U.S. FOOD & DRUG ADMINISTRATION

Rare Diseases – Why Another Forum?

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Disclosure Statement

- The views expressed in this presentation are entirely mine, and do not represent an official FDA position.

- I have no financial interests to disclose.

Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial

*Brent A Neuschwander-Tetri, Rohit Loomba, Arun J Sanyal, Joel E Lavine, Mark L Van Natta, Manal F Abdelmalek, Naga Chalasani, Srinivasan Dasarathy, Anna Mae Diehl, Bilal Hameed, Kris V Kowdley, Arthur McCullough, Norah Terrault, Jeanne M Clark, James Tonascia, Elizabeth M Brunt, David E Kleiner, Edward Doo, for the NASH Clinical Research Network**

	Obeticholic acid	Placebo	Relative risks or mean changes from baseline* (95% CI) (obeticholic acid vs placebo)	p value*
Primary outcome†				
Number of patients at risk‡	110	109		
Patients with improvement	50 (45%)	23 (21%)	1·9 (1·3 to 2·8)	0·0002
Changes from baseline in histological features				
Number of patients with biopsy specimens at baseline and 72 weeks	102	98		
Resolution§ of definite non-alcoholic steatohepatitis	22 (22%)	13 (13%)	1·5 (0·9 to 2·6)	0·08
Fibrosis¶				
Patients with improvement	36 (35%)	19 (19%)	1·8 (1·1 to 2·7)	0·004
Change in score	−0·2 (1·0)	0·1 (0·9)	−0·3 (−0·6 to −0·1)	0·01
Total NAFLD activity score				
Change in score	−1·7 (1·8)	−0·7 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Hepatocellular ballooning				
Patients with improvement	47 (46%)	30 (31%)	1·5 (1·0 to 2·1)	0·03
Change in score	−0·5 (0·9)	−0·2 (0·9)	−0·2 (−0·5 to 0·0)	0·03
Steatosis				
Patients with improvement	62 (61%)	37 (38%)	1·7 (1·2 to 2·3)	0·001
Change in score	−0·8 (1·0)	−0·4 (0·8)	−0·4 (−0·6 to −0·2)	0·0004
Lobular inflammation				
Patients with improvement	54 (53%)	34 (35%)	1·6 (1·1 to 2·2)	0·006
Change in score	−0·5 (0·8)	−0·2 (0·9)	−0·3 (−0·5 to −0·1)	0·0006
Portal inflammation‖				
Patients with improvement	12 (12%)	13 (13%)	1·0 (0·6 to 1·7)	0·90
Change in score	0·2 (0·7)	0·2 (0·7)	0·0 (−0·1 to 0·2)	0·59

