

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



James E. Heubi, M.D.  
Cincinnati Children's Hospital  
Medical Center  
NASPGHAN Annual Meeting  
FDA Concurrent Session 1  
October 9, 2015




---

---

---

---

---

---

---

---

---

---

## Financial Disclosures

- Equity interest in Asklepiion Pharma, LLC.
- Funding: NCATS, NIDDK, NICHD, and CFF
- Consultant to Nordmark, Retrophin
- Supported by grants from NCATS, NICHD, NIDDK, CFF




---

---

---

---

---

---

---

---

---

---

**1977-1981** James Carter

**1981-1989** Ronald Reagan

**1989-1993** George H. W. Bush

**1993-2001** William J. Clinton

**2001-2009** George W. Bush

**2009-present** Barack Obama

**1980** Development of FAB-MS for bile acid analysis in urine

**1981** Identification of 1st genetic defect in bile acid synthesis causing liver disease - HSD3B7 deficiency

**1985** Established International screening program at CCHMC for unexplained liver disease

**1988** Identification of 2nd genetic defect in twins - AKR1D1 deficiency

**1991** 4 more Genetic defects discovered (CYP7B1, CYP27A1, ZMACR, amidation)

**1993-2001** Wrote IND#45,470 for cholic acid therapy - approved by FDA - JE Heubi

**2006-2015** Founded Asklepiion

First patients treated with cholic acid under Compassionate Use Approval from FDA/CCHMC IRB

Sourced from:  
- Falk Pharma GmbH  
- PCA  
- Sigma (Chemical grade Not for Human Use)

**IDEA: Can Liver disease be caused by a defect in Cholesterol/Bile acid synthesis?**

---

---

---

---

---

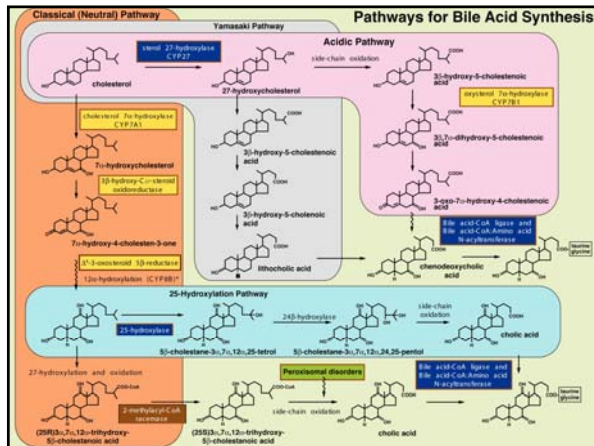
---

---

---

---

---




---

---

---

---

---

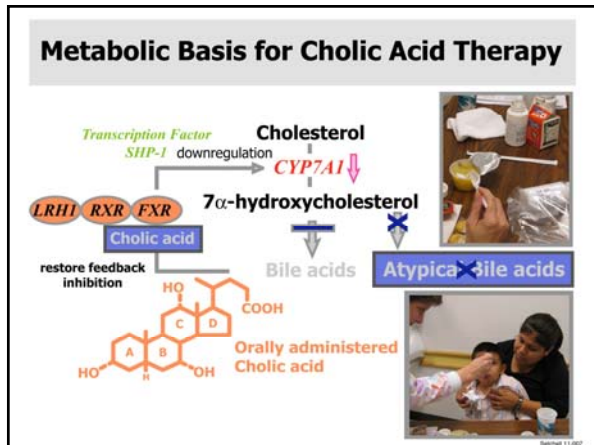
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

### $\Delta^4$ -3-oxosteroid-5 $\beta$ -reductase deficiency

- Initial description of monozygotic 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

change the outcome

---

---

---

---

---

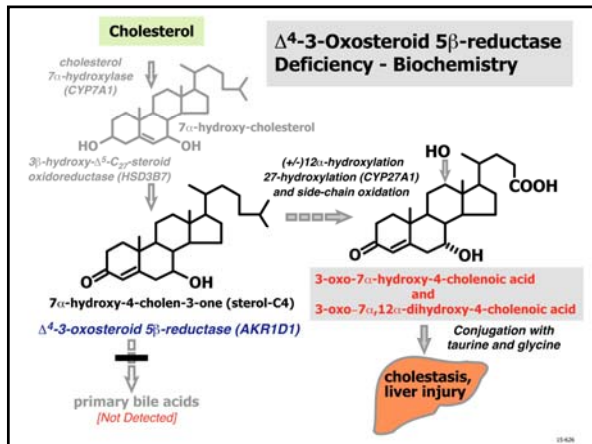
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

---

---




---

---

---

---

---

---

---

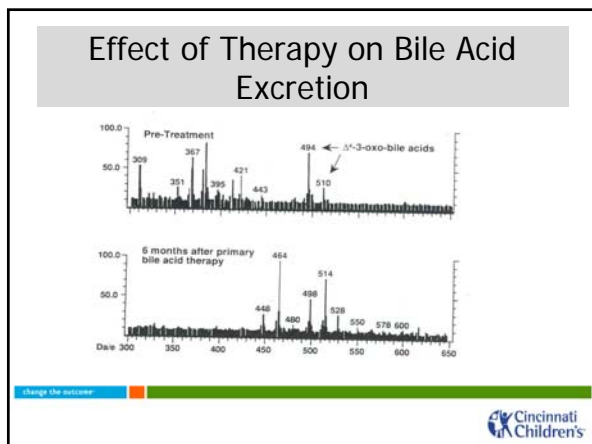
---

---

---

---

---




---

---

---

---

---

---

---

---

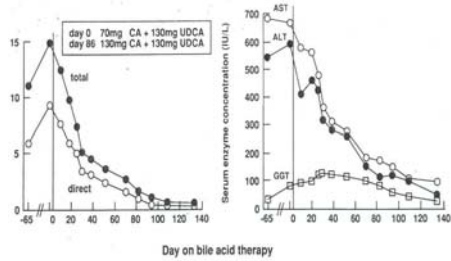
---

---

---

---

## Biochemical Response to Therapy



Change the outcome




---

---

---

---

---

---

---

---

---

---



Change the outcome




---

---

---

---

---

---

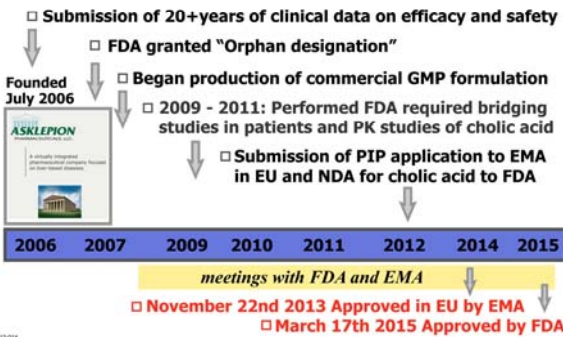
---

---

---

---

## Development Plan for Cholic Acid as an Orphan Product



13/214

---

---

---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

change the outcome



---

---

---

---

---

---

---

---

## 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

change the outcome



---

---

---

---

---

---

---

---

## 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

change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---

---

## 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

Change the outcome



---

---

---

---

---

---

---


---



## Record Retention

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

Change the outcome




---

---

---

---

---

---


---

---

## 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

Change the outcome




---

---

---

---

---

---


---

---

## 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

Change the outcome




---

---

---

---

---

---

---

---

## 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

change the outcome



---

---

---

---

---

---

---

---

## 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

change the outcome



---

---

---

---

---

---

---

---



**Questions?**

change the outcome



---

---

---

---

---

---

---

---