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Standardizing MASH NITs

Veronica Miller, *Forum &* ***Michelle Long,*** *Novo Nordisk*

Berkeley Public Health

Preparing for cross-trial (and PDB) analyses

Previous LF work on standardization & definitions

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Case Definitions for Inclusion and Analysis of Endpoints in Clinical Trials for Nonalcoholic Steatohepatitis Through the Lens of Regulatory Science

Mohammad Shadab Siddiqui,[1*] Stephen A. Harrison,[2*] Manal F. Abdelmalek,[3] Quentin M. Anstee,[4] Pierre Bedossa,[5] Laurent Castera,[6] Lara Dimick-Santos,[7] Scott L. Friedman,[8] Katherine Greene,[14] David E. Kleiner,[9] Sophie Megnien,[10] Brent A. Neuschwander-Tetri,[11] Vlad Ratziu,[12] Elmer Schabel,[13] Veronica Miller,[14] and Arun J. Sanyal[1]; on behalf of the Liver Forum Case Definitions Working Group

Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum

HEPATOLOGY
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Defining Improvement in Nonalcoholic Steatohepatitis for Treatment Trial Endpoints: Recommendations From the Liver Forum

Amanda Cheung,[1] Brent A. Neuschwander-Tetri,[2] David E. Kleiner,[3] Elmer Schabel,[4] Mary Rinella,[5] Stephen Harrison,[6] Vlad Ratziu,[7] Arun J. Sanyal,[8] Rohit Loomba,[9] Sophie Jeannin Megnien,[10] Richard Torstenson,[11] and Veronica Miller[12]; on behalf of the Liver Forum Case Definitions Working Group

Standardisation of diet and exercise in clinical trials of NAFLD-NASH: Recommendations from the Liver Forum

Oliver Glass[1], Claudia Filozof[2], Mazen Noureddin[3], Mark Berner-Hansen[4], Elmer Schabel[5], Stephanie O. Omokaro[6], Jörn M. Schattenberg[7], Katherine Barradas[8], Veronica Miller[8], Sven Francque[9,*,**], Manal F. Abdelmalek[10,*,**], for the Liver Forum Standard of Care Working Group[†]

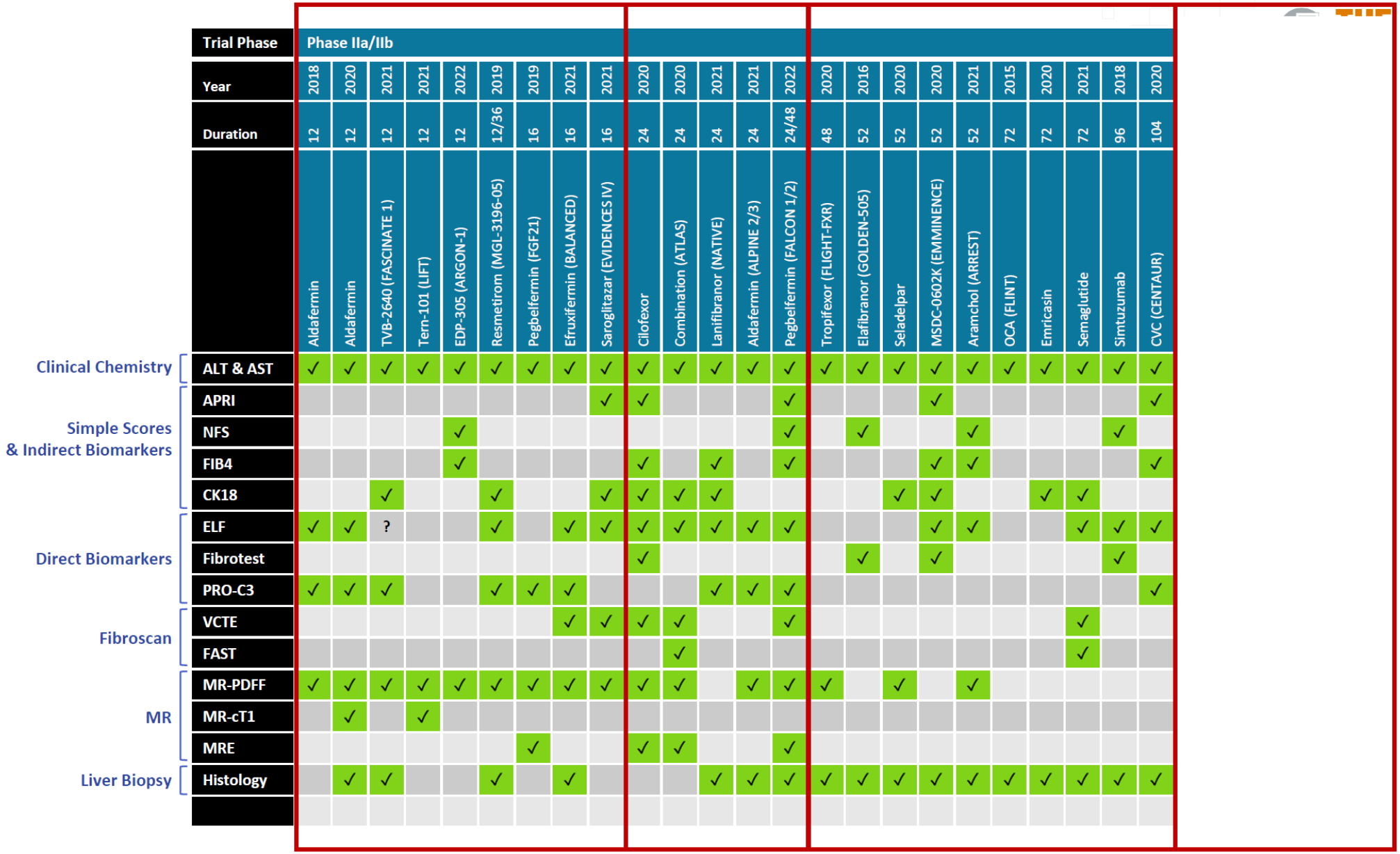
Attribution of Nonalcoholic Steatohepatitis as an Etiology of Cirrhosis for Clinical Trials Eligibility: Recommendations From the Multi-stakeholder Liver Forum

