Non-alcoholic steatohepatitis (NASH)-related compensated cirrhosis

Addressing questions old and new

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Conflict of Interest and Disclaimer Statement

I have no financial disclosures regarding pharmaceutical drug products.

Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Outline

1. FDA's guidance on NASH with compensated cirrhosis: Why now?

2. De-emphasis of surrogate endpoints for accelerated approval
   - Histologic endpoints
   - Alternative endpoint strategies

3. Enrollment criteria for trials of NASH-related compensated cirrhosis

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Evangela Covert 301-796-4075.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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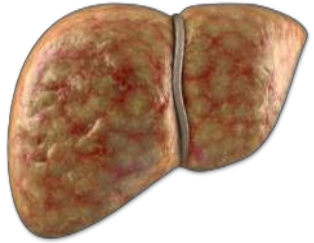
11/29/2018

NAFL
(Steatosis)



NASH with fibrosis

Spectrum of NAFLD

- Discusses bland steatosis→ NASH with F2-F3 fibrosis in phase 2 trials
- Provides guidance for subpart H (accelerated endpoint)
- Reviews rationale for the NAS scoring and fibrosis scoring system(s)
- Reviews phase 4 confirmatory trial

Expedited programs for serious conditions

- Fast track designation
- Breakthrough therapy designation
- Accelerated approval
- Priority review

https://ww.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

The accelerated approval pathway

Requirements:

Drug treats a serious condition

and

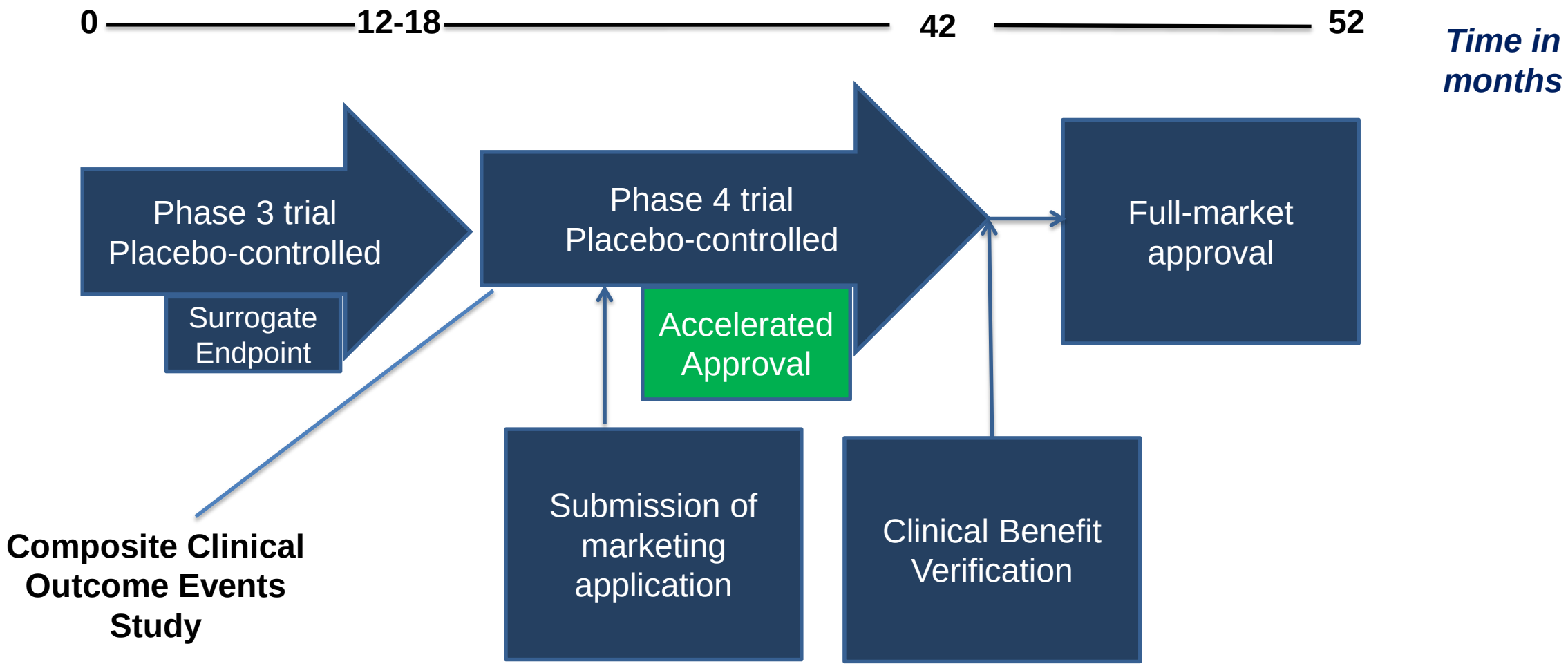
Provides a meaningful advantage over existing therapies

