

2024

*Updated Quarterly*

# CVrg Market Strategies™

## MASH – 1Q 2024



CardioVascular  
Resource Group



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# Methodology

This report is a comprehensive deep dive into the current drugs and future market for MASH 2024.

This report is updated and republished at the beginning of every quarter with new information highlighted in **blue text**. The blue text in the report represents new information included in the report during the current year. At the end of each year, the blue text is incorporated into the report and formatted back to black text to provide a fresh report for the new year.

Secondary sources for this report include publications from peer-reviewed literature, major cardiometabolic conference presentations and proceedings, company web sites, annual reports, SEC filings and press releases, electronic databases including Adis R&D Insight, and online databases including clinicaltrials.gov, and the EU Clinical Trials Register.

CVrg covers current treatment practices, emerging treatment trends, product pipelines, target product profiles, and unmet needs. Representatives from CVrg also gather information and conduct informal primary research at key conferences. In 2024, CVrg will attend EASL's [EASL Congress](#) (previously ILC), June 5-8 in Milan, Italy, and AASLD's [The Liver Meeting](#), November 15-19 in San Diego.

Please contact [Nina Brandt](#) or [Liz Poyner](#) with any MASH queries, or if you would like an overview of this report.

# Sentinel Headlines 2024

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# Executive Summary

## 1Q 2024 Key News

### Incretin Combinations

- **Survodutide** (BI/Zealand) meets primary histology endpoint in [Phase IIb](#) trial
- **Survodutide**, BI initiates [Phase III](#) trial in non-cirrhotic MASH
- **Tirzepatide** (Lilly) meets primary histology endpoint in Phase IIb trial [SYNERGY-NASH](#)

### Lipid Modulators

- **Denifanstat** (Sagimet) meets both primary histology endpoints in Phase IIb [FASCINATE-2](#)
- **ION224** (Ionis) meets primary histology endpoint in [Phase IIb](#)
- **Resmetirom** (Rezdifra, Madrigal) approved for MASH F2-F3 in the US
- **Resmetirom** (Madrigal), the EMA accepts MAA for MASH with fibrosis
- Terns discontinues development of **TERN-501/TERN-101**, for MASH to focus on obesity and cancer

### Metabolism Modulators

- **Efruxifermin** (Akero) shows sustained efficacy on histology at 96-weeks in Phase IIb trial [HARMONY](#) in NASH F2-F3
- **Pegozafermin** (89bio) Phase III trial [ENLIGHTEN-Fibrosis](#) in MASH F2-F3 initiated

## 2Q 2024 Key Events

### Lipid Modulators

- **VK2809** (Viking), expected histology data from Phase IIb trial [VOYAGE](#)

### Metabolism Modulators

- **Pegozafermin**, 89bio to initiate Phase III trial ENLIGHTEN-Cirrhosis in MASH F4
- **Efruxifermin**, Akero to initiate Phase III trial SYNCHRONY Outcomes
- **BOS-580** (Boston Pharma), expected histology data from [Phase II](#) trial

## 2024 News Headlines - January

### Combinations/Multi-MOA

JPM 2024: TERN-501/TERN-101, Terns discontinues development for MASH to focus on obesity and cancer [Terns press release](#)

### Glucose Transport Modulators

Henaglifllozin, academic Chinese [Phase IV](#) trial to evaluate efficacy on CAP and LSM in T2D with MASLD

Empagliflozin, completion of academic German Phase IV trial [COMBAT T2 NASH](#) in MASH F1-F3 with T2D delayed by 2 years

### Incretins

Semaglutide, Novo Nordisk updates endpoints of global Phase III trial [ESSENCE](#)

Observational data suggest adherence to GLP-1 therapy in chronic liver disease with T2D lowers risk of MALO [Gut 1/2024](#)

### Lipid Modulators

ALN-PNP, Alnylam/Regeneron updates protocol of [Phase I](#) trial in MASLD with PNPLA3 risk variant

Denifanstat (Sagimet) meets primary endpoint showing impressive histology improvements in Phase IIb trial [FASCINATE-2 Sagimet press release](#)

### Metabolism Modulators

Efruxifermin, Akero releases details of US Phase III trial [SYNCHRONY Histology](#)

### PPAR Modulators

Saroglitazar, Zydus updates primary endpoint of US Phase IIb trial [EVIDENCES X](#) and delays completion by 19 months

### Other

IMM-H014, Tianjin Chase Sun initiates Chinese [Phase I](#) FIH trial

BI and Ribo enter collaboration to develop RNAi-based therapies in MASH [BI press release](#)

Tebao enters licensing agreement with Suzhou Alphamab for GLP-1 agonist KN056 & KN069 (undisclosed) for MASH in China [Alphamab press release](#)

Novo Nordisk enters research collaborations with Omega and Cellarity in obesity and MASH [Novo Nordisk press release](#)

BI funds £30 million observational study ADVANCE to improve understanding of MASH cirrhosis [BI press release](#)

DA-1241 (DongA), preclinical data supports ongoing development in combination with DPP4i sitagliptin [PRNewswire](#)

NN6561 (Novo Nordisk) in Phase I development for MASH [Novo Nordisk 4Q 2023 presentation](#), [Novo Nordisk Annual report 2023](#)

INV-347 (Novo Nordisk) in Phase I development [Novo Nordisk Annual report 2023](#)

Three preclinical siRNA therapies targeting PNPLA3, HSD17B13, and CIDEB in development for MASH with Argo [Argo pipeline accessed 1/2024](#)

### NASH-TAG 2024

NASH-TAG 2024: PLN-1474 (Pliant) safe and well-tolerated in FIH study [P-45 NASH-TAG 2024](#)

NASH-TAG 2024: EPGN2154 (Epigen) shows anti-fibrotic activity independent of weight loss in murine MASH models [P-33 NASH-TAG 2024](#)

### 4Q 2024 Company News

[Novo Nordisk](#)

Please use link provided and/or refer to relevant CVrg Sentinel for broader coverage of monthly MASH headlines.

## 2024 News Headlines - February

### Anti-fibrotic/Anti-inflammatory Agents

AZD2389 (AZ) in [Phase I](#) development for MASH [AZ 4Q 2023 Company call](#)

### Combinations/Multi-MOA

Semaglutide/cilofexor/firsocostat, Novo Nordisk/Gilead removes MASH endpoint of Phase IIb combination trial [WAYFIND](#) in NASH F4

### Incretin Combinations

Survotutide (BI/Zealand) shows impressive histological improvements in [Phase IIb BI press release](#)

Tirzepatide (Lilly) meets primary histology endpoint in Phase IIb [SYNERGY-NASH Lilly 4Q 2023 Company call](#)

### Lipid Modulators

ALN-HSD, Regeneron reduces N and number of arms, delays completion of Phase IIb [NASHGEN-2](#) by 9 months

### PPAR Modulators

PXL065, Poxel hopes to finalize financing to progress development by end of 1Q 2024 [Poxel 4Q 2023 Company call](#)

Lanifibranor/empagliflozin, Inventiva completes enrollment and delays completion of Phase II trial [LEGEND](#) in MASH + T2D by 12m

Lanifibranor, Inventiva pauses screening/randomization in [NATIV3](#) due to liver-related AE in one patient [Inventiva press release](#)

### Company News 4Q 2023

[Viking](#)

Please use link provided and/or refer to relevant CVrg Sentinel for broader coverage of monthly MASH headlines.

## 2024 News Headlines - March (1 of 2)

### Combinations/Multi-MOA

Aramchol (Galmed), EU patent for combination Tx with resmetrirom (Madrigal) in MASH fibrosis granted [Galmed press release](#)

### Incretin Combinations

Survodutide, BI initiates [Phase III](#) trial in non-cirrhotic MASH

DD 15 (D&D) in preclinical development for obesity – included under MetSera collaboration [Korea Biomed](#), [D&D pipeline](#)

### Lipid Modulators

Rapirosiran sodium (ALN-HSD), Regeneron terminates UK [Phase I](#) trial due to business reasons

ALN-PNP, Regeneron adds MASLD cohorts and delays completion of US [Phase I](#) trial

GSK4532990, GSK updates protocol of US Phase IIb trial [HORIZON](#) to include F4 patients

ALG-055009, Aligos initiates US Phase II trial HERALD in MASH F1-F3 [Aligos press release](#)

VSA006, Visirna plans Chinese [Phase IIb](#) trial in MASH F2-F3

Resmetrirom, Madrigal delays completion of US Phase III trial [MAESTRO-NASH OUTCOMES](#) in MASH F4

ION224 (Ionis) potently reduces liver fat and improves MASH and fibrosis in [Phase IIb](#) [Ionis press release](#)

Rezdiflra (resmetrirom, Madrigal) approved for treatment of non-cirrhotic MASH F2-F3 in the US [Madrigal press release](#), [Madrigal presentation](#)

Resmetrirom (Madrigal), the EMA accepts MAA for MASH with fibrosis [Madrigal press release](#)

### Metabolism Modulators

Pegozafermin, 89bio initiates Phase III trial [ENLIGHTEN-Fibrosis](#) in MASH F2-F3 [89bio press release](#), [89bio corporate presentation](#)

J2H 1702, J2H announced ongoing S. Korean [Phase II](#) trial in MASH

Efruxifermin (Akero), 96-week data from Phase IIb trial [HARMONY](#) show sustained histology improvements in MASH F2-F3 [Akero press release](#)