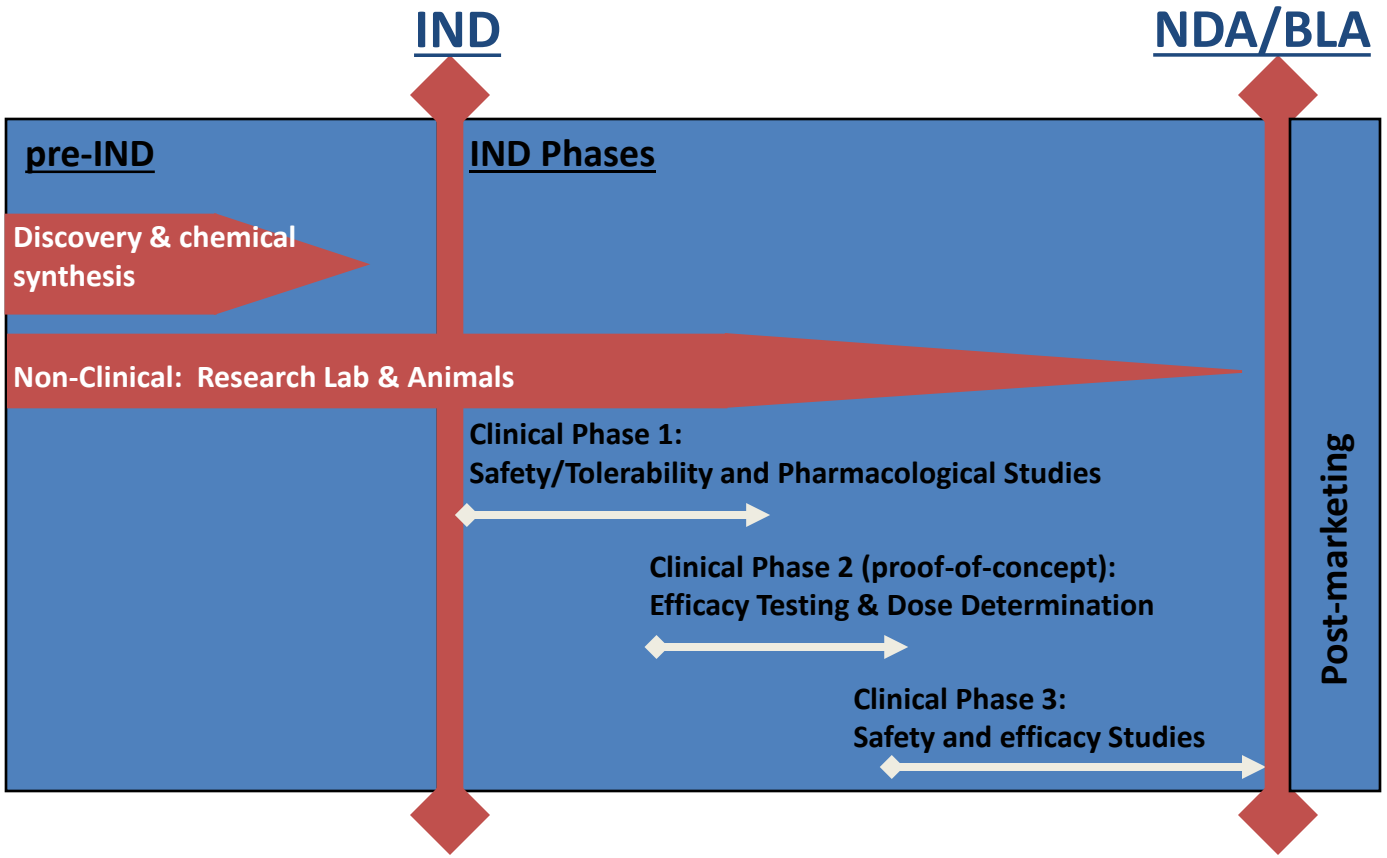
FDA Goals for the Rare Disease Forum

- Science and data based discussions focused on drug development in rare diseases
- “Bottom up” approach (not policy focused)
- Create a common vocabulary and experience with clinical investigators
- Transparency: share and explain FDA reviewers’ approaches to non-FDA stakeholders
  - Dispel misconceptions: “FDA’s heavy reliance on p-values”(frequentist vs. Bayesian or other new statistical approaches)
  - Explain “totality of data”
  - Regulatory flexibility

FDA Goals for the Rare Disease Forum - continued

- Hear stakeholder's take on practical challenges and potential solutions to facilitating drug development in rare diseases
- Discuss specific issues and how they will impact all rare diseases, e.g.:
  - Relevance and limits of animal models for rare diseases
  - Dose selection in absence of PD endpoints
  - Dose selection when PD biomarkers exist but their full understanding/relevance is unclear
  - Dose selection for drugs/biologics administered directly into CSF
  - Seamless trial designs and other novel trial designs for drug development in rare diseases

Traditional Drug Development



Drug Development in Rare Diseases

- Continuum that integrates traditional drug development phases (I/II/III)
  - new approaches and new ways of conceptualizing the program
- Drug development is global
  - communications with other regulators
- DGIEP wants to be involved at pre-IND stage
  - Identify program specific challenges and work collaboratively towards a solution
  - Provide early input
    - dose selection and whether dose exploration is sufficient
    - endpoint(s) selection
    - ensure that the trial design is informative for a regulatory decision

FDA Commitment to Drug Development via FDA Guidances

- Pediatric Rare Diseases — A Collaborative Approach for Drug Development Using Gaucher Disease as a Model - 2017
- Inborn Errors of Metabolism That Use Dietary Management: Considerations for Optimizing and Standardizing Diet in Clinical Trials for Drug Product Development-2018
- Slowly Progressive, Low-Prevalence Rare Diseases with Substrate Deposition That Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies-2018

Rare Disease Forum – Challenges for the Future

- Maintaining stakeholder commitment and involvement
  - marathon vs. 800m race
- Develop a flexible blueprint:
  - Lump vs. split?
    - focus on disease groups (e.g. MPS, subtypes of mitochondrial diseases, somatic vs. neurological manifestations, etc.) ?
    - focus on a specific disease and extrapolate/adapt knowledge to same or similar classes of diseases?
    - Combine approaches
    - Develop new ones

Rare Disease Forum – Challenges for the Future

- Stick to basic principles of drug development ("first principles") but reimagine them in a more dynamic , novel way
  - Individualize animal data requirements under current regulation to specific programs
  - Discuss Study Design Issues (e.g. adaptive designs)
  - Novel statistical approaches
  - Do not forget devices!
- Remain creative and avoid duplicative work with other forums – share information

FDA Presentations and Participation

- Provide regulatory context:
  - CDER
  - CBER
- Discuss 3 Case Studies – Issues and Solutions:
  - Palynzig – include patient's voice
  - Brineura – limitations of external controls
  - Mepsevii – impact of missing data
- Highlight two critical issues:
  - Data quality to support regulatory flexibility
  - Ethical considerations for initiation of pediatric studies

Thank you!