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Drug development in non-cirrhotic MASH based on non-invasive tests reasonably likely to predict clinical outcomes

Berkeley Public Health

LF16 Theme
“Build a Broad Coalition”

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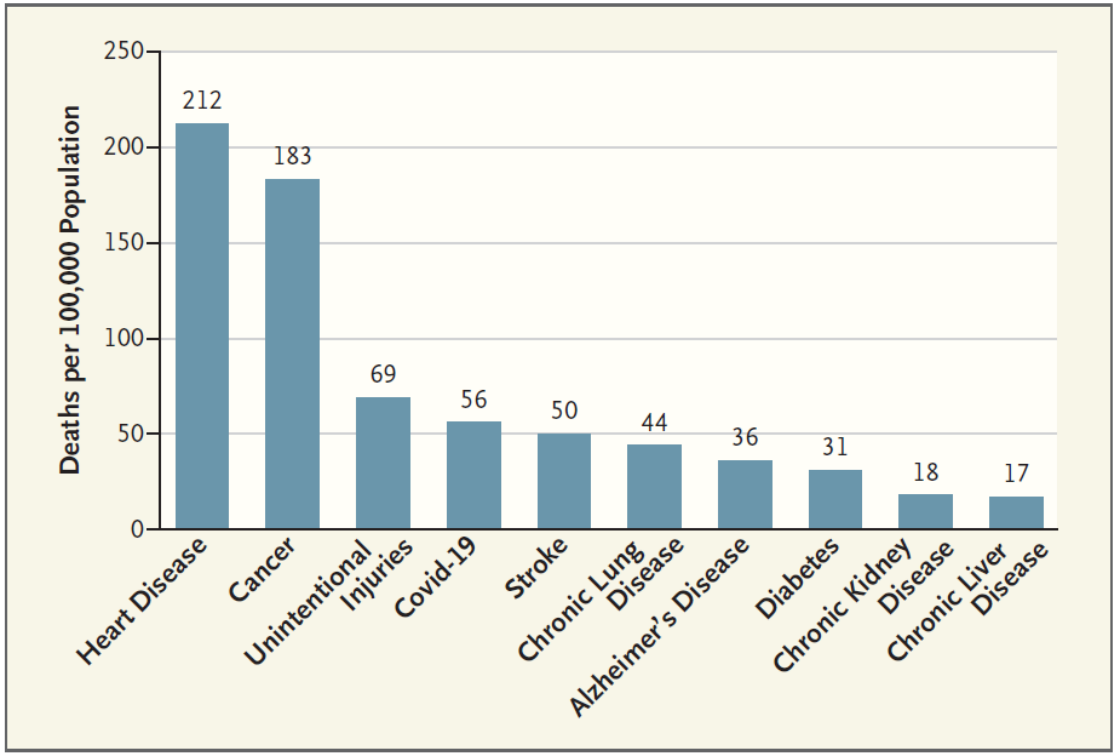
Addressing the Challenge of Common Chronic Diseases — A View from the FDA

Haider J. Warraich, M.D., Hilary D. Marston, M.D., M.P.H., and Robert M. Califf, M.D.



Crude Mortality for the 10 Leading Causes of Death in the United States, 2022.

Preliminary data are from the Centers for Disease Control and Prevention's WONDER database.

N ENGL J MED 390;6 NEJM.ORG FEBRUARY 8, 2024

- Wide disparities in prevalence and outcomes
- FDA: regulatory, scientific, and public health agency
  - Support development of effective and accessible interventions
  - Improve the way evidence is generated
  - Collaboration among stakeholders

Strategies:

- Transform evidence-generating methods
- Make better use of technology
- Develop coherent approaches to issues across chronic diseases
- Foster patient-centered innovation

"There is an urgent need for a research environment that facilitates prospective development and evaluation of reliable biomarkers and surrogate end points for outcomes of interest to overcome the challenge that many candidate therapeutics with promising results in phase 2 trials aren't found to effective in phase 3 trials"