Pegozafermin (89bio) receives PRIME designation in the EU [89bio press release](#)

NGM enters merger agreement with Atlas to go private [NGM press release](#)

### PPAR Modulators

Chiglitazar (Chipscreen), topline data of Chinese Phase II [CINAR](#) show improvements in liver fat [PRNewswire](#)

Lanifibranor (Inventiva) ± empagliflozin shows benefit on glycemic control and MASH in Phase II trial [LEGEND](#) [Inventiva press release](#), [Presentation](#)

Lanifibranor, Inventiva resumes screening/randomization in Phase III trial NATiV3 [Inventiva press release](#)

*Please use link provided and/or refer to relevant CVrg Sentinel for broader coverage of monthly MASH headlines.*

*Continued*

## 2024 News Headlines - March (2 of 2)

### Other

[Observational](#) Indian trial to evaluate genetic variants for prediction of disease progression

### Company News 4Q 2023

[Sagimet, 89bio](#)

*Please use link provided and/or refer to relevant CVrg Sentinel for broader coverage of monthly MASH headlines.*

# Disease Overview

Sedentary lifestyles and westernized diets are fueling the worldwide obesity epidemic leading to increasing prevalence of MASLD, where fatty deposits in the liver cause a wide spectrum of disease ranging from simple steatosis, through to MASH, fibrosis, and cirrhosis, which can result in liver cancer and end-stage liver disease.

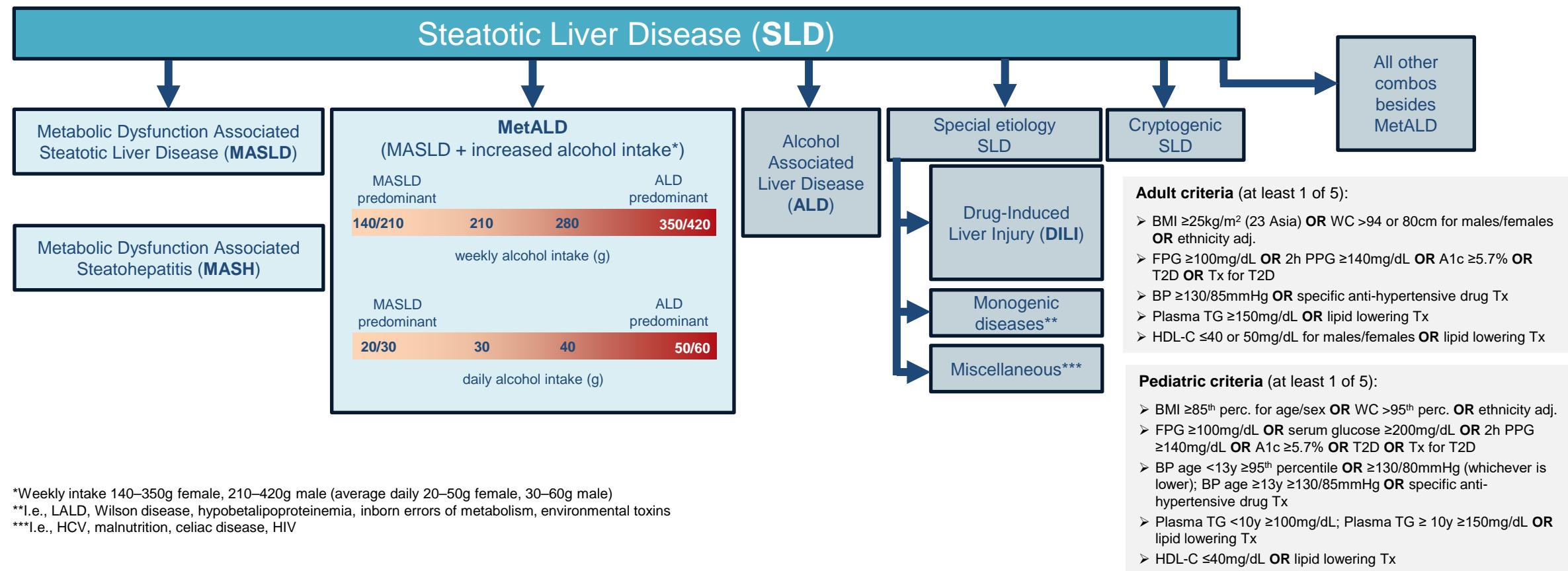
MASH is the most rapidly increasing indication for liver transplantation in the US and has replaced hepatitis C virus as the leading cause of end-stage liver disease and liver transplantation in adults under the age of 50. For both Americans and Europeans, up to one-third of the population have some form of fat in the liver. Alarmingly, the incidence of steatotic liver disease is rising in children.

While liver biopsy is the gold standard for characterizing liver histology in MASLD patients and thus far has been used as a surrogate endpoint for registrational purposes, it is not practical as a widely used screening tool. Serum markers, imaging tests, and algorithms combining the two and clinical lab tests are under development to better diagnose and monitor disease progression of MASLD/MASH.

This section highlights the difference between etiologies of steatotic liver disease including MASLD and MASH and summarizes the pathogenesis of the disease.

## Nomenclature Definitions

During the EASL 2023 meeting at a joint medical society announcement, the results of a three-year process to change the nomenclature of NAFLD were presented with a large majority of respondents (236 experts from 54 countries) approving the recommendation of nomenclature change from NAFLD to Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD). Steatotic liver disease (SLD) diagnosed histologically or by imaging has many potential etiologies – MASLD is defined as presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor and no other discernible cause. MASLD patients with steatohepatitis are designated as MASH while MASL refers to MASLD without steatohepatitis. MetALD is an overlap between MEASLD and ALD as a continuum between the two. [The MASLD nomenclature identifies the same patient population that was previously termed NAFLD, and this report has been updated to reflect the change in nomenclature.](#)



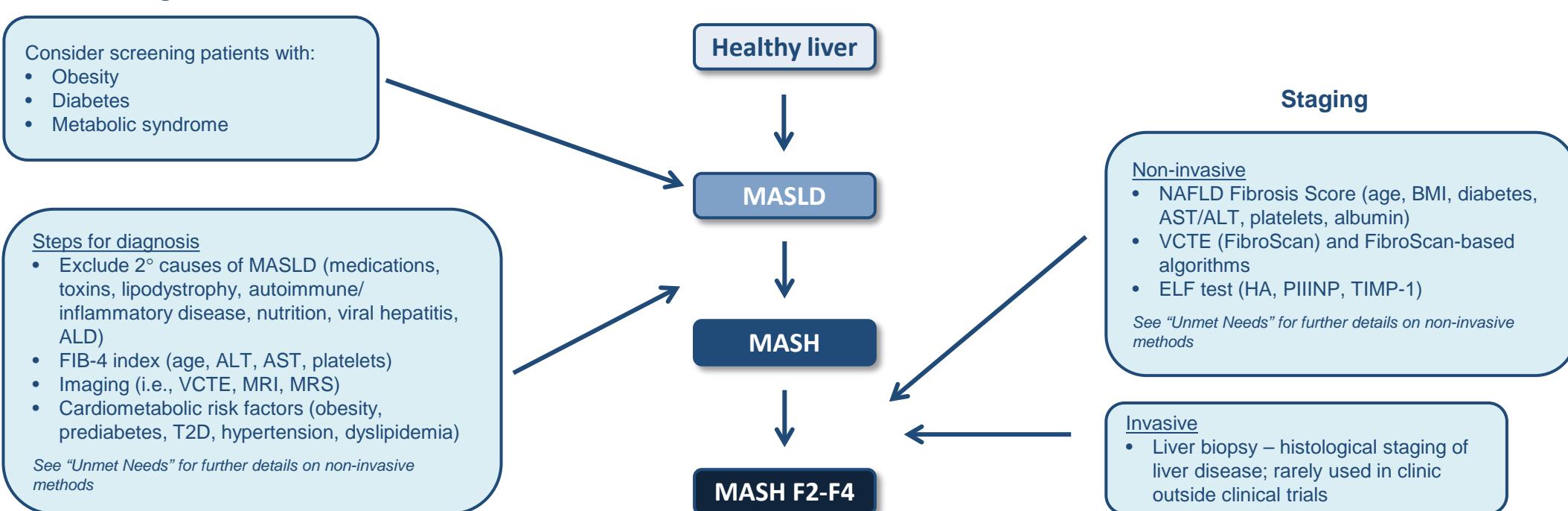
Sources: Kanwal F et al [Metabolic dysfunction-associated steatotic liver disease: Update and impact of new nomenclature on the AASLD practice guidance on NAFLD](#), Hepatology 11/2023

## Diagnosis and Staging

Diagnosis of MASLD requires evidence of hepatic steatosis, either by imaging or by histology. Scores based on clinical and laboratory results (i.e. FIB-4) and imaging tests such as ultrasound, vibration controlled transient elastography (VCTE – FibroScan), CT, and MRI are used for initial assessment, and while rapid advances in non-invasive tests for diagnosing, staging, and monitoring disease are underway (see “Unmet Needs” for further discussion of non-invasive tests), these techniques generally perform better at ruling out than identifying advanced disease.

Liver biopsy remains the gold standard for characterizing liver histology in MAFLD/MASH patients but is limited by cost and variability in pathology evaluation and carries some morbidity and very rare mortality risk. Liver biopsy is now rarely performed in clinic outside the setting of clinical trials. Routine screening for MASH in the general population is not recommended, while screening in high-risk groups seen in primary care, diabetes, or obesity clinics is advised by major .

