

LIVER FORUM 2020 NASH UPDATES WEBINAR

August 11, 2020

This 2-hour webinar provided a platform for short overview presentations of updates regarding updates and activity in the NASH field occurring in 2020.

Liver Forum Updates

Presenter: Katherine Barradas, Forum for Collaborative Research

Slides: <https://bit.ly/2GSUfKp>

Steering Committee Updates

- There have been several changes to the Liver Forum Steering Committee since the previous meeting:
 - Dr. Judith Ertle, Senior Clinical Lead for NASH at Boehringer Ingelheim has been appointed Industry Co-Chair
 - Dr. Joachim Musaus, Scientific Administrator at the European Medicines Agency
 - Wayne Eskridge, Founder and CEO of the Fatty Liver Foundation

Manuscript and Working Group News

- Two manuscripts have been accepted and published:
 - Attribution of Nonalcoholic Steatohepatitis as an Etiology of Cirrhosis for Clinical Trials Eligibility: Recommendations from the Multi-stakeholder Liver Forum
 - Mazen Nouredin, Jean Chan, Katherine Barradas, Lara Dimick-Santos, Elmer Schabel, Stephanie Omokaro, Frank Anania, Robert Myers, Veronica Miller, Arun Sanyal, Naga Chalasani, for the Liver Forum NASH Cirrhosis Working Group. *Gastroenterology*. August 2020; 159(2): 422-427.e1. <https://doi.org/10.1053/j.gastro.2020.04.039>
 - Standardization of Diet and Exercise in Clinical Trials of NAFLD-NASH: Recommendations from the Liver Forum
 - Oliver Glass, Claudia Filozof, Mazen Nouredin, Mark Berner-Hansen, Elmer Schabel, Katherine Barradas, Jörn M. Schattenberg, Veronica Miller, Sven Francque, Manal F. Abdelmalek, for the Liver Forum Standard of Care Working Group. *Journal of Hepatology*. September 2020; 73(3): 680-693. <https://doi.org/10.1016/j.jhep.2020.04.030>
- The currently active working groups are:
 - NASH Cirrhosis
 - Standard of Care: Comorbidity Management
 - Pediatric NASH
 - Estimands in NASH Clinical Trials (closed group)
- To join a working group, email kbarradas@forumresearch.org

NIMBLE Updates

Presenter: Tania Kamphaus, Foundation for the National Institutes of Health

Slides: <https://bit.ly/2GSSRB8>

Overview of Foundation for the National Institutes of Health (FNIH) and Biomarkers Consortium

- The mandate of FNIH is to promote the mission of NIH, which is accomplished through creating and leading public/private partnerships.
- Among these initiatives led by FNIH is the Biomarkers Consortium which brings together FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations to form projects to work on biomarker development and qualification.

- The Biomarkers Consortium has been established for ~13 years and is comprised of four Steering Committees that are aligned to specific therapeutic areas: Metabolic Disorders, Inflammation & Immunity, Cancer, Neuroscience.
 - Each therapeutic area has several projects, and NIMBLE (Non Invasive BioMarkers of MetaBolic Liver Disease) is a project within Metabolic Disorders.
- Successes of the Biomarkers Consortium include 14 therapeutics advanced based on tools generated; 9 clinical tools being used in drug development; 5 FDA guidance documents supported by work; 1 clinical safety biomarker qualification; 50+ publications and 800+ citations.
- Each project of the Biomarker Consortium is member driven and collaboration between members is key to moving the projects forward.
- A consortium approach to drug development tools and biomarkers is encouraged by Center for Drug Evaluation and Research (CDER) as a strategy for qualification¹.

