirrhosis in infancy: Previously presumed affected sibling died in infancy
Effect of Therapy on Bile Acid Excretion

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Biochemical Response to Therapy

Development Plan for Cholic Acid as an Orphan Product

- Submission of 20+ years of clinical data on efficacy and safety
  - FDA granted “Orphan designation”
- Began production of commercial GMP formulation
- 2009 - 2011: Performed FDA required bridging studies in patients and PK studies of cholic acid
- Submission of PIP application to EMA in EU and NDA for cholic acid to FDA
- November 22nd 2013 Approved in EU by EMA
- March 17th 2015 Approved by FDA


meetings with FDA and EMA
Lessons learned: Hindsight is always 20:20

- Work was passion to treat affected infants/children started more than 30 years ago
- Although regulatory requirements existed 30 years ago, enforcement less intense
- Until the last 10 years, there was never a plan to get FDA approval
- Only now can we see what we should have done in designing the study, i.e. design the study and data collection with the end in mind

Definitions

- **Investigational New Drug** is a new drug or biologic used in a clinical investigation
- **IND application** is a request for authorization to administer an investigational drug or biologic to humans or a marketed drug in a new indication and/or patient population
- **Sponsor** is an individual, company, academic institution, or other organization that takes responsibility for and initiates a clinical investigation
- **Investigator** is an individual under whose immediate direction a drug is administered or dispensed

Sponsor-Investigator

- Individual who both conceives, initiates, designs and conducts a clinical trial and under whose direction the study drug is administered 21 CFR 312.3
- Investigator subjects and holds the IND
- Investigator must comply with requirements of both the investigator and sponsor-plans, designs, conducts, monitors, manages data, prepares reports, oversees regulatory and ethical issues and publishes results
Why are investigator-initiated trials important?

• Benefit from investigators expertise, experience, ingenuity, academic resources and creativity
• Offer opportunity to explore off-label therapies in unique populations and treatment regimens
• BUT:
  - Standards same as applied to industry trials
  - Challenges for safety and data quality
  - Greater risk and liability

Sponsor-Investigator Responsibilities (Initial)

• Protocol development
• IND submission
• Registration of trial on Clinicaltrials.gov
• Select qualified investigators, sites, and monitors
• Provide all information needed to conduct study
• Ensure all sites get appropriate IRB approval
• Develop MOOs and CRFs
• Provide investigational drug or device

Selecting Qualified Investigators

• Considerations when selecting investigators at separate sites to conduct trial:
  - Site and PI selection criteria: Is PI qualified and is site capable of completing study?
  - Review of FDA regulations and GCP guidelines with site
  - Review investigator commitments as defined under 1572
  - Failure to comply may lead to investigator termination from study
Task Delegation

- PI may delegate tasks to study staff with appropriate qualifications
- Recommended having delegation log with the defined tasks and signatures of staff
- Specific tasks may not be amenable to delegation which require expertise of PI

Sponsor-Investigator Responsibilities (ongoing)

- Monitor and ensure conduct of study per protocol and GCP
- Ensure compliance with regulations
- Provide study related materials
- Inform FDA re: safety issues
- Create DSMP and if appropriate, DSMB
- Perform data analysis
- Final results

IND Reporting

- Safety Reports
  - Adverse Event reporting
    - SAE unexpected and related:
      - Report within 7 days of occurrence
    - Written report within 15 days
  - Annual report within 60 days of anniversary that IND went into effect
Ensure ongoing monitoring

- Ensure proper monitoring
- Ensure PI compliance or discontinue shipments of investigational drug
- Review and evaluate drug safety and effectiveness
- Discontinue investigation within 5 working days of unreasonable or significant risk to subjects
- Ensure IRB and FDA approval to resume terminate study

Informing Investigators

- Provide all clinical investigators with Investigator's Brochure
- Inform investigators of new observations that might be relevant to the continuation of the study

Drug Accountability

- Sponsor responsible for record of drug disposition
- Maintain adequate records of receipt and shipment of investigational drug
- Assure return of all unused investigational drug from individual investigators
- Maintain written records of any disposition of drug
Record Retention

- Retain records for 2 years after marketing or 2 years after investigational use is discontinued and FDA notified.

EMA/FDA Inspection

- As lead site, regulatory inspection is expected
- Review of laboratories, case report forms, documentation of compliance with regulatory requirements
- FDA/EMA officers may access, copy and verify any records or reports that have been made by the investigator during the NDA process

What did we learn? Key Points(1)

- Regulations and compliance are different in 2015 vs. 1992!!!!!!!!!!
- Understand what is expected if you think you will approval from FDA/EMA for drug/device
  - Review regulations carefully and get advice from experienced regulatory staff
- If there is potential IP, make sure you and institution protected
- Develop protocol with data collection with windows that allow minimal protocol deviations
- Develop robust CRFs
What did we learn? Key Points (2)

• Meticulously collect data
• If collecting data from multiple labs, be sure you have accreditation status and normal values from each lab
• Create a monitoring plan from Day 1 and assign needed resources ($$)
• Be sure that your hospital/university compliance office is actively involved with the process

Final comments

• As a Sponsor-Investigator, there may be direct conflict of interest
  - Consult your institution about a mitigation plan, if appropriate
  - Comply with requirements set by your IRB to ensure research subjects understand your relationship to them as their doctor vs. clinical scientist

Questions?