### Diagnosis



**Sources:** Rinella M.E. [AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease](#), Hepatology 5/2023; 77(5) 1,797-1,835  
 Chalsani N et al. [The diagnosis and management of NAFLD: Practice Guideline by the American Association for the Study of Liver Diseases](#). Hepatology. 1/2018; 67(1) 328-357.  
 Schwenger KJP, Allard JP. [Clinical approaches to non-alcoholic fatty liver disease](#). World J Gastroenterol. Feb. 21, 2014; 20(7): 1712-1723.

# Current Treatment

Until recently, no drugs were approved for the treatment of MASLD or MASH, but in March 2024, Madrigal's THR $\beta$  agonist resmetirom (marketed Rezdiffra) in conjunction with diet and exercise was approved for the treatment of MASH with F2-F3 fibrosis in the US. Lifestyle changes, including diet and exercise to reduce weight, as well as treatment of obesity, diabetes, and dyslipidemia, are routinely accepted as the standard of care, but have not been shown to prevent disease progression.

Patients with MASLD have excellent prognosis from a liver standpoint, and treatments aimed at improving liver disease should be limited to those with MASH and fibrosis.

Various drugs used off-label for the treatment of MASH, include vitamin E, metformin, gemfibrozil, pentoxifylline, and ursodiol, but none of these have been approved by the FDA or EMA as a treatment for MASH.

This section summarizes the recommended treatment algorithm for MASLD/MASH according to the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association.

## Background

### First drug approved for MASH

With MASH being the [most rapidly growing](#) indication for liver transplant in patients without HCC there is an urgent unmet need to develop effective treatments for MASH patients. From a rapidly growing pipeline of potential drugs being tested in MASH patients [the US FDA recently approved THR \$\beta\$  agonist resmetirom \(marketed Rezdiffra, Madrigal\)](#) for the treatment of MASH patients with F2-F3 in conjunction with diet and exercise. Rezdiffra was launched in the US in April 2024 and the drug will be distributed through a limited specialty pharmacy network focusing on patients diagnosed with MASH F2-F3 seen by specialists including hepatologists and gastroenterologists

Patients with MASLD have excellent prognosis from a liver standpoint given the commonly slow progression rate, and pharmacotherapies aimed at improving liver disease should be limited to those with MASH and fibrosis. Current management of MASLD/MASH consists of treating liver disease as well as the associated metabolic co-morbidities with pharmacotherapy approved for diabetes, insulin resistance, obesity, and dyslipidemia. These treatments (TZDs in particular) can have deleterious effects with chronic use. Large, high-quality clinical trials with rigorous methodology are needed to establish long-term safety of current agents as well as novel drugs.

### Management Strategies for MASLD

All current practice guidance and management documents were published when no drugs were approved for the treatment of MASH and will likely be updated to reflect the option of pharmacotherapy for patients with MASH F2-F3.

Recommended lifestyle and treatment approaches according to the **American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association** published in [2012](#), Practice Guidance updated in [2022](#):

- **Weight loss:** Generally, reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.  
- while weight loss yields improvement in disease activity, impact on fibrosis especially in patients with advanced (F3-F4) fibrosis is unclear (AASLD 2021, oral 2156).
- **Thiazolidinediones:** Pioglitazone (generic since 2012) can be used to treat steatohepatitis in patients with biopsy-proven MASH. However, the long-term safety and efficacy of pioglitazone in patients with MASH have not been established.
- **Vitamin E:** Administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven MASH and therefore should be considered a first-line pharmacotherapy. Until further data supporting its effectiveness become available, vitamin E is not recommended to treat MASH in diabetic patients, MASH cirrhosis, or cryptogenic cirrhosis.
- **Omega-3 fatty acids:** May be used as first-line agents to treat hypertriglyceridemia in patients with MASLD.

# 2016 EASL/EASD/EASO Clinical Practice Guidelines for Management & Tx of MASLD

The 2016 Clinical Practice Guidelines provide recommendations for the diagnosis, treatment and follow-up of MASLD patients, and are the product of a joint effort by the **European Association for the Study of the Liver** (EASL), **European Association for the Study of Diabetes** (EASD) and **European Association for the Study of Obesity** (EASO).

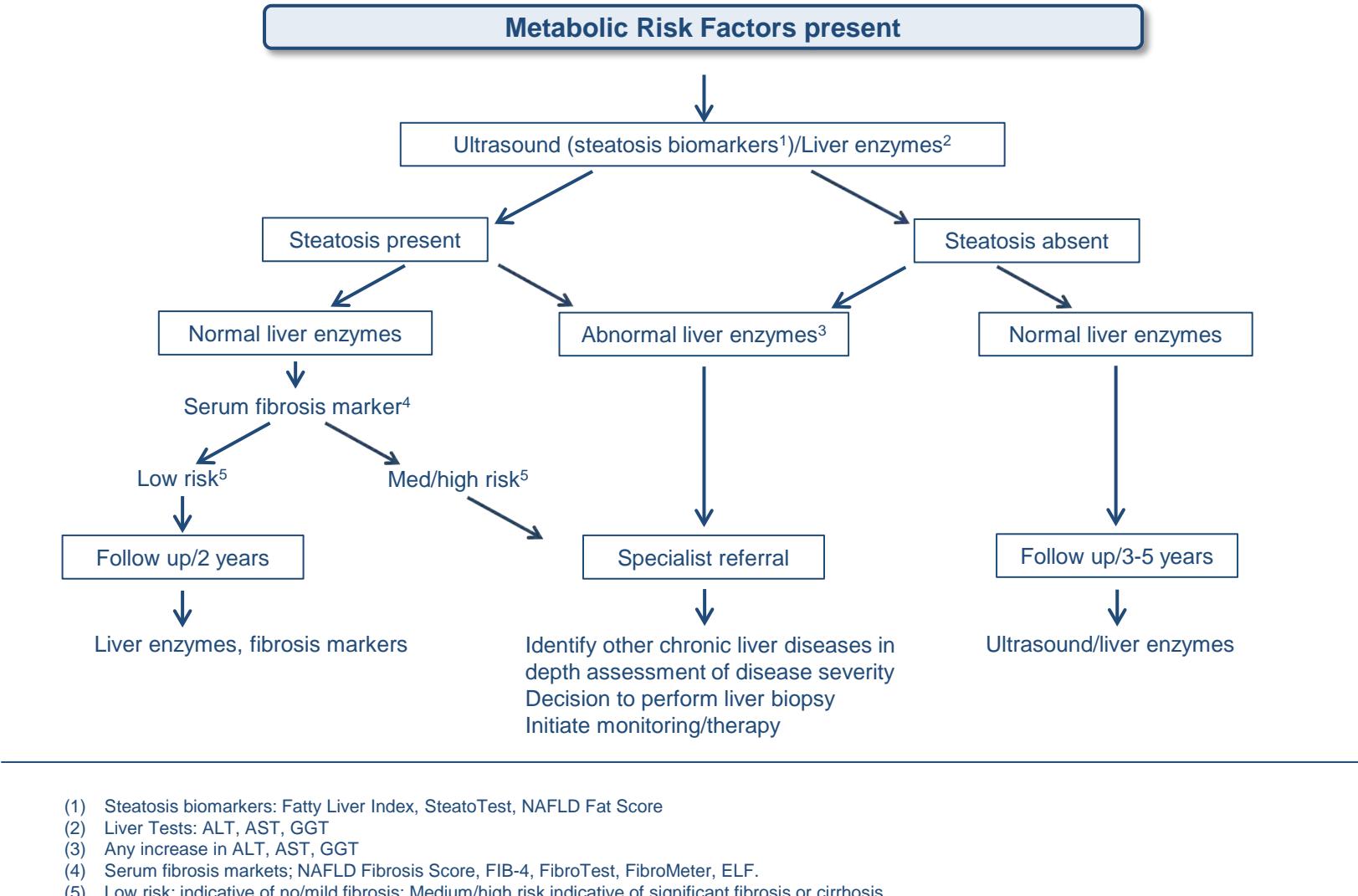
The guidelines are an update to a [position statement](#) based on the 2009 EASL Special Conference that proposed expert opinion on MAFLD/MASH patient care.

The new guidelines were presented at ILC 2016, and simultaneously published in the journals: [Diabetologia](#), [Obesity Facts\\*](#), [Journal of Hepatology](#). \*Link to full guidelines

The guidelines were well received at ILC, with KOLs pleased to see that they acknowledge certain populations at risk including T2D:

- In persons with MASLD, screening for diabetes is mandatory, by fasting or random blood glucose (A1c), and if available, by the standardized 75g OGTT in high-risk groups.
- In patients with T2D, the presence of MASLD should be investigated, irrespective of raised liver enzymes, since T2D patients are at high risk of disease progression.

**Source:** ILC 2016: [EASL clinical practice guidelines: NAFLD](#)



# 2021 AGA Clinical Care Pathway (1 of 2)

In collaboration with four professional organizations (the American Diabetes Association, American Osteopathic Association, Endocrine Society, and the Obesity Society), the American Gastroenterological Association (AGA) assembled a taskforce of 15 experts (medical professionals from collaborating societies) to develop a MASLD/MASH Clinical Care Pathway providing practical guidance across multiple disciplines of care.