Need for non-invasive biomarkers for NASH

- There is a great need for non-invasive biomarkers for diagnosing and monitoring response to treatments for NASH. This need was highlighted in the FDA NASH guidance document released in December 2018²:
 - *“At this time, reliable diagnosis and staging of NASH can only be made by histopathological examination of a liver biopsy specimen. Liver biopsy, however, is an invasive procedure that is associated with occasional morbidity and, in rare circumstances, mortality. The use of liver biopsies in clinical trials poses significant logistical challenges (e.g., cost, availability of pathologists with specific expertise in NASH); in addition, some patients are reluctant or unwilling to undergo biopsy. Therefore, noninvasive biomarkers are needed (including imaging biomarkers) to supplant liver biopsy and provide a comparable or superior ability to accurately diagnose and assess various grades of NASH and stages of liver fibrosis. Identification and validation of such biomarkers could significantly accelerate drug development in NAFLD. FDA encourages sponsors to consider biomarker development.”*

Overview of NIMBLE Project

- NIMBLE: Non Invasive BioMarkers of MetaBolic Liver Disease
- The NIMBLE project plan is divided into two stages:
 - Retrospective assessment of existing biobank data sets and cohorts to generate enough data for well validated biomarkers to meet the evidentiary standards for biomarker qualification; and, assessment of methodology for imaging modalities across manufacturers to establish and standardized repeatability and reproducibility.
 - All FNIH projects are managed by milestone criteria- for NIMBLE to progress to Stage 2, the team must provide and present the results from Stage 1 to the FNIH Executive Committee for approval of a subset of robust candidate biomarkers to be implemented in Stage 2.
 - Prospective interventional trial with biopsies – use biomarkers for diagnosis and assessing response to therapeutic intervention.
- The focus of NIMBLE is on qualifying biomarkers, and prioritizing the contexts of use that will be most impactful for decision-making:
 - Diagnosing and staging NASH
 - Detecting and quantifying changes in NASH status

¹ Qualification Process for Drug Development Tools. Guidance for Industry and FDA Staff. December 2019. <https://www.fda.gov/media/133511/download>

² Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment. Guidance for Industry. December 2018. <https://www.fda.gov/media/119044/download>

- NIMBLE utilizes a cross-stakeholder, team science approach, with partners from academic institutions, pharmaceutical companies, diagnostic companies, patient advocacy groups, FDA, NIH, FNIH.
 - All except diagnostic companies sit on the steering committee and steer the project
 - Academic institutions and investigators execute the project and help steer the science; pharmaceutical companies fund the project, and help steer the science; diagnostic companies provide the assays, but they are not involved in steering.
 - All management of conflict of interest, contracting, funding, and management of deliverables is conducted by FNIH.
 - The project is organized by work streams and the leadership manages the various workflows and decision points.

Milestones & Project Successes

- Milestones 1A and 1B
 - Selection of candidate circulating biomarkers
 - QC of extant biobank samples
 - Assessment of analytical performance assays
 - Generation of draft letter of intent (LOI³)
 - Acceptance of LOI (complete, Feb 2020⁴)
- Milestones 2A and 2B
 - Assessing repeatability and reproducibility across candidate imaging biomarkers (ongoing)
 - Assessing correlation of candidate biomarkers with histologic diagnosis (ongoing)
- Milestone 2C
 - Results will be published in a white paper and presented to FNIH Executive Committee, who will assess if the milestone has been met, and can move to Stage 2 (prospective study)

Timeline for Next Milestones

- Q4 2020
 - Early read out from retrospective study
 - Submission of LOI 2 to FDA from imaging workstream
- Q1 2021
 - Early read from the prospective imaging study, both for ultrasound and MR
- Q3 2021
 - Present results to the FNIH Executive Committee for a set of biomarkers to move forward into the prospective study (Stage 2)
- Q4 2021
 - Pending approval, Stage 2 will be initiated.
 - Developing white paper, which will be available publicly
- Q1 2022
 - Developing full qualification package

LITMUS Updates

Presenter: Richard Torstenson, AbbVie/ Allergan

Slides: <https://bit.ly/3nHwJdH>

LITMUS Overview and Objectives

- LITMUS: Liver Investigation - Testing Marker Utility in Steatohepatitis
- Objectives: develop, validate, and advance biomarkers toward regulatory qualification for three distinct concepts of use in drug discovery for NASH – diagnostic screening, prognostic enrichment, monitoring disease progression