"Requires a broad coalition"

LF16: Post-Marketing Authorization Challenges

- Perspectives
  - Patient: preference for biopsy-free trials
  - Sponsor: difficulty enrolling, larger and >larger trials
  - Clinician: diminishing equipoise
- Lessons learned
  - Clinical liver related outcomes – what to expect
    - Intercept data: progression to cirrhosis
  - Challenges in long-term placebo-controlled trials post-marketing authorization
    - COBALT experience: patients don't stay in placebo arm
  - Challenges in using RWD/RWE
    - Hero Study: "it takes a lot of work to make RWD feel like an RCT"

https://forumresearch.org/liver-forum/liver-forum-meetings/1823-liver-forum-16

LF16 Take-aways

- Patients need a voice from the start
- Challenges with long-term placebo arm require novel solutions
  - E.g. shared placebo arms, placebo-arm cohorts
- Non-invasive tests are indispensable for moving forward
  - Biopsy as RLSE not fit-for-purpose for next generation of RCTs
- Characterizing RLSE requires collaborative analyses across data sets
  - Ditto for validation to full endpoints
- Efficient use of existing data is essential

Commitment to join the "broad coalition"

Noncirrhotic MASH:
Current paradigm in drug development

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Patient population	Reasonably likely surrogate endpoint	Clinical benefit
Histologically defined	MASH resolution Fibrosis improvement	Composite events driven by progression to histologic cirrhosis
▪ Differs from clinical practice ▪ Many with significant risk excluded from clinical trials ▪ Burdensome to patients	▪ Requires 2nd biopsy ▪ Poor agreement between and among pathologists ▪ Spatial heterogeneity in disease severity ▪ Potential to underestimate meaningful treatment effects	▪ Requires 3rd biopsy even though patients may have access to drug through accelerated approval ▪ Differs from clinical practice

Noncirrhotic MASH:
Future paradigm in drug development

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Patient population	Reasonably likely surrogate endpoint	Clinical benefit
Defined by risk of outcome (NIT)	Disease modulation (change in NIT)	Progression to clinical cirrhosis and events
▪ Aligns to clinical practice ▪ Many with significant risk have access to clinical trials ▪ Less burdensome	▪ Aligns to clinical practice ▪ No 2nd biopsy ▪ Objective; able to demonstrate progress over time within CT program	▪ Aligns to clinical practice ▪ No 3rd biopsy

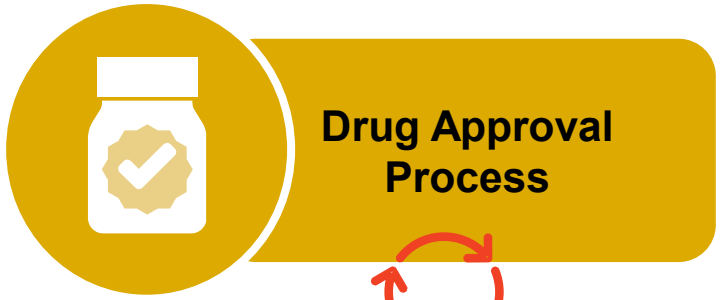
To fully remove liver biopsy in noncirrhotic MASH drug develop, innovations in all three categories are needed

Opportunities for Improved Integration of Biomarker Development Activities within Drug Development

Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

Three pathways to biomarker validation: a long-term endeavor

Intercept
Madrigal Pharmaceuticals
+ all MASH sponsors



~2028-2029

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~ 100 partners
+ OTHERS

2025-2026?

Can the scientific community come to consensus?