The guidance ranges from screening and diagnosis to management of individuals with MASLD and MASH, to facilitate value-based, efficient, and safe care that is consistent with evidence-based guidelines.

## Screening and diagnosis

- 1) Identify patients at risk for clinically significant fibrosis
  - fibrosis is the most important determinant of outcomes in MASLD patients
- 2) Conduct standard history and blood tests
  - these tests may help identify presence of other chronic liver and biliary diseases beyond MASLD/MASH
- 3) Non-invasive testing for liver fibrosis using a two-tier approach (FIB-4, LSM [4])
  - FIB-4; cheap, best diagnostic accuracy and correlates with outcomes
- 4) Liver stiffness measurement (LSM)
  - proprietary, commercially available NITs recommended in patients with indeterminate FIB-4 and unavailable LSM

1: Metabolic risk factors: central obesity, high TG, low HDL-C, hypertension, prediabetes, insulin resistance

2: For patients aged  $\geq 65$  use FIB-4 <2.0 as lower cut-off

3: Other NITs derived from routine labs can be used instead of FIB-4

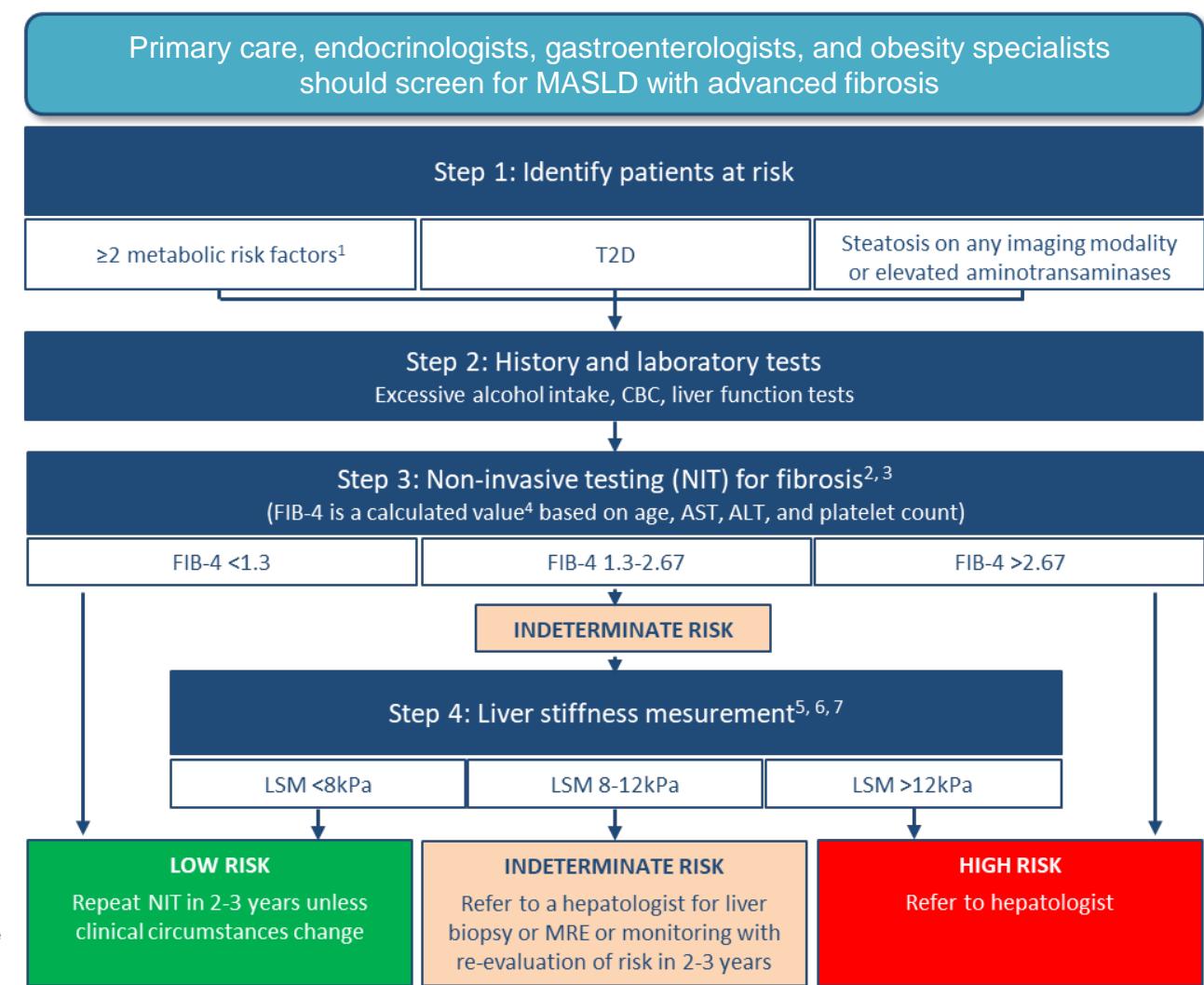
4: Many online FIB-4 calculators are available:

<https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis>

5: Ultrasound acceptable if VCTE, FibroScan is unavailable. Consider referral to hepatologist for patients with hepatic steatosis on ultrasound who are indeterminate or high risk based on FIB-4.

6: LSM values are for VCTE FibroScan. Other techniques such as bidimensional shear wave elastography or point shear wave elastography can also be used to measure LSM. Proprietary commercially available blood NITs may be considered for patients considered indeterminate or high risk based on FIB-4 or APRI, or where LSM unavailable.

7: [Eddowes et al.](#), used 8.2 and 12.1kPa as cut-offs for LSM using VCTE. Validation of simple (rounded) cut-offs reported by [Papatheodoridi et al.](#)



## 2021 AGA Clinical Care Pathway (2 of 2)

### Management

The primary goal of screening high-risk groups is to implement early interventions and prevent the development of cirrhosis and liver-related and all-cause mortality. Successful intervention requires a cohesive multidisciplinary team including PCPs, endocrinologists (patients with T2D), and gastroenterologists/hepatologists.

Management strategies based on risk assessment from FIB-4, LSM, and liver biopsy are described in figure.

Application of the 2021 AGA algorithm to identify “at-risk” MASH in the general US population (NHANES 2017/18) presented at AASLD 2022 (oral 088) substantially reduced the need for referral to specialty care:

- 73% of 4,459 subjects with available FIB-4 score had FIB-4 ≤1.3 classified as low risk.
- By further using FibroScan on 1,112 subjects with indeterminate FIB-4, additional 19% had LSM ≤8kPa classified as low risk; by using the algorithm only 8% of subjects needed specialty referral.
- Of 3,196 subjects with FIB-4 ≤1.3, 384 had LSM ≥8kPa and might have fibrotic MASH.
- Subjects classified as “high-risk” either by FIB-4 ≥2.67 or LSM ≥8kPa were older, had higher liver related lab values, and higher A1c.
- In patients with T2D (39% of total population) only 11.2% would have needed referral to hepatology.

	LOW RISK FIB-4 <1.3 or LSM <8kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3-2.67 or LSM 8-12kPa and liver biopsy not available	HIGH RISK FIB-4 >2.67 or LSM >12kPa or liver biopsy F2-F4
Lifestyle intervention <sup>2</sup>	Management by PCP, dietitian, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietitian, endocrinologist, cardiologist, others)	
Weight loss recommended if overweight or obese <sup>3</sup>	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes <sup>4, 5, 6</sup>	Yes <sup>4, 5, 6, 7</sup>
CVD risk reduction <sup>8</sup>	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1)

1: Patients with F4 or cirrhosis (based on biopsy, LSM values based on VCTE (FibroScan) or >5.0 kPa on MRE) should undergo HCC surveillance. Varices screening is recommended if LSM > 20 kPa or platelet count of <150,000/mm<sup>3</sup>

2: All patients require regular physical activity, healthy diet, avoid excess alcohol intake

3: Weight loss recommended for cardiometabolic benefit and reversal of steatosis. Greater weight loss is often associated with more benefit, such as reversal of steatohepatitis (usually with weight loss ≥7%) or fibrosis (usually with weight loss ≥10%)

4: Individualize based on further work-up and efforts to confirm the diagnosis of MASH. A liver biopsy provides helpful information and should be considered for cases where there is diagnostic doubt i.e., patients with indeterminate, unreliable, or conflicting noninvasive assessments or as part of Phase II or III trials

5: No pharmacological agent is FDA-approved for the treatment of MASH. Patients with T2D may benefit from some diabetes medications, such as pioglitazone and some GLP-1 RAs that have reported histological improvement in patients with MASH, either with or without diabetes. Among GLP-1 agonists, semaglutide has the strongest evidence of liver histological benefit

6: Vitamin E improves steatohepatitis in patients with MASH without diabetes, with less evidence in patients with T2D.

7: Pharmacotherapy in patients with MASH cirrhosis is very limited and should be avoided until more data become available

8: Statins can be used safely in patients with steatohepatitis and liver fibrosis; to be avoided in decompensated cirrhosis

## AASLD Practice Guidance for Clinical Assessment and Management of MASLD

The American Association of Clinical Endocrinology (AACE) issued a [2022 update](#) to the [2018 guidance document](#), now including 34 evidence-based clinical practice recommendations for the diagnosis and management of patients with MASLD and/or MASH – a further AASLD [2023 update](#) reflects advances in the field based on more than 1,400 new publications – the most profound advances in MASLD relevant to clinical practice are in biomarkers and therapeutics.