³ LOI Submission <https://www.fda.gov/media/135355/download>

⁴ LOI Acceptance <https://www.fda.gov/media/135356/download>

- Background: funded by IMI and building off of the work and networks of the FLIP (2010-2013) and EPoS (2015-2019) consortia's, LITMUS (2017-2022) includes an expanded partner network of 53 partners from 14 countries.
- Work Packages:
 - WP1: Administration
 - WP2: Methodological Evaluation and Evidence Synthesis
 - WP3: Patient Cohorts and Biobanks
 - WP4: Central Lab
 - WP5: Imaging
 - WP6: Reverse Translation and Pre-Clinical Models
 - WP7: Qualification, Exploitation, and Dissemination

Clinical Data Package

- Meta-cohort
 - Existing prospective data collection from EPoS/FLIP
 - Approximately 1000 patients with histology-based diagnosis, and 6000 patients with cross-sectional data, which will be used to evaluate biomarker performance
- LITMUS study (ongoing)
 - Prospective data collection
 - Imaging sub-study
 - Patient Reported Outcomes for qualification
 - Both the MetaCohort and LITMUS study data sets are included in the European NAFLD registry and it has been suggested this could be a source of post-marketing surveillance in the future
- Pharma-data
 - Industry partners are sharing blinded clinical data and collected blood samples to be used as an external validation cohort.
 - Have collected data for more than 2000 patients, and growing.

Work Package 7: Qualification Strategy and Status

- Strategy has been to obtain early feedback from regulatory authorities on the qualification feasibility and applicability of MetaCohort data (EPoS/FLIP) for exploratory work and the LITMUS trial for confirmation of the biomarker performance for each context of use.
- Aim to facilitate the qualification of several biomarkers for several contexts of use; however, the typical approach and the guidance documents are targeted for a single biomarker and a single context of use.
 - Have submitted two biomarkers for each context of use, included both wet and imaging biomarkers
- Progress update – Qualification status
 - Regulatory interactions between EMA and FDA are ongoing
 - EMA:
 - Two briefing packages submitted- one diagnostic context of use, one prognostic context of use
 - Two scientific advice face-to-face meetings
 - Received qualification advice
 - FDA:
 - Two letters of intent submitted
 - Diagnostic LOI approved early May
 - Should receive response for prognostic LOI soon
 - Development of formal qualification plan is pending the work of WP2.

Work Package 2: Methodological Evaluation & Data Synthesis

- WP2 will now use the systematic literature review and data from analysis of the MetaCohort samples to prioritize the most promising markers for further qualification.

- Over 10 publications have already been submitted for this project and many more are expected as additional data is collected

New IMI2 “Restricted Call” for LITMUS Follow-on Project

- LITMUS will submit a new grant application: Mechanisms of Steatohepatitis: Artificial Intelligence & Clinical Science (MOSAICS)
- Key Topic Areas:
 - Set up of a post-marketing surveillance platform
 - Opportunity to further explore pharmacodynamic biomarkers
 - Evaluate the use of artificial intelligence and machine learning in NASH

Recent NASH Trial Results & Implications

Presenter: Mazen Nouredin, Cedars Sinai Medical Center

Slides: <https://bit.ly/2SN9tMW>

Timeline of NASH developments⁵

- 1980: Description by Jurgen Ludwig and colleagues⁶ of histology of NASH
- 2005: Development of NASH CRN histological scoring and assessment system set the stage for multiple clinical trials
- 2008: Identification of association of PNPLA3 mutation with NASH
- 2010: Results of TONIC and PIVENS trials
- 2013: FDA/AASLD workshop⁷ discussing surrogate endpoints for NASH and creating a viable path for drug development
- 2014: Liver Forum established to continue momentum generated by FDA/AASLD workshop
- 2015: Results of FLINT trial
- 2018: Creation of NIMBLE and LITMUS consortia to focus on biomarker qualification
- 2019: First readout from pivotal NASH trials
 - Many lessons learned, from successes as well as failures

NASH Drug Classes & Clinical Trial Results

- The major NASH drug classes include thyroid hormone receptors (THR), GLP1s, FGFs, fat synthesis inhibitors, PPARs, FXRs, anti-fibrotics, and mitochondrial sensitizers
 - FXR agonists
 - REGENERATE, phase 3 study of Obeticholic acid (OCA)⁸
 - ~2,400 patients randomized 1:1:1 to 25mg, 10mg, and placebo
 - Success defined as achievement of one of the two primary endpoints: fibrosis improvement by one stage without the worsening of NASH, or, NASH resolution without worsening of fibrosis
 - In interim analysis (ITT) at month 18, the trial met one of the primary endpoints, with 23.1% in the 25mg treatment arm compared to 11.9% in the placebo arm achieving a fibrosis improvement of ≥ 1 stage with no worsening of NASH.
 - The other primary endpoint, resolution of NASH without worsening of fibrosis was not met, with 11.7% of the 25mg treatment arm compared to 8% in the placebo arm.