LITMUS
NIMBLE
+ OTHERS

~2032-2034

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Liver Forum Proposal:

Facilitate scientific community consensus on RLSE* NITs

New Working Group

*Reasonably Likely Surrogate Endpoints

Forum NIT RLSE Working Group

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Initial Members

- Alina Allen, Mayo Clinic
- Quentin Anstee, LITMUS/ Newcastle University
- Laurent Castera, Beaujon Hospital, University of Paris
- Judith Ertle, Boehringer Ingelheim
- Richard Haubrich, FCR and University of California, San Diego
- Michelle Long, Novo Nordisk
- Rohit Loomba, University of California, San Diego
- Veronica Miller, FRC and UC Berkely
- Sune Nygard, Novo Nordisk
- Vlad Ratziu, Sorbonne University / Hopital Pitie Salpetriere
- Arun Sanyal, Virginia Commonwealth University

Need to Add

- Patients/Patient Representatives
- Regulators
- Statisticians
- Radiologists
- Additional industry
- Additional trialists
- Ethicists

Reasonably likely surrogate endpoint for noncirrhotic MASH drug development

What could this look like?

What is a RLSE?

BEST (Biomarkers, EndpointS, and other Tools)
Classification: *Pharmacodynamic / Response BMs*

FDA

To support approval, FDA expects substantial evidence of effectiveness – that shows that a drug improves meaningful clinical outcomes: how a patient ***feels, functions, or survives***

- A **validated surrogate endpoint**: accepted by FDA that the effect on the biomarker is expected to predict a specific clinical outcome
  - Validated endpoints have *strong and diverse evidence* supporting the relationship of the BM and the outcome
- A **"reasonably likely" surrogate endpoint**: supported by strong mechanistic and/or epidemiologic rationale - effect on the surrogate endpoint is *reasonably likely* to predict clinical benefit

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Histology (improvement in fibrosis and/or NAS) is a RLSE

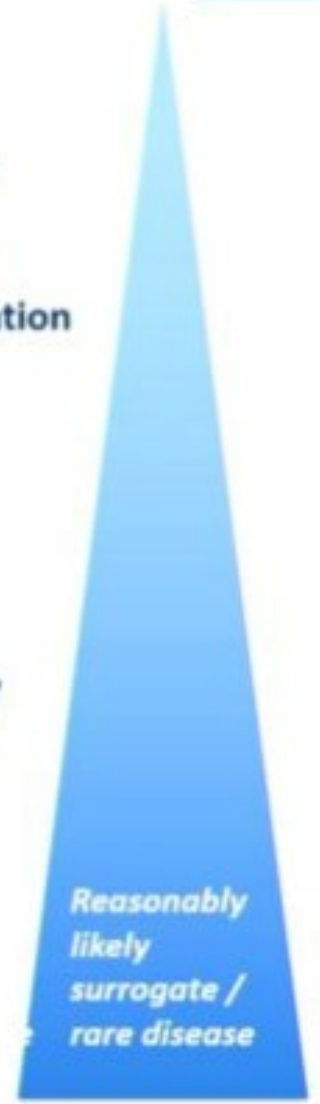
Potential sources of data to support a RL surrogate

- Randomized clinical trial **treatment-group level** data evaluating relationship between change in surrogate and change in clinical endpoint
- Individual **patient-level** data from intervention trials
  - May or may not be a correlation; interpretation and limitations if present or not present

Usually more limited Information

- **Observational data**
  - *Natural history study / cohort* data (e.g., registry)
  - *Epidemiological* data
- **Mechanistic data** showing the role of proposed surrogate in disease pathogenesis
- **Human drug pharmacodynamic studies** showing changes in surrogate leading to modulation of putative causative pathways
- **Human genetic data**
- **Translational animal models**