Key updates include:

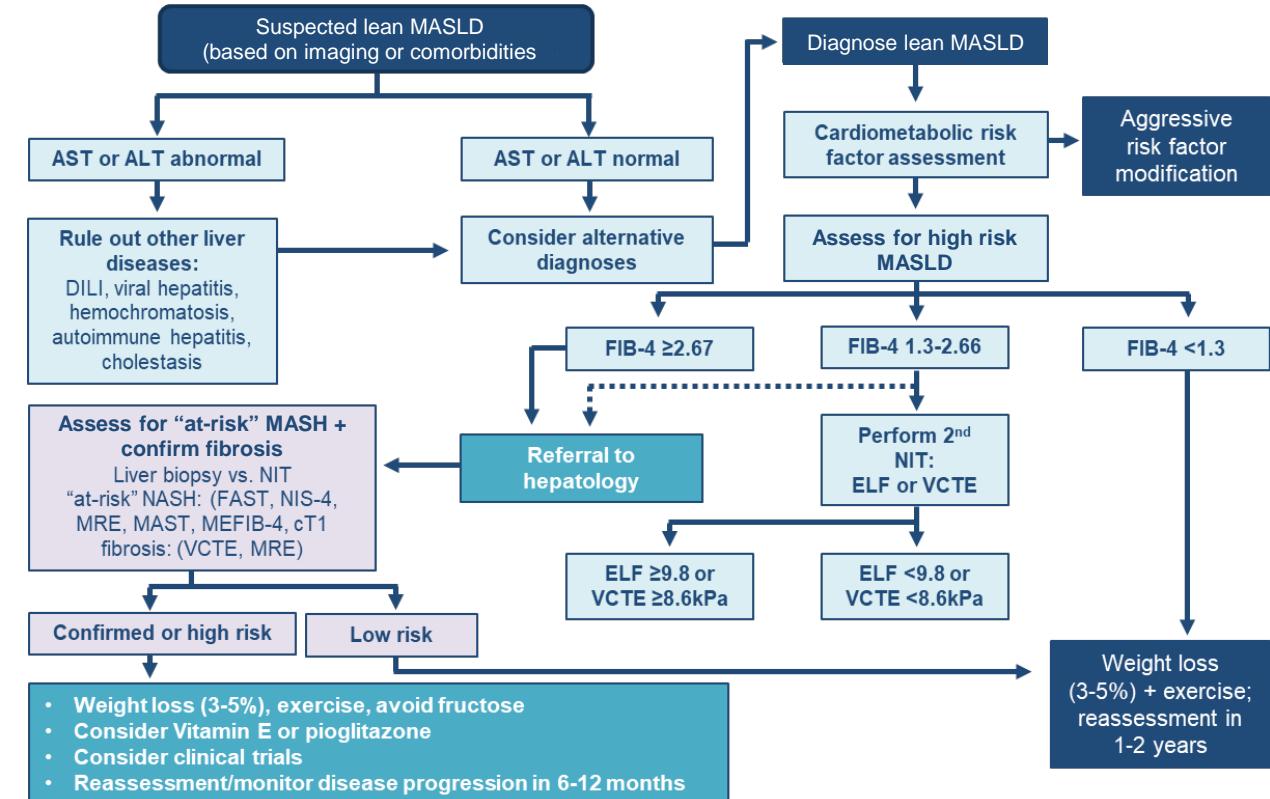
- Pediatric MASLD is now separated into an independent guidance document.
- Screening now recommended for advanced fibrosis in high-risk populations** including T2D, medically complicated obesity, MASLD in the context of moderate alcohol use, and first degree relative of a patient with cirrhosis due to MASLD.
- Updates to the risk stratification algorithm: **Secondary risk assessment with VCTE or ELF if FIB-4 ≥1.3** in either primary care or hepatologist care.
- Non-invasive diagnosis** of “at-risk” MASH, advanced fibrosis, and cirrhosis: FAST, MEFIB, cT1 for at-risk MASH, and FIB-4, VCTE, ELF, and MRE for advanced fibrosis and cirrhosis (with separate rule-in and rule-out values, see below).
- Off-label use of available medications for comorbid conditions: liraglutide, semaglutide, tirzepatide, pioglitazone, SGLT-2 inhibitors, and vitamin E dose recommendations were provided. Statins can now be considered in MASLD patients with high CVD risk.
- Bariatric surgery should be considered as a therapeutic option for patients with MASLD who meet the criteria for metabolic weight-loss surgery.
- An optimal care model that integrates weight management, cardiology and lipid management, and health psychology of the patient with MASLD.

Diagnosis of steatosis	Identification of “at-risk” MASH:	Detection of advanced fibrosis:	Diagnosis of cirrhosis:			
<u>Likely</u> <b>Ultrasound</b> “detected” <i>- semiquantitative: mild/moderate/severe</i> <b>FibroScan :</b> $\geq 288\text{dB/min}$ <b>CAP</b> <i>Limited accuracy for quantification</i> <b>MRI-PDFF</b> $\geq 5\%$ <i>Most sensitive – accurate to assess dynamic change</i> <u>Unlikely</u>	<u>Likely</u> <b>FAST</b> $\geq 0.67$ <b>MAST</b> $\geq 0.242$ <b>MEFIB</b> FIB-4: $\geq 1.6+$ <i>MRE <math>\geq 3.3\text{kPa}</math></i> <b>cT1</b> $\geq 875\text{ms}$	<u>Unlikely</u> $<0.35$ $<0.165$ FIB-4: $< 1.6+$ <i>MRE <math>&lt; 3.3\text{kPa}</math></i> $<825\text{ms}$	<u>Likely</u> <b>FIB-4</b> $\geq 2.67$ <b>NFS</b> $\geq 0.672$ <b>ELF</b> $\geq 9.8$ <b>FIBROspect</b> $\geq 17$ <b>VCTE</b> $\geq 12\text{kPa}$ <b>ARFI</b> $\geq 1.34$ <b>SWE</b> $\geq 12\text{kPa}$ <b>MRE</b> $\geq 3.63\text{kPa}$	<u>Unlikely</u> $<1.3$ $<-1.44$ $<7.7$ $<17$ $<8\text{kPa}$ $<1.3$ $<8\text{kPa}$ $<2.55\text{kPa}$	<u>Likely</u> <b>FIB-4</b> $\geq 3.48$ <b>ELF</b> $\geq 11.3$ <b>VCTE</b> $\geq 20\text{kPa}$ <b>MRE</b> $\geq 5\text{kPa}$	<u>Unlikely</u> $<1.67$ $<7.7$ $<8\text{kPa}$ $<3\text{kPa}$

## 2022 AGA Clinical Practice Update for Diagnosis & Management of lean MASLD

The American Gastroenterological Association (AGA) commissioned and approved an expert review entitled “*Clinical Practice Update: Diagnosis and Management of NAFLD in Lean Individuals*” outlining best practice advise to assist clinicians in evidence-based approaches to the diagnosis, staging, and management of MASLD in lean individuals.

1. Lean MASLD should be diagnosed in individuals with MASLD and BMI <25kg/m<sup>2</sup> (non-Asian race) or BMI <23kg/m<sup>2</sup> (Asian race)
2. Lean MASLD patients should be evaluated routinely for comorbid conditions, such as T2D, dyslipidemia, and hypertension
3. Lean MASLD patients should be risk stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis
4. Lean individuals in the general population should not undergo routine screening for MASLD; however, screening should be considered for individuals older than 40 years with T2D
5. MASLD should be considered in lean individuals with metabolic diseases (T2D, dyslipidemia, and hypertension), elevated liver biochemical tests, or incidentally noted hepatic steatosis
6. Clinicians should query patients routinely regarding alcohol consumption patterns in all patients with lean MASLD
7. In patients with lean MASLD, other causes of liver disease should be ruled out, including other causes of fatty liver, such as HIV, lipodystrophy, lysosomal acid lipase deficiency, familial hypobetalipoproteinemia, and medication-induced hepatic steatosis (methotrexate, amiodarone, tamoxifen, and steroids)
8. Current evidence is inadequate to support routine testing for genetic variants in patients with lean MASLD
9. Liver biopsy, as the reference standard, should be considered if there is uncertainty regarding contributing causes of liver injury and/or the stage of liver fibrosis
10. Serum indices (NFS and FIB-4) and imaging techniques (TE and MRE) may be used as alternatives to liver biopsy for fibrosis staging and patient follow-up
  - these tests can be performed at the time of diagnosis and repeated at intervals of 6 months to 2 years, depending on fibrosis stage and the patient's response to intervention
11. If noninvasive tests (e.g., NFS and FIB-4) are indeterminate, a second noninvasive test (e.g., VCTE or MRE) should be performed to confirm the stage and prognosis of MASLD
12. In lean patients with MASLD, lifestyle intervention, including exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to target a modest weight loss of 3–5% is suggested
13. Administration of vitamin E may be considered in lean persons with biopsy-confirmed MASH, but without T2D or cirrhosis; pioglitazone (oral 30mg QD) may be considered in lean persons with biopsy-confirmed MASH without cirrhosis
14. The therapeutic role of GLP-1 agonists and SGLT-2 inhibitors in the management of lean MASLD is not fully defined and requires further investigation
15. HCC surveillance with abdominal ultrasound with/without serum  $\alpha$ -fetoprotein twice per year is suggested in patients with lean MASLD and clinical markers compatible with liver cirrhosis