⁵ Sanyal AJ. Past, present and future perspectives in nonalcoholic fatty liver disease. *Nature Reviews Gastroenterology & Hepatology*. 2019;16:377–86.

⁶ Ludwig J et al. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clinic Proceedings*. 1980;55(7):434-8.

⁷ Friedman S et al. Challenges and Opportunities in Drug and Biomarker Development for Nonalcoholic Steatohepatitis: Findings and Recommendations From an American Association for the Study of Liver Diseases-US Food and Drug Administration Joint Workshop. *Hepatology*. 2015; 61(4),1392-405.

⁸ Younossi Z et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *The Lancet*. 2019;394(10215):2184-96.

- Improvement seen in liver enzymes (ALT, AST, GGT, ALP)
- Side effects included lipid changes and pruritus.
- Tropifexor, phase 2 randomized, double-blind, placebo controlled, 3-part study
 - Part C: Assessment of safety, tolerability, efficacy of TXR on biomarkers and histology of biopsy proven NASH F2-3
 - 12-week interim results:
 - MRI PDFF relative change of 31% in the TXR 200µg treatment arm compared to 10% in the placebo arm (p<0.001)
 - Significant decreases in weight (p<0.001), ALT (p=0.013), and GGT (p<0.001) were observed.
- Cilofexor, phase 2, RCT⁹
 - At week 24 patients in the 100mg treatment arm had a median relative decrease in MRI-PDFF of -22.7%, compared to an median relative increase of 1.9% for patients in the placebo arm (p=0.003).
 - The percentage of patients with >30% relative reduction in MRI-PDFF was 38.9% for the 100mg treatment arm, compared to 12.5% in the placebo arm (p=0.011)
- MET 409, phase 1b, proof-of-concept, 12-week study
 - Results shared from press release¹⁰, final analysis pending
 - Relative mean liver fat content relative to placebo decreased 55% for 80mg dose, 38% for 50mg dose, and 6% for placebo.
 - 93% of patients with 80mg dose, and 75% of patients with 50mg dose achieved a ≥30% reduction in liver fat content. The placebo group data was not noted for this component in the press release.
 - Side effects included pruritus
- FGFs
 - NGM282 (FGF 19), multicenter, randomized, double-blind, placebo-controlled, phase 2, 12-week trial
 - Previously reported results¹¹ that 74% of 3mg dose group and 79% of 6mg dose group achieved at least 5% reduction in absolute liver fat content from baseline, compared to 7% in the placebo group.
 - New data published¹² on open label study without placebo arm, where analysis showed improvement in NAS by 2 points in 12-weeks, for both 1mg (50%) and 3mg (68%) doses.
 - One of the first studies looking at histology at 12-weeks.
 - Fibrosis improved in this study within 12 weeks as well, with 42% of patients improving fibrosis in 3mg dose, and 25% of patients improving fibrosis in the 1mg dose.
 - Pegbelfermin (BMS-986036) randomized, double-blind, placebo-controlled, phase 2a, 16-week trial¹³
 - Observed mean absolute change in hepatic fat fraction of -6.8% (p=0.0004) for 10mg daily dose, and -5.2% (p=0.008) for 20mg weekly dose, compared with -1.3% in placebo.

⁹ Patel K et al. Cilofexor, a Nonsteroidal FXR Agonist, in Patients With Noncirrhotic NASH: A Phase 2 Randomized Controlled Trial. *Hepatology*. 2020; 72(1):58-71.

¹⁰ Press Release: Metacrine Demonstrates Best-in-Class FXR Drug Program with Positive Clinical Results in NASH Patients. January 22, 2020. <https://investors.metacrine.com/node/6461/pdf>

¹¹ Harrison S et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet*. 2018;391(10126):1174-85.