and

Demonstrates effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality

§ 21 CFR part 314, subpart H
§ CFR part 601, subpart E
506(c) of the FD&C Act, as amended by section 901 of the FDASIA

Accelerated approval for compensated cirrhosis



http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

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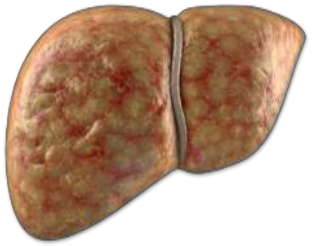
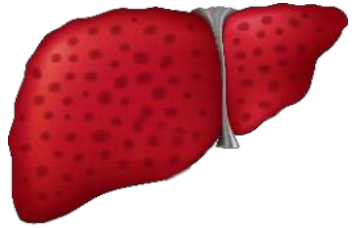


NASH with fibrosis

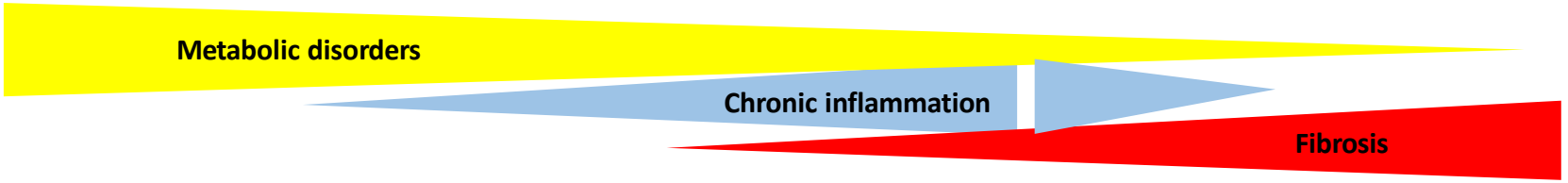


Compensated Cirrhosis

Spectrum of NAFLD

Therapeutic goals of hepatologist/ internist/clinician

- Reduce risk of hepatocellular carcinoma
- Reduce cardiovascular morbidity and mortality
- Reduce all-cause mortality
- Reduce risk of non-hepatic malignancies
- Prevent/reverse progression of disease based on histology
- Reduce need for liver transplantation



Adapted from Nature Outlook 23 Nov 2017;551:S86; AM Diehl & C. Day. *New Engl J Med* 2017;377:2063-72

4th Annual NASH Summit 2020

For the rest of the presentation, please contact info@hansonwade.com

Following slides include:

- Like heart-failure, cirrhosis is an end-stage clinical condition
- Treatment of NASH-related compensated cirrhosis may reduce the growing demand for liver transplantation
- Clinical outcome trial design for NASH-related cirrhosis
- Establishing NASH-related cirrhosis in clinical trial subjects
- Establishing cirrhosis secondary to NASH
- Clinical trial population with NASH-related compensated cirrhosis
- Efficacy endpoints for clinical trials
- Phase 3 trials for NASH-related cirrhosis prior to the issuance of the Guidance of 6 June 2019
- The future of the accelerated endpoint for NASH-related compensated cirrhosis
- FDA Guidance compared to EMA
- An alternative approach for NASH drug development