Source: Long et al., "AGA Clinical Practice Update: diagnosis and management of NAFLD in lean individuals: Expert review, Gastroenterol. July 2022

## Developments on Vitamin E

### April 2015:

A meta-analysis of patients in the vitamin E and placebo arms of Phase III [PIVENS](#) and Phase III [TONIC](#) as well as those in the Phase II [FLINT](#) placebo group (grouped by those who did and did not report using vitamin E at baseline) was presented at ISL/EASL 2015. When pooled, significantly more patients on vitamin E had histologic improvement ( $\geq 2$  point improvement in NAS and resolution of MASH) vs. placebo. There was no difference between groups in cardiac events and in serum lipid levels. While a previous [2005 meta-analysis on vitamin E supplementation](#) found increased risk of all-cause mortality in patients taking vitamin-E supplements for cardiovascular disease or cancer, these data indicate that **MASH patients do benefit with vitamin E.**

### November 2015:

A meta-analysis of patients in the vitamin E and placebo arms of Phase III [PIVENS](#) and Phase II [FLINT](#) placebo group (grouped by those who did and did not report using vitamin E at baseline) was presented at AASLD 2015. When pooled, there was histologic improvement in both diabetic and non-diabetic patients with vitamin E vs. not on vitamin E, although fibrosis was significantly improved only in non-diabetics, and there was no significant increase in resolution of MASH in either group. Importantly, incidence of cardiac events was similar between treatment arms in diabetics and non-diabetics. Change from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, or triglycerides were similar between treatment groups in both diabetics and non-diabetics. While this new analysis also indicates that **vitamin E is safe in T2D patients**, additional long-term studies are needed to confirm these results, as there has been insufficient research evidence to date concerning the safety of vitamin E in this particular group of patients.

### June 2018:

An academic trial investigating efficacy of oral vitamin E alone and in combination with pioglitazone in T2D patients with MASH was presented at ADA 2018. In contrast to findings from the meta-analysis performed on data from [PIVENS](#), [TONIC](#), and [FLINT](#), no effect of vitamin E alone was found on the primary composite endpoint (2-point improvement in NAS from two different components without worsening of fibrosis), however, a significant effect on steatosis and MASH resolution was found with vitamin E alone. The combination of vitamin E and pioglitazone on NAS improvement without worsening in fibrosis as well as MASH resolution in T2D patients was better than placebo, but no different from the effect of pioglitazone alone patients, suggesting vitamin E is not effective in treatment of MASH in T2D patients.

### March 2021:

An academic Phase II trial, [VEDS](#), aiming to determine the minimum effective dose of vitamin E on change in ALT in 200 MASLD patients was initiated in August 2022. The study will evaluate daily doses of 200, 400, or 800IU QDAM vs. placebo and is expected to complete in 2H 2025.

# Unmet Needs

MASLD/MASH is largely an asymptomatic disease in the early stages which makes identifying patients at-risk for advanced disease challenging. While liver biopsy is the gold standard for evaluating histology it is rarely used outside the setting of clinical trials and identification and approval of biomarkers for diagnosing at-risk patients, monitoring disease progression, prediction of outcomes, as well as evaluating efficacy of therapy is imminent.

This section highlights the following unmet needs:

- Better biomarkers for early detection/staging, prognosis, and evaluation of therapy
- Regulatory and Clinical Practice Guidance regarding non-invasive biomarkers

# Less Invasive Diagnostics and Disease Progression - LITMUS and NIMBLE

## Less Invasive Diagnostic Tests

Less expensive, non-invasive tests/biomarkers that can be used to diagnose and stage MASH and fibrosis and monitor disease progression/improvement are major unmet needs (see following pages). In 2017, the €34 million EU research project [LITMUS](#) (Liver Investigation: Testing Marker Utility in Steatohepatitis) was initiated, funded by the European Innovative Medicines Initiative and coordinated by Newcastle University. LITMUS unites 54 international partners from academia and industry with an ultimate goal to establish and advance toward regulatory qualification of biomarkers that alone or in combination enable diagnosis, risk stratification, and monitoring of disease progression/regression of MASLD, MASH, and cirrhosis.

The overarching aim of LITMUS is to develop, robustly validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor MASLD/MASH progression and fibrosis stage. "Letters of Intent" for a composite biomarker consisting of PRO-C3 and FAST score, and cT1 and ELF test have been submitted to the FDA and EMA, and in fall 2023 an initial Qualification Package including PRO-C3, ADAPT, and FAST for "Diagnostic enrichment" was submitted to the US FDA in collaboration with NIMBLE.

- Protocols and processes for the European NAFLD Registry have been published, and training datasets and atlases of histological images have been made available.
- Patient reported outcomes measure [NASH-CHECK](#) has been developed, qualitatively validated, published, and is now used in a number of clinical trials.

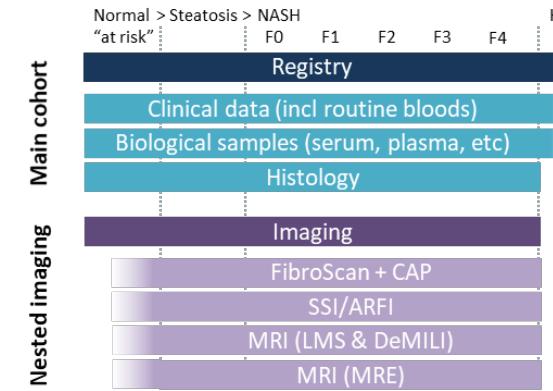
## Basic Understanding of MASLD/MASH Disease Progression

There is **great need for a clearer understanding of the natural course of MASLD and MASH**, which would help identify which patients should be aggressively treated. Unfortunately, this area of research is still hindered by the lack of reliable non-invasive tests and biomarkers for MASLD/MASH, and the limitations of current animal models which do not represent the entire disease spectrum of MASLD.

KOLs involved in The Liver Forum ([Disease Definitions Working Group](#)) are performing an evidence-based review of definitions of MASLD/MASH stages, to provide benchmarks for both disease pathophysiology studies and diagnostics development.

[The European NAFLD registry](#) is recruiting MASLD patients at >40 European centers, aiming to include 10,000 patients by 2030.

- Academic registry at the center of LITMUS recruiting patients in 14 countries.
  - containing 13,483 records across 8,984 individual patients (as of October 2021)
  - the LITMUS study cohort comprises 21% (>2,289) baseline events
- Cross sectional and longitudinal data collection
  - rich clinical data set
  - activity, diet, PROs
  - centrally read histopathology
  - long-term disease outcomes



[NIMBLE](#) (non-invasive biomarkers of metabolic liver disease) is the US counterpart to LITMUS, a public-private initiative under Foundation-NIH (FNIH) consisting of 31 partners with the goal to standardize and validate a set of non-invasive biomarkers for the diagnosis and staging of MASH, assess biomarkers for the ability to identify "at risk" patients, and standardize and advance a set of NITs to assess response to therapeutic intervention in MASH patients.

# Less Invasive Diagnostics and Disease Progression - NAIL-NIT

## NAIL-NIT Consortium

During the 2022 NASH-TAG conference, two sessions addressing the use of non-invasive tests as trial endpoints for non-cirrhotic and cirrhotic MASH included a discussion with participation of MASH KOLs, leaders in pharma, artificial intelligence experts, and Steven Berman and Joseph Turner from the US FDA, where representatives from the FDA again showed optimism and willingness to further the use of NITs as approvable endpoints. Inspired by the discussions, the NAIL-NIT (**N**ASH **A**ssessment for the **I**nvasive **T**esting in **M**onitoring **I**nterventions and **T**reatment **R**esponse and **M**ajor **L**iver **R**elated **O**utcomes) Consortium was founded with the intent to link non-invasive testing and specific tests directly to outcomes - further details on NAIL-NIT were presented at [Liver Forum 12 2022](#). NAIL-NIT will function in parallel as a complement to existing consortia [LITMUS](#), [NIMBLE](#), GOLDMINE, and [TARGET-NASH](#), and build on findings from these consortia regarding reproducibility of specific NITs, to focus on diagnosing patients with “at-risk” MASH, measuring therapeutic efficacy of a drug, and predicting long-term liver and CV outcomes.

**NAIL-NIT Consortium Objective:** To close the current gaps in the NIT field especially in the longitudinal assessment for response to treatment as well as correlation with Major Liver Related Outcomes (MALO). This will lead to the replacement of liver biopsy in late-stage clinical trials and clinical practice guidance.

NAIL-NIT's activities will include a **retrospective** analysis of 1,000s more cases to mine existing data in parallel with a six-year **prospective** real-world study of 1,000-1,300 patients that will be followed to a major adverse liver outcome (MALO), to establish the best ways to make use of the growing number of non-invasive testing methods in diagnosis, monitoring, and treatment of MASH patients.

The NAIL-NIT Consortium spearheaded by Dr. Stephen A. Harrison and Dr. Mazen Noureddin will join academic as well as industry leaders to gather data to present to the FDA for evaluation with the goal to replace liver biopsy within a 4-6 year-timeframe.