Primary Source



Considerations When Advocating a New Surrogate Trial Endpoint

- **Relationship of Surrogate Endpoint with Clinical Outcome**
  - Relationship of the Surrogate Endpoint with the Causal Pathway(s)
    - *What pathophysiological pathways are being measured, is the Surrogate Endpoint biologically plausible?*
  - Rationale for Using the Surrogate Endpoint as a Primary Endpoint
    - *What evidence supports a relationship between the Surrogate Endpoint and the clinical outcome?*
  - Threshold for Change Required to Demonstrate Clinical Relevance
    - *Do changes in the Surrogate Endpoint reflect changes in the clinical outcome or their probability?*
    - *What is the extent and timing of change in the SE that would predict the outcome of interest?*
  - Consistency of Surrogate Endpoint Response under Various Conditions
  - Reliably Quantifying Changes in the Clinical Outcome Before and After Treatment
    - *How specific/sensitive is the current standard to measure the clinical endpoint that the SE is intended to predict?*
- **Relationship of the Surrogate Endpoint with the Therapeutic Product**
  - Predictive Value of Therapeutic-Induced Changes in the Surrogate Endpoint
  - Off-Target Effects of the Therapeutic Product
- **Reliability of the Measurement Tool(s) Used to Detect the Surrogate Endpoint**
  - Operations Manual, Performance Characteristics of the Measurement Tool(s)

For Discussion: Fulfilment of all features would be considered a requirement for a *full surrogacy* endpoint, but what level of evidence for each domain is necessary to qualify as a *likely accepted surrogate* predictive of clinical outcomes?

[1] FDA Considerations for Discussion of a New Surrogate Endpoint(s) at a Type C PDUFA Meeting Request, https://www.fda.gov/media/115120/download

LF Consensus: NIT for MASH Drug Development

- Context of use (COU):
  - Disease Prognosis
  - Patient Selection
  - Treatment Response
    - RLSE

LF Consensus: NIT- based RSLE

NIT Properties & Measurements

- Pathophysiological properties *expected* to correlate w clinical benefit
  - Physical (liver stiffness) – e.g. MRE, VCTE-LSM
  - Biological (fibrosis/inflammatory-related NITs) – e.g. ELF, pro-C3

LF Consensus: NIT- based RLSE

NIT Dynamic Properties & Measurements

- Are changes in NITs expected to correlate with changes in clinical benefit?
  - Degree of change?
  - Over what time frame?
  - Single or composite?

LF Consensus: NIT- based RSLE

Data & Evidence Sources

- Mechanistic and observational data to support our assumptions:
  - RCT treatment-group level data
  - RCT individual patient-level data
  - Observational data
  - Mechanistic data
  - Human PK studies
  - Human genetic data

Proposed White Paper Outline - 1

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1. Background
    a. Challenges with biopsy as RLSE
    b. Challenges with Clinical Liver Related Events
    c. Challenges with long-term placebo-controlled trials
2. Non-invasive tests as reasonably likely surrogate endpoints
    a. Definition
    b. Criteria
3. Patient preference for non-biopsy pathway

Proposed White Paper Outline - 2

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4. Data supporting NIT as RSLE for noncirrhotic MASH

a. Prognostic COU: predict risk of progression to cirrhosis and hepatic decompensation
    a. Inter and intra-NIT concordance
    b. Prognostic performance equal to or better than histology
b. Patient Selection COU: select high-risk patient population
    a. Selected patients have unmet medical need
c. Treatment Response COU: identify threshold change for each IT
    a. Test performance characteristics – what is above background noise
    b. Threshold change for each NIT
    c. Clinically meaningful change for each NIT (individual and/or combination)?
    d. Do stable NIT's represent clinical benefit? (lack of progression)

