Primary Sclerosing Cholangitis Regulatory Updates And Knowledge Gaps

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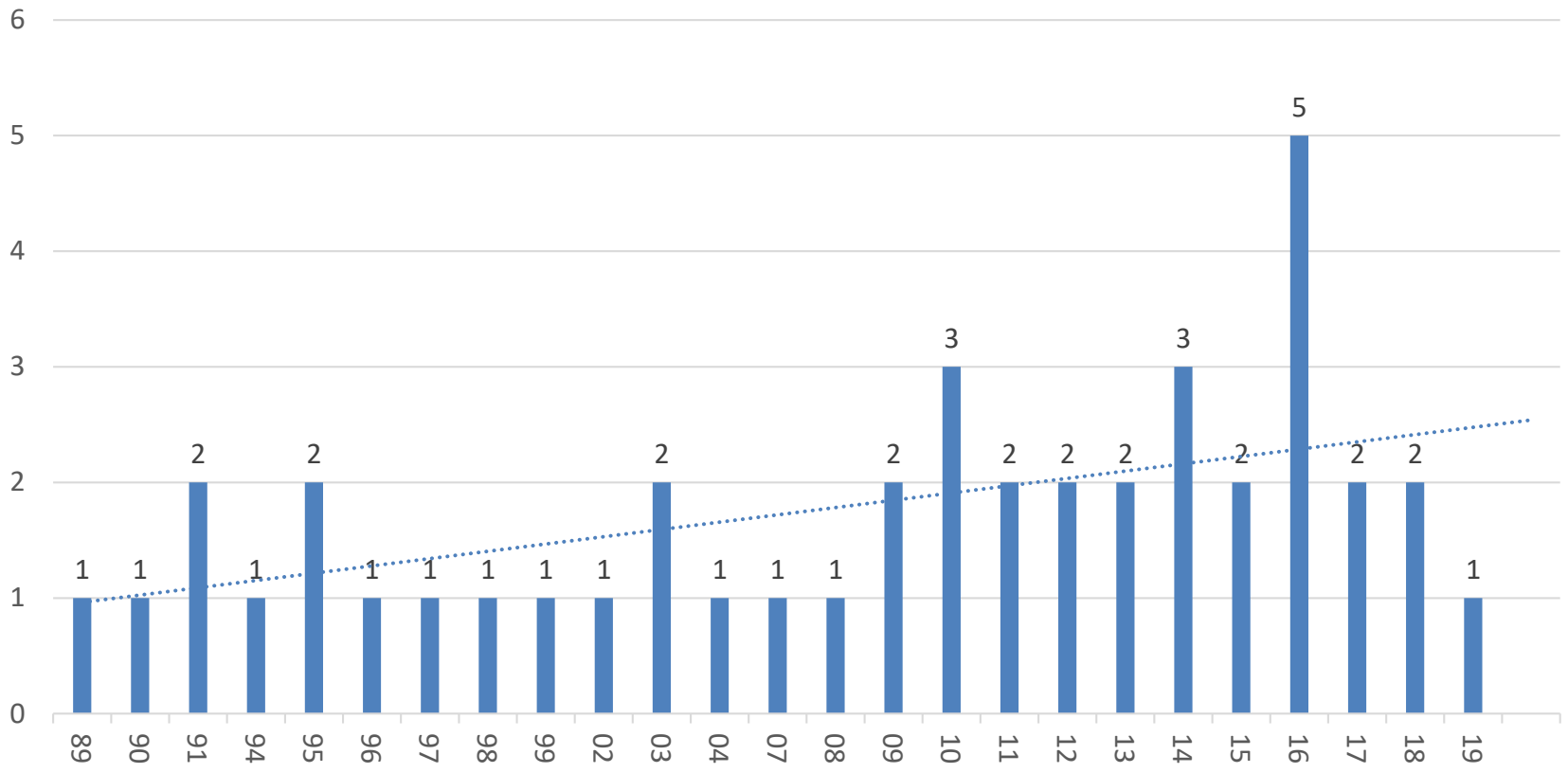
September 19 , 2019