Retrospective analysis	Prospective study
<p><b>Value contribution for industry</b></p> <ul style="list-style-type: none"> <li>Decrease of screen failure rates</li> <li>Decrease screening costs</li> <li>Decrease study timelines</li> <li>Identification of NIT to enhance enrollment and monitor MALOs for future trial designs</li> <li>Identification of NITs to enrich study population for clinical trials</li> </ul>	<p><b>Value contribution for industry</b></p> <ul style="list-style-type: none"> <li>Identification of NIT/combination of NITs which correlate to MALOs</li> <li>Identification of NITs to replace liver biopsy for Phase IIb/III trials which lead to:           <ul style="list-style-type: none"> <li>shorter trial durations</li> <li>less screening failure</li> <li>major cost saving</li> </ul> </li> </ul>

At EASL and AASLD 2023, multiple talks/posters **based on screening data** (lab values, FibroScan, MRI-PDFF, MRI cT1, and liver biopsy) from eight therapeutic non-cirrhotic US MASH trials including 6,558 patients with treatment durations ranging 12-52 weeks were presented. Key findings include:

- Using the AGA pathway in an enriched clinical trial setting may lead to missing patients with biopsy-proven at-risk MASH.
- Two-thirds of patients considered high-risk as per AGA have at-risk MASH and may benefit from entering a clinical trial and future pharmacological treatment.
- FAST and Agile 3+ are better screening tests for MASH F2-F3 and MASH F3 than LSM alone. These tests are recommended as screening criteria in Phase IIb/III MASH trials to decrease screen failure rate in biopsy-proven trials.
- High screen failure rates in MASH clinical trials pose a high burden for patients, study centers, and sponsors. Simple biomarkers were different between patients' screen failing on liver biopsy. AST <20U/L suggested an absence of at-risk MASH and could help avoid unnecessary biopsies.
- In T2D patients, A1c levels as a surrogate of glycemic control appeared to be an independent risk factor for biopsy-proven MASH and at-risk MASH. Additionally, regardless of T2D status A1c was an independent predictor of hepatocyte ballooning.
- Hispanic ethnicity has been associated with higher risk of MASH with advanced fibrosis, but in this cohort, Hispanics had less advanced fibrosis vs. non-Hispanics. Further studies including genotyping are needed to further evaluate importance of minority groups.
- Agile 4 showed better performance than FIB-4 and VCTE to exclude F4 patients from MASH F2-F3 clinical trials.

## Challenges of Histopathological Assessment - Artificial Intelligence/Machine Learning (AI/ML)

### Challenges of Histopathological Assessment - Artificial Intelligence/Machine Learning (AI/ML)

While **liver biopsy has been the gold standard** for staging and diagnosing MASH, and current surrogate endpoints for conditional subpart H approval of drugs for the treatment of MASH with the FDA and EMA are based on histology, liver biopsy has many limitations. In addition to being invasive which can be associated with risks, using liver biopsy for diagnosis of MASH is neither practical nor cost-effective given the prevalence of the disease. In clinical trials, use of liver biopsy is challenging given the low kappa (inter-observer variation) of liver histology features which necessitates long trial durations and large sample sizes. The FDA recently proposed using two pathologists trained in evaluating liver biopsies together with a third pathologist for discordant readings to ensure histological endpoints are reliable and consistent.

Utilizing artificial intelligence and machine learning to evaluate liver biopsies can eliminate some variability and standardize biopsy read; furthermore, with the vast number of ongoing late-stage trials and consequently biopsies to read, alongside a limited number of expert pathologists, utilizing artificial intelligence can allow for more expedient evaluation.

- **Automated analysis** of histopathology using **Path AI** may assist with both enrollment and evaluation of treatment response allowing for reproducible, quantitative assessment of MASH histology (removing intra-observer variability and temporal variability, overcoming the placebo effect).
- Using **HistoIndex' Second Harmonic Generation (SHG)**, a pilot system evaluating slides without staining on a continuous scale may allow for detection of more subtle short-term changes.

AI has applications beyond eliminating variability of histopathological analysis including identification of subpopulations, diagnosis, guidance of therapies, response monitoring, complex gene-environmental interactions, and population health.

# Regulatory and Clinical Practice Guidance for NITs

## FDA Guidance on Use of Non-Invasive Tests

The FDA's thinking on use of non-invasive markers in MASH trials was discussed at a [webinar](#) on January 29, 2021:

- While **non-invasive biomarkers** (NITs) are under study for consideration as surrogate markers, **none have to date demonstrated reliability and consistency to be reasonable likely to predict clinical benefit**; to qualify as surrogate efficacy endpoints for accelerated approval while post-marketing trials confirm clinical benefit based on how a patient feels, functions, or survives.
- sponsors are encouraged to use NITs to demonstrate proof-of-concept in early Phase II studies and as secondary/exploratory endpoints in late-stage trials.

The topic was discussed further at a [webinar](#) on September 18-19, 2023, and while the FDA is well aware of the limitations of the current regulatory pathway utilizing histology as a surrogate endpoint but are quite hesitant to provide an alternative pathway that will have different limitations.

## EASL Clinical Practice Guidelines on NITs - 2021 update

At ILC 2021, **EASL** announced updated **Clinical Practice Guidance on the use of non-invasive tests** (NITs) for the evaluation of liver disease severity and prognosis focusing on topics with relevant evidence published since the last edition in [2016](#); guidelines were simultaneously published in [Journal of Hepatology](#).

- These guidelines are directed at consultant hepatologists, specialists in training, and general practitioners and refer specifically to adult patients.
- The guidelines are aimed at providing guidance on the best available evidence on the use of NITs to assess chronic liver disease.

Critical considerations when using NITs include availability, cost, and context of use. An overview of advantages and disadvantages with several NITs used to diagnose and stage liver fibrosis was included in the Clinical Practice Guideline update. Main topics addressed in the MASLD/MASH space based on new available data in this update included:

- Assessment of liver disease severity and prognosis in patients with MASLD/MASH.
- Monitoring liver lesions under treatment, as MASLD is massively increasing worldwide and novel therapies for MASH are being tested and will require the identification of the right patients.

A French study presented at ILC 2022 (Oral OS099) evaluating the diagnostic accuracy of an algorithm for the diagnosis of advanced liver fibrosis included in the updated 2021 EASL guidelines validated the sequential testing approach with need for liver biopsy in only 6.8 - 14.4% of patients.

Diagnosis of steatosis	Evaluation of MASLD severity	Prediction of liver-related outcomes	Patient selection/evaluation of Tx response in trials
<ul style="list-style-type: none"> <li>Conventional ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations</li> <li>MRI-PDFF is more suited to clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>Liver biopsy remains the reference standard for the diagnosis of MASH</li> <li>NITs recommended to rule-out advanced fibrosis in clinical practice: <ul style="list-style-type: none"> <li>- LSM by TE &lt;8 kPa</li> <li>- ELF &lt;9.8 or FibroMeter &lt;0.45 or FibroTest &lt;0.48</li> <li>- FIB-4 &lt;1.3 or NFS &lt;-1.455</li> </ul> </li> <li>Referral with FIB-4 &gt;1.3: TE and/or ELF, FibroMeter, FibroTest should be used to rule out/in advanced fibrosis</li> <li>MRE is more suited to clinical trials</li> </ul>	<ul style="list-style-type: none"> <li>Serum scores APRI, FIB-4, NFS, ELF, and LSM by TE should be used to stratify the risk of liver-related outcomes in MASLD</li> <li>Repeated NITs can refine risk stratification <ul style="list-style-type: none"> <li>- despite lack of evidence on the optimal timeframe, it seems reasonable to repeat NITs every 3 years in early stage and every year in advanced stage patients</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Liver biopsy remains the reference for patient selection in phase IIb and phase III therapeutic trials</li> <li>MRI-PDFF can be used to assess steatosis evolution under treatment</li> <li>Liver biopsy remains the reference to evaluate MASH resolution and liver fibrosis improvement</li> </ul>

See CVrg's ILC 2021 Conference report for further details

# Routine and Novel Serum Biomarkers, Imaging Technologies

## Serum Biomarkers for Early Detection

There is a major unmet need for better biomarkers than liver enzymes, **alanine aminotransferase (ALT)** and **aspartate aminotransferase (AST)**, as non-invasive surrogates for MASH. Studies (*Cusi ADA 2014*) have found that  $\geq 60\%$  of non-obese T2D patients and  $\sim 80\%$  of obese T2D patients with normal AST/ALT levels have fatty liver as measured by magnetic resonance spectroscopy (MRS). Although MASLD/MASH patients can have normal liver enzyme levels, an **ALT reduction of  $\geq 17 \text{ U/L}$**  has shown to be correlated with **histological improvement** ( $\geq 2$ -pt improvement in NAS without worsening of fibrosis). Cytokeratin-18 (CK-18), both total protein and caspase cleaved form, may provide clues to hepatocyte cell death, but since CK-18 is also elevated in other liver conditions. An analysis of patients in the [PIVENS trial](#) found that CK-18 is no more predictive of MASH than AST/ALT.

A range of combination scores/algorithms utilizing routine lab biomarkers and clinical measures (e.g., BMI, waist circumference, and T2D status) have had greater success in more accurately diagnosing MASH. In addition to routine lab biomarkers, serological markers of inflammation, collagen turnover, and fibrosis are being explored as single markers, in combination, and in algorithms combined with clinical measures (see slide 34 for overview of biomarkers and combination scores).