¹² Harrison S et al. NGM282 Improves Liver Fibrosis and Histology in 12 Weeks in Patients With Nonalcoholic Steatohepatitis. *Hepatology*. 2020;71(4):1198-212.

¹³ Sanyal A et al. Pegbelfermin (BMS-986036), a PEGylated fibroblast growth factor 21 analogue, in patients with non-alcoholic steatohepatitis: a randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet*. 2019;392(10165):2705-17.

- 56% of patients on 10mg daily dose and 54% of patients on 20mg weekly dose achieved $\geq 30\%$ relative reduction in hepatic fat fraction, compared to 24% for placebo
- BALANCED, Efruxifermin, 16-week, phase 2a trial
 - Data from a press release¹⁴ noting
 - 84% of patients in 28mg dose ($p < 0.001$), 85% of patients in 50mg dose ($p < 0.001$), and 75% of patients in 70mg dose ($p < 0.001$) achieved a $\geq 30\%$ relative reduction compared to 10% in placebo
- ACC inhibitors
 - Firosocostat, GS-0976, randomized, placebo-controlled, phase 2, 12-week trial
 - Previously published results¹⁵ demonstrating relative reduction in MRI-PDFF of -28.9% in the 20mg dose ($p = 0.002$) compared to -8.4% placebo
 - 47.8% of patients in 20mg dose ($p = 0.004$) achieved $\geq 30\%$ relative reduction compared to 15.4% placebo
 - PF'1304, phase 2a, dose-ranging, 16-week study
 - Recently presented data¹⁶ $\geq 30\%$ relative reduction in MRI-PDFF was achieved in 90% of patients in the 50mg group, 87% in the 25mg group, 74% in the 10mg group, compared with 6% placebo.
 - The rise in triglycerides is an issue with ACC inhibitors, FXRs, and FGFs, along with the concomitant use of medications such as statins.
- PPAR agonists
 - EVIDENCES IV: Saroglitazar phase 2, 16-week trial
 - Recently presented data¹⁷ demonstrating achievement of the primary outcome of improvement in ALT. Change in ALT from baseline was -44.39% in the 4mg dose ($p < 0.0001$) -33.16% in the 2mg dose ($p < 0.0001$) compared with 4.16% in the placebo.
 - Improvement of liver fat content was also achieved in the 4mg dose, with 40.74% of patients in the 4mg group achieving $\geq 30\%$ relative reduction in MRI-PDFF ($p = 0.0096$) compared to 8% placebo.
 - NATIVE, Lanifibranor, IVA337, phase 2b, 24-week trial
 - Data from recent press release¹⁸ ITT analysis demonstrating 44% of patients in 1200mg dose ($p < 0.001$) and 34% of patients in 800mg dose ($p = 0.011$) achieved the endpoint 'resolution of NASH with no worsening of fibrosis', compared to 9% placebo.
 - Additionally, 42% of patients in the 1200mg dose ($p = 0.011$) achieved 'improvement of fibrosis by at least one stage and no worsening of NASH', compared to 28% (not significant) in the 800mg group, and 24% in placebo.
 - RESOLVE-IT, Elafibranor, phase 3, 72-week trial

¹⁴ <https://ir.akerotx.com/news-releases/news-release-details/all-akr-001-dose-groups-met-week-12-efficacy-endpoints-nash>

¹⁵ Loomba R et al. GS-0976 Reduces Hepatic Steatosis and Fibrosis Markers in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2018;155(5):1463-73.

¹⁶ Amin NB et al. PF-05221304 (PF'1304), a liver-targeted acetyl-CoA carboxylase inhibitor (ACCI), in adults with nonalcoholic fatty liver disease (NAFLD) demonstrates robust reductions in liver fat and ALT-Phase 2a, dose-ranging study. The Liver Meeting 2019. https://www.natap.org/2019/AASLD/AASLD_69.htm

¹⁷ A phase 2, prospective, multi-center, double-blind, randomized study of Saroglitazar Magnesium 1mg, 2 mg or 4mg versus placebo in patients with nonalcoholic fatty liver disease and/or nonalcoholic steatohepatitis (EVIDENCES IV). The Liver Meeting 2019. https://www.natap.org/2019/AASLD/AASLD_82.htm