Disclaimer

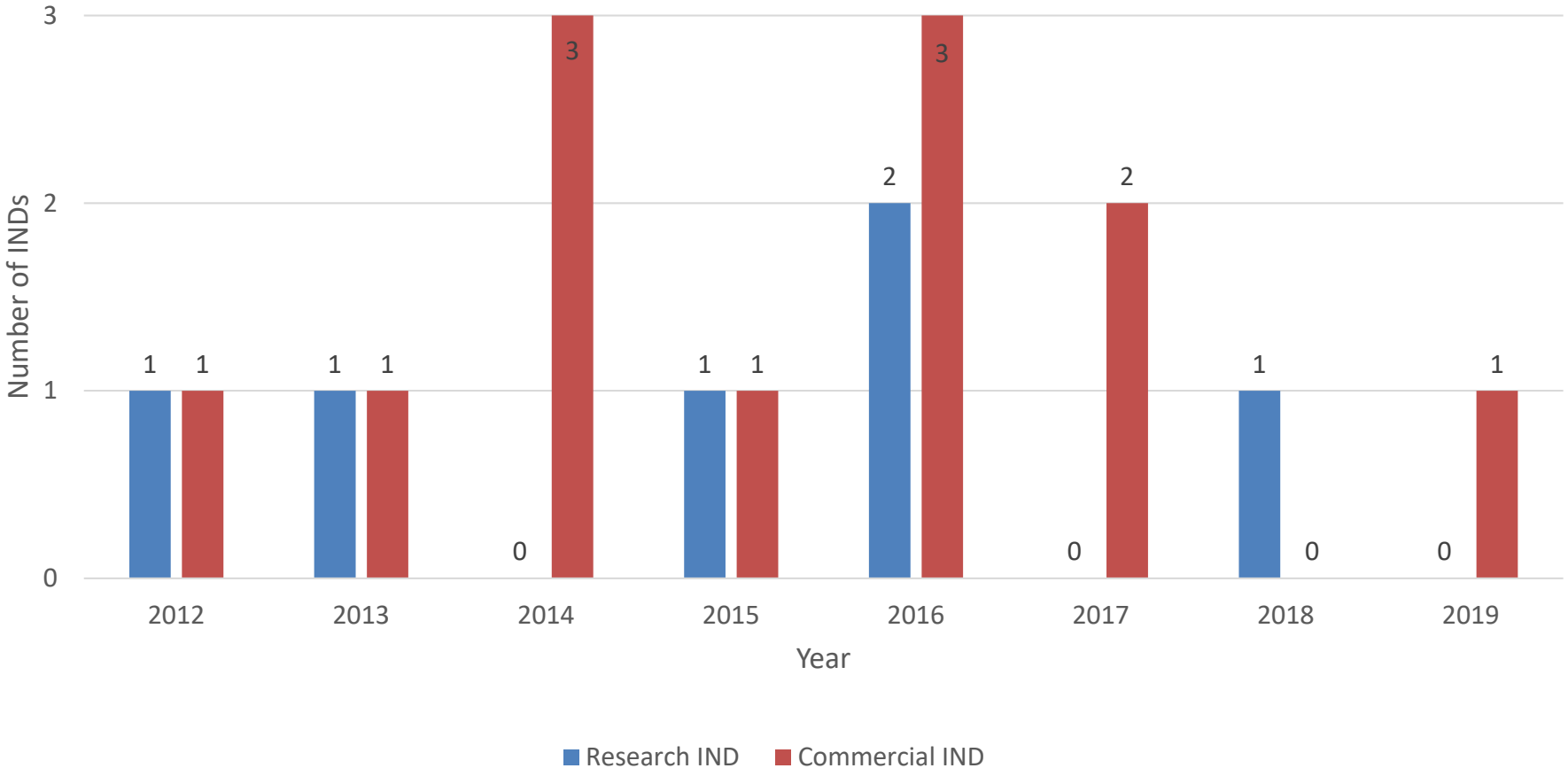
The views and opinions expressed here are my own and do not represent official guidance from the FDA

