NASH Regulatory Landscape

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Disclosures

- Liver Forum sponsors (last slides)
- Advisory (Sanofi)
Outline

• Collaborative stakeholder model
• Regulatory paths
• Regulatory hurdles in NASH
• Opportunities for innovation in NASH
Perspective

Forum for Collaborative Research

• CMV Forum
• HBV Forum
• HCV Forum
• HIV Forum
• Liver Forum
• PSC Forum
Accelerating Access to Better and Safer Drugs for All

• Forum Model:
  • Stakeholder collaborative model
    • Process of dialogue and deliberation
    • Government, industry, academia, community
  • Identify gaps and barriers
    • Recommend consensus, solutions, fund/engage in new research path
Forum’s Operating Principle

“Once new drug candidates and therapeutic strategies are identified, their efficient, safe development is in the best interest of all stakeholders, most of all, the patients”
Key Characteristics

- “Information Democracy”
- Non-competitive, safe environment
- Independent
- Co-ownership
- Synergy vs. duplication
- Transparency

Allow everyone to contribute what they do best
Safe space for ongoing co-evolution of science and regulatory guidance
5. A Collaborative Platform as Scientific Accelerator

A. One-on-one sponsor-agency dialogue with no information sharing

Conventional drug development and regulatory review is a competitive, “go-it-alone” endeavor. Oversight is restricted to the specific company concerned with the development of the drug and the reviewers of the respective regulatory agencies. Research output is not shared, building redundancy and inefficiency in the system. Academic experts and other stakeholders have occasional input.
B. Collaborative platform model to collectively share information to resolve regulatory challenges with scientific rigor

The working group based model, by contrast, creates an open, voluntary, collaborative process involving a broad range of stakeholders, who identify and solve scientific barriers to demonstrations of safety and efficacy. The Forum has successfully used this model to provide researchers and regulators with an incentive and a setting to share knowledge, exchanging the possible advantages of maintaining secrecy for the benefits of collective pursuit of the therapeutic goal.
NASH??

• NASH
  – We don’t know how to find it
  – We don’t know how to define it
  – We can’t diagnose it
  – We don’t have an indication for treatment

• We don’t even know how to name it

• BUT –
  – We know it’s an unmanageably huge public health problem for children, adolescents and adults across the world
NASH Challenge to Industry

• Development of new therapeutics in absence of
  – Realistic and pragmatic regulatory path
  – Validated and accepted biomarkers
    • Diagnostic, prognostic, predictive and surrogate endpoint
  – Precise definitions of disease stages/progression

• Requires co-evolution of diagnostics and therapeutics
Challenge to Regulators

• Develop regulatory guidance in an area where none existed
  – Complex pathogenesis
  – Short-term vs. long-term effects
    • Benefits
    • Risks
  – In the context of “life-style”
  – In the context of co-morbidities

• Safeguard the health of the public while fostering innovation
Challenge to NASH Community

• Likely need for combination treatment
  – When is it safe to combine?
• Long-term follow up vs. placebo
  – Ethics? Feasibility?
• Research in pediatrics
  – When is it appropriate to test new drugs in children and adolescents?
Need for ongoing dialogue and interaction
One-off efforts raise issues but do not resolve them
Apply HIV Forum model
The Liver Forum: Facilitating Drug Development For NASH

• Independent and neutral venue for evolving consensus on drug development and regulatory issues
  – *Increase* clarity, efficiency, innovation
  – *Decrease* uncertainty, redundancy, time, risk
• Safe space
• Collaboration
• Win-Win

One table:
• Regulators
  – FDA
  – EMA
• Academic
  – US
  – Europe
• Societies
  – AASLD
  – EASL
• Industry
  – Pharma, biotech, diagnostic
• Patients
The Liver Forum: Assets

• Cross-Atlantic regulatory, industry and academic perspectives
• Safe/neutral space to allow consensus to evolve
• Infrastructure for collaborative efforts within Liver Forum
• Infrastructure for coordination across efforts among Liver Forum members and partners
Progression of NAFLD—Need for Biomarkers

- Normal Liver
- Steatosis
- Steatohepatitis
- Intermediate stages of fibrosis
- Cirrhosis
- Death
- Transplant
- HCC

Hard outcomes
Baseline

Diagnostic Prognostic

Natural History

Clinical Endpoint

Surrogate markers?