¹⁸ Press Release: <https://inventivapharma.com/wp-content/uploads/2020/06/Inventiva-PR-NATIVE-top-line-results-EN-15062020.pdf>

- Press release¹⁹ noting the trial did not demonstrate a statistically significant effect on the primary endpoint of NASH resolution without worsening of fibrosis.
- SCD1 inhibitors
 - ARREST: Aramchol, global, randomized, placebo-controlled, phase 2b, 52-week trial²⁰
 - The primary outcome of $\geq 5\%$ absolute reduction in liver fat from baseline was achieved in the 600mg group with 47% ($p=0.0279$) compared to 24.4% placebo.
 - 16.7% of patients in 600mg dose ($p=0.0514$) achieved NASH resolution without worsening of fibrosis compared to 5% placebo.
- Thyroid hormone receptors
 - Resmetirom (MGL-3196), randomized, double-blind, placebo-controlled, phase 2, 36-week trial²¹
 - The primary endpoint was relative change in hepatic fat as assessed by MRI-PDFF. At 36-weeks, a 50% reduction was observed for patients in the 80mg dose, 39% reduction in the 60mg dose, compared with 14% reduction in placebo arm.
 - At 36 weeks the absolute reduction in hepatic fat was -10.8% for the 80mg dose, -8% for the 60mg dose, compared with -2.3 for placebo.
 - 56.2% of the treatment group ($p=0.024$) achieved a ≥ 2 -point NAS improvement compared to 32.4% in the placebo group.
 - 24.7% of the treatment group ($p=0.032$) achieved NASH resolution without fibrosis worsening, compared to 6.5% in the placebo group.
 - VK2809, randomized, placebo-controlled, phase 2, 12-week trial²²
 - The primary endpoint of change in LDL-C was met, with a placebo-adjusted % change of -21.8% ($p=0.0061$) for all treatment groups at week-12.
 - The mean absolute reduction in liver fat at 12-weeks for all treatment groups was -9.7% compared to -0.9% in placebo, and the median relative change in liver fat at 12-weeks -58.1% for all treatment groups, compared with -8.9% in placebo.
- GLP-1 agonists
 - Semaglutide, multicenter, randomized, double-blinded, placebo-controlled, phase 2, 72-week trial
 - Financial report²³ from company included data and statements noting the trial achieved the primary endpoint of resolution of NASH with no worsening of liver fibrosis.
 - For the 0.4mg group, 59% of patients achieved NASH resolution without fibrosis worsening, compared to the 17% in the placebo

¹⁹ Press Release: <https://ir.genfit.com/news-releases/news-release-details/genfit-announces-results-interim-analysis-resolve-it-phase-3>

²⁰ One-year results of the Global Phase 2b randomized placebo-controlled ARREST Trial of Aramchol, a Stearoyl CoA Desaturasemodulator in NASH patients. The Liver Meeting 2018. https://www.natap.org/2018/AASLD/AASLD_222.htm

²¹ Harrison S et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet*. 2019;394(10213):2012-24.

²² VK2809, a novel liver-directed thyroid receptor beta agonist, significantly reduces liver fat with both low and high doses in patients with non-alcoholic fatty liver disease: A phase 2 randomized, placebo-controlled trial. The International Liver Congress 2019.

²³ Novo Nordisk Q1 Financial Report. May 6, 2020.

https://www.novonordisk.com/content/dam/Denmark/HQ/investors/irmaterial/quarterly_financial_reports/2020/Financial%20report%20for%20Q1%202020.pdf