Data Supporting Response COU: Change in NIT and Treatment Response

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NIT(s)	Endpoint	N	Drug	Outcome related to change in NIT	Reference
Δ W 24 or 72 FIB-4, APRI, NFS	↓ fibrosis stage ≥ 1 W72	200	OCA	FIB-4, NFS P < 0.05, NFS ns[1]	Chalasani Liv Int 2020
Δ AST, ALT, GGT, FIB-4, ELF, VCTE	↓ fibrosis stage ≥ 1 (no worse NAS) M18	931	OCA (25, 10, Plecebo)	OCA v Plc: sig reduction ALT, AST, GGT FIB 4, ELF, VCTE ↓ fibrosis stage ≥ 1 M18 sig (P<0.05) assoc: ALT, AST, FIB-4, ELF, Pro-C3, VCTE (AUROC 0.58- 0.62)	Rinella J Hepatol 2022; 76: 536
Change from base to W 12 Pro-C3, ELF, cT1 MRI-PDFF	↓ NAS ≥ 2, no worse fibr OR ↓fib ≥ 1, no worse NAS- W12	43	NGM282	↓ Pro-C3, ELF and cT1 in histologic responders	Harrison Hepatology 2020
Δ ELF, MRE, MRI-PDFF	↓ fibrosis stage ≥ 1 W24	72	Selonsertib, simtuzumab	VCTE, MRE, CK 18 (M30 &65), ELF associated ↓ fibrosis stage	Loomba Hepatology 2018; 67:549
Base and Δ VCTE, ELF, NFS, FIB-4	LRE- decomp, transplant, MELD≥15, death[2] Fibrosis regression-↓ fibrosis stage ≥ 1	1135	Selonsertib, simtuzumab	Assoc LRE: base VCTE, ELF, NFS, and FIB-4; ↑ NFS, LS assoc ↑ LRE Assoc Fibrosis Regress: base VCTE, ELF, NFS, and FIB-4; Δ VCTE and ELF	Sanyal Hepatol 2022; 75:1235
Δ AST, ALT, GGT, VCTE	↓ ≥2 points W24 SAF-A score and no worsening of fibrosis	247	Lanifibranor (1200, 800, placebo)	Greater improvement in NIT tx v Plc: ALT, AST, GGT, PRO C3, cytokeratin 18, ELF, FIB 4 (no stats or compare with primary endpoints)	Francquw NEJM 2021; 385: 1547
ALT, ELF, FIB-4, P3NP	↓ fibrosis stage ≥ 1 (no worse NAS) W72	48	Apararenone	Greater improve tx v Plc (some not sig): ELF, P3NP, FIB-4, fibrosis stage	Okanoue Hep Res 2021; 51: 943

Proposed White Paper Outline - 3

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5. NITs for prognosis and patient selection:
    1. **Physical** liver property: elastography
        a. e.g. VCTE or MRE
    2. **Biological** measure of pathophysiology: collagen marker
        a. e.g., ELF, pro-C3, etc

Research & Analysis

- Define cut-off values for risk prediction and at-risk patient selection
- Consider analyses of both measures in combination

Proposed White Paper Outline - 4

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5. NITs for treatment response:
    1. **Physical** liver property: elastography
        a. e.g. VCTE or MRE
    2. **Biological** measure of pathophysiology: collagen marker
        a. e.g., ELF, pro-C3, etc

Research & Analysis

- Specify magnitude of change that defines *drug mediated activity*
- Specify magnitude of treatment related change that *predicts clinical benefit*
    - Primary evidence: reduction in progression of clinical liver related events
    - Secondary: prevention or regression of histologic-assessed cirrhosis

Path Forward

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- Broader engagement within the LF (LF17) and alignment on the needs and approach
- Engagement with health authorities
- Development and publication of LF white paper
- Consider survey of providers and patients to provide more evidence of community support
- LF sponsored workshop to further develop RLSE and review and outline current evidence and gaps
  - Planned for December 2024

Discussion Questions

Questions for Discussion

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- Do you agree with the basic approach taken by the working group?
- What collaborative activities will be necessary? Will there be support?
- Do you agree that the NIT analysis should focus on clinical liver events/
  - Or should the link between NIT changes and histology be relegated to demonstration of the causal pathway?
- Should ***stable*** MASH disease be considered as a NIT RLSE composite (with reduction in NIT and fewer liver-related clinical events)?