Adult Pediatric
Two Scenarios

• Accelerated approval based on surrogate marker “reasonably likely to predict” followed by traditional approval

• Surrogate marker “accepted to predict”
  – Primary endpoint
  – Traditional approval
Clinical Benefit - Regular Approval

- How a patient feels, functions or survives

- Example of clinical benefit in NASH:
  - Reduction in all-cause mortality
  - Prevention of liver transplant
    - MELD increase to 15 from $\leq 12$ (listing for transplant)
  - Prevention or reduction of decompensation events
Surrogates Reasonably Likely to Predict Clinical Benefit

• Potential Examples for NASH:
  – Complete resolution of steatohepatitis and no worsening of liver fibrosis
  – At least 1 point improvement in fibrosis (Brunt/Kleiner scale) and no worsening of steatohepatitis (no increase in ballooning or inflammation on NAS score)
  – The acceptability of surrogates is evaluated for each drug and disease combination
Validated Surrogate

• Can be used for Regular Approval
  – For a specific disease setting and class of interventions
  – Recognized as validated by definitive studies
  – There are no validated surrogate endpoints for NASH
Learning while doing – doing while learning
• The previously proposed/presented co-primary evaluation of two composite endpoints for the interim has been accepted:

  - Composite of complete resolution of steatohepatitis (0 for ballooning, 0-1 for inflammation) and no worsening of fibrosis stage
  - Composite of one point improvement in fibrosis stage (at least 1 stage) and no worsening of steatohepatitis (balloning and inflammation score)

• The endpoint combines different aspects of individual response (the composites) and response at the population level

• The strength of the endpoint is required based on the following:
  - The interdependence of inflammatory changes and fibrotic changes and their alteration by interventions is at this point unknown
  - The endpoints at the interim analysis have to be sufficiently strong to conclude on a positive benefit-risk at the time of the interim analysis (despite the data to be presented later)
(How) can the interim evaluation account for different mechanism of action?

- E.g. a primary anti-inflammatory agent might not be able to show improvement in fibrosis at interim time-point already
- The composite of NAS resolution and no worsening of fibrosis not considered sufficient
- Co-primary evaluation of NAS resolution and no worsening of fibrosis would at least be expected in order to show independent effects on fibrosis (in the case prevention of deterioration only can be shown)

Addition 2017: Best: effects should be shown on the individual level (the composite) and at the population level (the co-primary)
Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

• New situation:
• No relevant anti-inflammatory activity, but relevant effects on fibrosis expected
  • Resolution of NASH not an appropriate endpoint (see CENTAUR trial)
  • „Change in character of inflammation“ may or may not be demonstrated (immunohistochemistry based evaluation of included cell-types, inflammatory cytokine profiles, etc.)
  • How can a „sufficiently strong“ interim endpoint (see above) be established?
  • 1-Stage improvement of fibrosis sufficient in a fibrosis stage 2/3 population?
  • Solution: Composite (at the individual/patient level) of 2-stage improvement of fibrosis and no worsening of NASH
Regulatory update from Europe – Interim endpoints in NASH phase 3 trials

• New situation:
• No relevant anti-inflammatory activity, but relevant effects on fibrosis expected
• But also different population intended: Stage 3 and 4 (cirrhosis!)
  • 1-stage reduction for cirrhotic patients (without worsening of inflammation (as composite at the individual level) regarded to be sufficiently strong in cirrhotics!
  • Stage 3 would still need an at least 2-stage reduction of fibrosis (without worsening of fibrosis (as composite at the individual level)
• Consequences: Conduct 2 trials in the two different populations? However, responder based evaluations could be combined also!
• Question unresolved: Is an interim analysis/endpoint necessary for stage 4 patients?
• Can these strong endpoints be met within a realistic time-frame?