- group. The other doses (0.2mg, 0.1mg) were noted to have also met the endpoint but did not provide data in the report.
- Galectin-3 inhibitors
 - Belaepectin, phase 2b, 52-week trial in compensated NASH cirrhosis population²⁴
 - The primary endpoint was change in HVPG compared to baseline, and secondary endpoints included changes in liver histology and development of liver-related outcomes.
 - There was no significant difference in change of HVPG between the 2mg or 8mg group and placebo, and did not meet the primary endpoint.
 - However, in a subgroup analysis of patients without varices at baseline, the 2mg group had a reduction in HVPG ($p=0.02$) and reduced development of new varices ($p=0.03$)
 - ASK1 inhibitors
 - STELLAR-3 and STELLAR-4, Selonsertib²⁵
 - Both trials did not meet the primary endpoint, but generated useful and interesting data regarding disease progression from F3 to F4, and F4 to decompensation.
 - Insulin sensitizers
 - MSDC-0602K, randomized, double-blind, placebo-controlled phase 2b, 52-week study²⁶
 - The primary endpoint was histological improvement of ≥ 2 points NAS, and secondary endpoints included resolution of NASH, and fibrosis improvement with no worsening of NASH.
 - Statistically significant effects were not observed for the primary or secondary endpoints; however, improvements in metabolic indices were observed.
 - Pan-caspase inhibitors
 - Emricasan, double-blind, randomized, NASH-related cirrhosis and severe portal hypertension, phase 3, 48-week trial²⁷
 - Primary outcome of reducing portal hypertension was not achieved.
 - Trials generated a lot of valuable information about HVPG, and associated challenges with use in clinical trials.
 - Results still to come in 2020/ 2021
 - AURORA²⁸, Cenicriviroc, phase 3, 52-week trial
 - Primary outcomes are improvement in fibrosis by ≥ 1 stage and no worsening of NASH (12 months), and composite endpoint of progression to cirrhosis, liver-related outcomes, and all-cause mortality (~5 years)
 - Anticipated interim results in October 2021
 - Combination Trials
 - Semaglutide, Firsocostat, Cilofexor²⁹, open label study, primary outcomes are safety and adverse events

²⁴ Chalasani N et al. Effects of Belaepectin, an Inhibitor of Galectin-3, in Patients With Nonalcoholic Steatohepatitis With Cirrhosis and Portal Hypertension. *Gastroenterology*. 2020;158(5):1334-45.

²⁵ Harrison S et al. Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: Results from randomized phase III STELLAR trials. *Journal of Hepatology*. 2020;73(1):26-39.

²⁶ Harrison S et al. Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study. *J Hepatol*. 2020;72(4):613-626.

²⁷ Garcia-Tsao G et al. Randomized placebo-controlled trial of emricasan for non-alcoholic steatohepatitis related cirrhosis with severe portal hypertension. *Journal of Hepatology*. 2020;72(5):885-95.

²⁸ <https://clinicaltrials.gov/ct2/show/NCT03028740>

²⁹ <https://clinicaltrials.gov/ct2/show/NCT03987074>

- TANDEM³⁰: Tropifexor & Cenicriviroc, 48-week study, primary outcomes are safety and occurrence of adverse events. Secondary endpoints are improvement in fibrosis by ≥ 1 stage and no worsening of NASH, and resolution of NASH.
- PF-05221304, PF-06865571³¹ – 6-week, study, primary outcomes are relative change in liver fat by MRI-PDFF, and secondary endpoints are safety and adverse events.
- ATLAS³²: Selonsertib, Firsocostat, Cilofexor, alone and in combinations, phase 2, 48-week study of F3 and F4 NASH patients
 - Press release available, also noting further results to be presented at an upcoming conference.
 - Primary outcomes are safety and improvement in fibrosis by ≥ 1 stage and no worsening of NASH.
 - The study did not meet the primary histological outcome of fibrosis improvement, but the combination of Firsocostat and Cilofexor had statistically significant improvements in secondary endpoints of improvement in fibrosis by ≥ 2 -point reduction in NAS, ≥ 1 -point reductions in steatosis, hepatocellular ballooning and lobular inflammation, and non-invasive tests of fibrosis, liver injury, and function.

Common Challenges in the field

- Pathologist/ histology issues
 - Recent article: Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials ³³, brought questions meriting further discussion
- Understanding the placebo
- Correlation with outcomes
- Non-invasive tests

Implications from 2020

- There have been many failures in 2020 but also many lessons have been learned, and both successes and failures help to increase understanding of the disease.
- More drugs are meeting phase 2 and phase 3 endpoints
- Issues with histology in recent NASH trials need to be addressed, perhaps with the assistance of artificial intelligence, to be able to move to a different outcome that can be more effective for a chronic liver disease that needs multiple endpoint assessments.
- Patient enrollment for clinical trials has been challenging due to the impact of COVID-19.
- Ongoing efforts to correlate with hard outcomes.
- NASH is a multi-organ disease, and efforts have been made to link NASH to outcomes relating to other organs, particularly cardiovascular outcomes.
- Progress being made with biomarkers and generating more data to be able to utilize biomarkers in the future.