Review

JOURNAL OF HEPATOLOGY

A proposal from the liver forum for the management of comorbidities in non-alcoholic steatohepatitis therapeutic trials

Raluca Pais[1,2], Bertrand Cariou[3], Mazen Noureddin[4], Sven Francque[5,6], Jörn M. Schattenberg[7], Manal F. Abdelmalek[8], Gadi Lalazar[9], Sharat Varma[10], Julie Dietrich[11], Veronica Miller[12], Arun Sanyal[13], Vlad Ratziu [1,14,*], on behalf of the Liver Forum NAFLD-Associated Comorbidities Working Group



	Trial Phase	Phase IIa/IIb									Phase IIb					Phase III										
	Year	2018	2020	2021	2021	2022	2019	2019	2021	2021	2020	2020	2021	2021	2022	2020	2016	2020	2020	2021	2015	2020	2021	2018	2020
	Duration	12	12	12	12	12	12/36	16	16	16	24	24	24	24	24/48	48	52	52	52	52	72	72	72	96	104
		Aldafermin	Aldafermin	TVB-2640 (FASCINATE 1)	Tern-101 (LIFT)	EDP-305 (ARGON-1)	Resmetirom (MGL-3196-05)	Pegbelfermin (FGF21)	Efruxifermin (BALANCED)	Saroglitazar (EVIDENCES IV)	Cilofexor	Combination (ATLAS)	Lanifibranor (NATIVE)	Aldafermin (ALPINE 2/3)	Pegbelfermin (FALCON 1/2)	Tropifexor (FLIGHT-FXR)	Elafibranor (GOLDEN-505)	Seladelpar	MSDC-0602K (EMMINENCE)	Aramchol (ARREST)	OCA (FLINT)	Emricasin	Semaglutide	Simtuzumab	CVC (CENTAUR)
Clinical Chemistry	ALT & AST	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Simple Scores & Indirect Biomarkers	APRI									✓	✓				✓				✓						✓
	NFS					✓									✓		✓			✓				✓	
	FIB4					✓					✓		✓		✓				✓	✓					✓
	CK18			✓			✓			✓	✓	✓	✓					✓	✓			✓	✓		
Direct Biomarkers	ELF	✓	✓	?			✓		✓	✓	✓	✓	✓	✓	✓				✓	✓			✓	✓	✓
	Fibrotest										✓						✓		✓					✓	
	PRO-C3	✓	✓	✓			✓	✓	✓				✓	✓	✓										✓
Fibroscan	VCTE								✓	✓	✓	✓			✓								✓		
	FAST											✓											✓		
MR	MR-PDFF	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓		✓					
	MR-cT1		✓		✓																				
	MRE							✓			✓	✓			✓										
Liver Biopsy	Histology		✓	✓			✓		✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

From Anstee presentation LF12

Meta-Thoughts on Response Biomarkers in NASH Drug Development

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1. **Rapidly attaining a NIT 'response threshold' is not a guarantee of early efficacy.**

2. **Interpret changes in 'Simple Panels' (APRI, FIB4, NFS) with caution.**

3. **In the absence of a single 'gold standard' biomarker, undertake a wholistic assessment of biomarker response and demonstrate change *at the patient level*.**

4. **We should agree and define a common set of biomarkers that will be measured *and reported* in all future clinical trials.**

Update recommendations

Initially proposed by Quentin Anstee LF 14 and 15

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- Which biomarkers should be prioritized?
- If not already assessed, are there biobanks available for subsequent testing?
- Should there be a centralized effort?
- Who would lead the effort?