• There are measures to increase the chances of success:
  • Good phase 2 data can help to estimate the effect sizes that can be achieved in a certain time frame
  • Prolong the time until interim analysis (=increase the effect size)
  • Increase the number of patients to be included in the interim (= strengthen the statistical basis)
Challenge

• Validation of surrogate endpoints requires validation
Baseline

**Diagnostic**

**Prognostic**

**Natural History**

End of Follow Up

**Clinical Endpoint**

Surrogate markers?

Adult

Pediatric
Biomarkers & Endpoints

**Disease focused**
- Natural history
- Absence of intervention
  - Diagnostic
  - Prognostic

**Response to Intervention**
- Predictive
  - Efficacy
  - Safety
- Pharmacodynamic
  - Dose selection
- Efficacy
  - Predicts clinical outcome
Case Definitions for Inclusion and Analysis of Endpoints in Clinical Trials for Nonalcoholic Steatohepatitis Through the Lens of Regulatory Science

Mohammad Shadab Siddiqui, Stephen A. Harrison, Manal F. Abdelmalek, Quentin M. Anstee, Pierre Bedossa, Laurent Castera, Lara Dimick-Santos, Scott Friedman, Katherine Greene, David Kleiner, Sophie Megnien, Brent A. Neuschwander-Tetri, Vlad Ratzin, Elmer Schabel, Veronica Miller, and Arun J. Sanyal; on behalf of the Liver Forum Case Definitions Working Group
Baseline Case Definitions

- Framework for integration of new diagnostics/biomarkers as science evolves
- Framework for defining outcomes
  - EG NASH resolution
    - NASH resolution working group
Facilitate Cross-Study Analysis

- Standardization of baseline parameters
Coordinated Biomarker Development

FDA      EMA

LITMUS (IMI)      NIMBLE (FNIH)

Drug Developers      Diagnostic Developers
Natural history

TACKLING CHALLENGES THROUGH INNOVATION
Totality of Evidence

• Integration of evidence from multiple sources
  – Eg RCT+RWE
• TARGET-NASH
• NASH CRN
• Waxing and waning of disease
• Need for long-term placebo exposure

Figures courtesy of Brent Tetri, 2nd International NASH Biomarker Workshop
Increasing Natural History Knowledge

• Placebo arm cohort
  – Completed and un-blinded phase 2 and 3 studies

• Apply novel analytic approaches to identify risk factors for “waxing and waning” of disease
  – Disease progression
  – Disease resolution
New trial design options
TACKLING CHALLENGES THROUGH INNOVATION
Adaptive Trial Designs

• Seamless trial designs
  – Moving from phase 2 through phase 3
  – More efficient post-marketing assessments

• Patient enrichment trial designs
  – E.g. subpopulations responding differently to treatment

• Dose adjustment

• Randomization probabilities
Potential impact

TACKLING CHALLENGES THROUGH INNOVATION
Traditional development path

COST

Phase 1  Phase 2  Phase 3  Phase 4  Expand Indication  Marketing-1  2

Innovative development paths

1\textsuperscript{st} in human  PoC  Dose finding  Confirmatory  Post marketing

+ Novel Analytics (e.g. Targeted Learning)
+ Placebo arm cohort (multiple use datapoints)

COST??
Start from ground up

• Common language
  ✓ Disease Case Definitions (Baseline)
    ✓ Siddiqui et al (under review)
  ✓ Resolution of NASH (definition)
    ✓ Under construction

• Common Elements
  ✓ Standardization of Baseline Parameters
    ✓ Patel et al (Gastroenterology, 2017)
Acknowledgement & Disclaimers

- Presentation informed by Liver Forum deliberations
- Any opinions expressed are my own and do not necessarily represent Liver Forum views
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