Regulatory Updates

U.S. Food and Drug Administration Updates:

- NASH with fibrosis is a serious and life-threatening disease, and is an unmet medical need.

³⁰ <https://clinicaltrials.gov/ct2/show/NCT03517540>

³¹ <https://clinicaltrials.gov/ct2/show/NCT03776175>

³² Press Release: <https://www.gilead.com/news-and-press/press-room/press-releases/2019/12/gilead-announces-topline-results-from-phase-2-atlas-study-in-patients-with-bridging-fibrosis-f3-and-compensated-cirrhosis-f4-due-to-non-alcoholic-s>

³³ Davison B et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials. *Journal of Hepatology*. 2020. Epub ahead of print.

- In 2018, the FDA published the draft guidance: Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis³⁴
 - The draft guidance still represents the current thinking for developing drugs for noncirrhotic NASH with fibrosis stage 2 and 3.
 - The endpoints noted in the guidance are still accepted:
 - Resolution of steatohepatitis on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis; OR
 - Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis)
- There are certain limitations to the surrogate endpoint assessment, and sponsors are highly encouraged to discuss with regulators how to resolve issues with the liver biopsy.

European Medicines Agency Updates:

- The EMA Gastroenterology Drafting Group is currently not operating due to EMA Business Continuity on COVID prioritizing targeted activities.³⁵
- Finalization of the reflection paper is tentatively anticipated in the second half of 2021.

Global Liver Institute Updates

Presenter: Donna Cryer, Global Liver Institute

Slides: <https://bit.ly/3dmAro9>

Recent GLI NASH Activities

- International NASH Day
 - Occurred on June 12, 2020
 - Participation of 80 partners from 26 countries
 - Report is now available³⁶
 - IND targets the lack of awareness of NASH that has been a key barrier to the field.
- NASH Council policy workgroup
 - GLI lead a request³⁷ for change for the ICD-10 code to provide greater granularity in coding between early and advanced fibrosis within the NASH codes.
 - This request was approved by CMS³⁸ for 2021, and will improve the ability to conduct public health research, as well as identify and treat patients
 - GLI sent a letter to the CDC Division of Diabetes regarding the lack of inclusion of NASH in their revised diabetes education materials.
- Patient Engagement with Regulatory Authorities
 - GLI, Fatty Liver Foundation, and NASH Knowledge requested a meeting with FDA to share the perspective of the NASH patient community regarding the recent regulatory actions around OCA.

³⁴ U.S. Food and Drug Administration. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/noncirrhotic-non-alcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment>

³⁵ European Medicines Regulatory Network COVID-19 Business Continuity Plan. https://www.ema.europa.eu/en/documents/other/european-medicines-regulatory-network-covid-19-business-continuity-plan_en.pdf

³⁶ 2020 International NASH Day Report. <https://www.international-nash-day.com/s/IND-report-2020-20806.pdf>

³⁷ <https://www.cdc.gov/nchs/data/icd/Topic-packet-March-2019-Part-2Vs3.pdf>

³⁸ <https://www.cms.gov/medicare/icd-10/2021-icd-10-cm>

- Expressed disappointment with cancellation of the AdCom and lack of ability to provide patient input.
 - Sent letter to FDA and EMA regarding urgency of the unmet medical need of NASH, and expectations of patient engagement and transparency in terms of determining benefit and risk assessments.
- Beyond the Biopsy Campaign Virtual Tour
 - Communications campaign launching August 31
 - Will highlight the work of NIMBLE, LITMUS, and others working on non-invasive diagnostics and will bring in examples from healthcare delivery systems in different areas of the country to demonstrate how they are being implemented and how patients can access those new diagnostic tools.
- NASH Council U.S. Action Plan Workgroup
 - Actively recruiting for new Workgroup to develop a roadmap forward for NASH for patients, clinicians, and policy-makers.