Annual PSC IND Submissions



IND Subtype

Research Vs. Commercial



Submissions for PSC

- No breakthrough therapy designation granted
- Single phase 3 IND
- Clinicaltrials.gov has 168 PSC trials listed including observational studies
  - 104 clinical intervention trials
  - 23 pediatric patients trials
  - 10 trials in phase 3
    - 3 trials actively recruiting
    - 1 agreed-upon with FDA

Current Scientific Gaps and Needs

- Understanding of natural history of PSC to better inform:
  - Trial design (duration, sample size, and endpoints)
  - Identify important characteristics of outcome variables
    - Biochemical biomarkers
    - Imaging biomarkers
    - Clinical benefit
- Data on performance of non-invasive biomarkers
- Perform liver biopsy or document historical biopsy at enrollment for correlation purposes

Endpoints for Phase 3 Trial(s)

- For drugs that provide symptomatic improvement (for example: pruritus, fatigue etc.):
  - Regular approval pathway – is possible
  - Instruments/scales should be developed as early as possible in the time-course of drug development (consider submitting meeting requests to COA and DGIEP in tandem)
  - Endpoints should also be discussed early
    - What a clinical meaningful change on “scale” means
  - Early statistical planning on how the outcomes would be appropriately assessed (binary, continuous etc.)

Endpoints or Phase 3 Trial(s)

- Curative intent or prevention of progression of PSC:
  - Progression to cirrhosis in subjects who do not have cirrhosis (enrich population for patients likely to progress to cirrhosis)
  - Patients with compensated cirrhosis (enrich population with CSPH*) reach decompensation events, death or liver transplant (composite endpoint)
- Greater understanding of natural history of PSC to establish time required to progress to cirrhosis or decompensation events
  - Natural history studies needed early in drug development

*CSPH-clinically significant portal hypertension

Endpoints for Phase 3 Trial(s)

- Other biomarker endpoints:
  - Can MRCP be used quantitatively for assessing biliary disease burden?
  - Limitations of current biomarkers
    - ALP, TB, ALT, GGT
    - Fibroscan and MRE
    - Other non-invasive BM (e.g., ELF, PRO-C3, Fibrosure)
- Role of liver biopsy (at baseline and end-of-treatment [EOT] versus only at EOT)
  - Is there a potential of not performing a baseline liver biopsy
- Feasibility and challenges with conducting phase 4 confirmatory trial(s)

Natural History Comparators

- Limitations of using natural history data as comparators for phase 3 trials:
  - Lack of rigor
  - Biases such as sampling bias, recall bias, selection bias, information bias, reporting bias and other bias; risk of unmeasured confounders when comparing outcomes*
  - Missing data and lack of quality control
  - Lack on internal validity
  - Safety cannot be assessed using historical data
    - Trial data appears better due to inclusion/exclusion criteria applied
    - Filter out complex patients, and matching may not account for unmeasured confounders
- How to get around multiple source of bias and confounders?

*Camm AJ et al OpenHeart 2018

Phase 3 Trial in PSC

- DB, PC, R trial evaluating safety, efficacy in non-cirrhotic subjects with PSC
  - Sample size ~ 400 subjects
  - Duration 96 weeks
- Primary endpoint
  - Progression of ≥1 stage fibrosis (according to Ludwig's classification)

Acknowledgements

SUPERVISORS

- Dragos Roman, MD – Acting Director
- Bindi Nikhar, MD – Acting Deputy Director
- Lisa Soule, MD – Associate Director

TEAM LEADS

- Frank Anania, MD (Acting)
- Veronica Pei, MD (Acting)
- Stephanie O. Omokaro, MD (*On Detail: Acting Deputy Director, Division of Medical Policy Development*)

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- Lara Dimick-Santos, MD
- Ruby Mehta, MD
- Yao-Yao Zhu, MD, PhD

Thank you!

- Questions?


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