- Most commonly used scores include the **NAFLD Fibrosis Score (NFS)** incorporating age, BMI, hyperglycemia, platelet count, albumin, and AST/ ALT, and the **Fibrosis-4 (FIB-4)** index incorporating age, ALT, AST, and platelets.
- The **Enhanced Liver Fibrosis (ELF)** panel incorporating hyaluronic acid, TIMP-1, PIIINP is used to predict advanced fibrosis.

Clinical tests which have been shown to be nonspecific include: HOMA-IR, oxidized LDL, and inflammatory agents TNF $\alpha$ , IL-6, IL-8, CRP, ferritin, adiponectin (*Cusi ADA 2014*).

## Imaging Modalities for Steatosis

While **conventional ultrasound** is routinely used and can confirm the presence of  $>20\%$  fat in the liver, its low sensitivity results in low predictive value; even in the 10-15% fat range, sensitivity only reaches 60-70%. **Controlled attenuation parameter (CAP)** assessed by **vibration-controlled transient elastography (VCTE)** (FibroScan) is a rapid point-of-care assessment with good sensitivity and specificity for diagnosing MASLD; specific limitations of CAP include identifying the optimal cut point ([288dB/m](#)), and the impact of probe selection (M or XL). **MRS** is the gold standard for fat quantification but is expensive, not available on routine scanners, and requires expertise. **MRI proton density fat fraction (PDFF)** corrects for imaging confounders that can affect assessment of liver fat and is widely available in commercial MRI systems. MRI-PDFF allows for assessing multiple regions of interest that can be followed longitudinally to evaluate changes, overcoming potential issues of heterogeneity of liver fat deposition. **MRI-PDFF improvement by  $\geq 30\%$**  has been associated with improved liver histology.

## Imaging Modalities for Fibrosis

A more accurate diagnostic tool for determining the extent of fibrosis in MASH patients is needed to aid in early diagnosis. Fibrosis has no direct molecular signature, so imaging is used to assess fibrosis indirectly. **VCTE** by FibroScan is the most widely used technique, however, it has a high failure rate (30%), especially when patients have obesity or have advanced fibrosis or acute inflammation. While recent studies show MRE outperforms VCTE with a lower failure rate (1-2%), high diagnostic accuracy for earlier stages of fibrosis, and better predict which patients will progress to hepatic decompensation, access to MRE is a limiting factor in clinical practice. Diagnostic scores combining VCTE or MRE with serum markers (FAST, MAST, and MEFIB - see following page) have shown good diagnostic accuracy identifying patients with “at-risk” MASH.

**Sources:** Ajmera V et al. [Imaging biomarkers of NAFLD, NASH, and fibrosis](#) Mol Metab 2021; Loomba R et al. MRI-PDFF to predict treatment response on NASH liver biopsy: A secondary analysis of the resmetirom randomized placebo-controlled Phase II clinical trial, OR AS077, ILC 2020

## Overview of Non-invasive Tests for Diagnosis and/or Monitoring of MASH

Fibrosis is the most important predictor of long-term outcomes but has no molecular signature detectable by current imaging techniques, and liver stiffness is currently the leading biomarker for non-invasive assessment of fibrosis.

- Non-invasive serum tests of fibrosis generally have good negative predictive values for ruling out MASH with significant fibrosis.
- Elastography methods can confirm advanced fibrosis.
- Sequential use of non-invasive tests minimizes the proportion of patients falling in the indeterminate range.

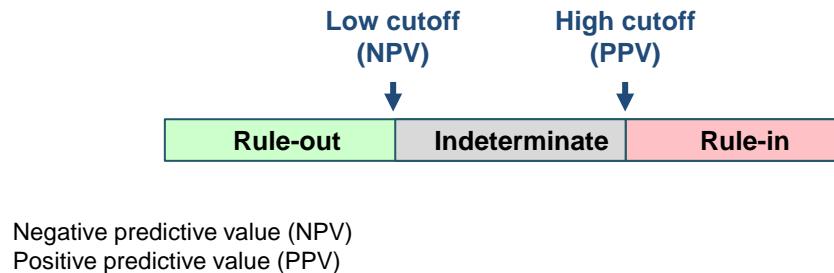
The table below lists tests used for assessing presence of MASLD, MASH, and/or fibrosis. Most commonly used tests are highlighted in blue.

Serological tests (Clinical/Lab)	Serological tests (Biomarkers)	Imaging	Serological + Imaging (Algorithm)
AST/ALT ratio	ALT, AST	ADAPT/PRO-C3 age, T2D, PRO-C3, platelets	Ultrasound liver fat
AST/platelet ratio (APRI)	AST, platelets	α2-macroglobulin (α2-M) α2-macroglobulin (α2-M)	CT scan liver fat
BARD score	ALT, AST, BMI, ±T2D	hyaluronic acid (HA) hyaluronic acid (HA)	Magnetic Resonance Imaging (MRI-PDFF) liver fat
CK18	CK18	Enhanced Liver Fibrosis (ELF) [Siemens] HA, PIIINP, TIMP-1	LiverMultiscan [ <a href="#">Perspectum Diagnostics</a> ] liver fat liver stiffness inflammation
Fatty Liver Index (FLI)	BMI, waist circumference, GGT, TG	FIB-C3 age, BMI, T2D, platelets, Pro-C3	Magnetic Resonance Spectroscopy (MRS) liver fat
<b>FIB-4 Index</b>	age, ALT, AST, platelets	FIBROspect [ <a href="#">Prometheus</a> ] α2-M, HA, TIMP-1	<b>Vibration-controlled transient elastography (VCTE) - FibroScan [Echosens]</b> liver stiffness
FIB-8	BMI, FIB-4, albumin/globulin, GGT, ± T2D	FibroTest/ <a href="#">FibroSure</a> α2-MA, haptoglobin, APOA1, GGT, bilirubin, ALT	Acoustic Radiation Force Impulse (ARFI) liver stiffness
FibroMeter	Age, weight, platelets, AST, ALT, ferritin, FPG	General Liver Fibrosis score (GLFS) BMI, age, PIIINP, platelets, ALT, AST, ±T2D, statin use	Magnetic Resonance Elastography (MRE) liver stiffness
MACK-3	HOMA-IR, AST, CK18	Hepascore bilirubin, GGT, α2-MA, HA	
<b>NAFLD Fibrosis Score (NFS)</b>	age, BMI, ±T2D/pre-diabetes, ALT, AST, platelets, albumin	HepQuant cholate clearance test	
TUFTS NASH score	AST, ALT, INR, platelets	Metabolomics-Advanced Steatohepatitis Fibrosis Score (MASEF) [ <a href="#">OWL</a> ] BMI, AST, ALT, serum lipids	<ul style="list-style-type: none"> <li>Ultrasound and CT: inexpensive and accessible; cannot distinguish fibrosis/steatosis.</li> <li>MRS, MRE, LiverMultiscan: requires radiology referral, most accurate imaging tool for liver stiffness.</li> <li>VCTE: limited by obesity and operator experience - most widely used</li> </ul>
		NIS2+ [ <a href="#">Genfit</a> ] miR-34a, YKL-40	
		NIS4 [ <a href="#">Genfit</a> ] miR-34a, α2M, YKL-40, A1c	
		N-terminal type III collagen propeptide (PRO-C3) PRO-C3, PRO-C3x	
			<i>List of NITs is not exhaustive</i>

## Single vs. Sequential NITs - Minimizing the Indeterminate Range

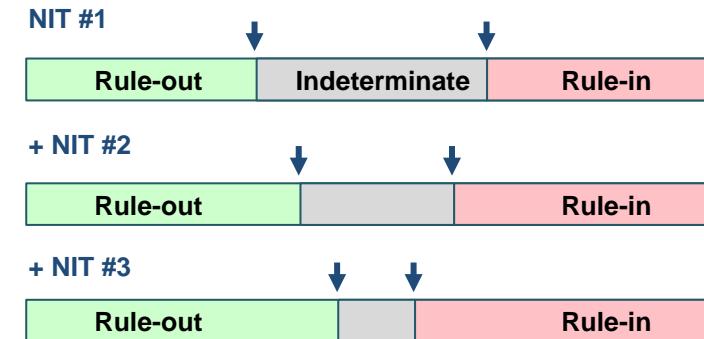
### Single NIT:

When evaluating each individual NIT, a low - and a high cutoff is identified; patients with values below the low cutoff have a low probability of advanced fibrosis, and patients with values above the high cutoff have a high probability of advanced fibrosis (see figure). See overview of single tests on the next slide.



### Use of sequential NITs:

Patients with test values between the low- and high cutoff fall in the “indeterminate” category where advanced fibrosis can not be ruled in or out. Sequential use of different NITs reduces the number of patients with an indeterminate result enabling classification of a larger proportion of patients (see figure below).



Various combinations of NITs in sequence are being explored; see below examples of sequential algorithms to detect advanced fibrosis:

#### Oral 56 (AASLD 2020) J. Boursier:

- Study of baseline data from Phase III [REGENERATE](#) (N=4,133) investigating performance of single NITs, two simultaneous NITs, and sequential NITs

*Single NITs:* APRI, ELF, FIB-4, NFS, and TE

*Simultaneous NITs:* NFS + ELF, FIB-4 + ELF, NFS + TE, FIB-4 + TE

*Sequential NITs:* NFS→ELF, FIB-4→ELF, NFS→TE, and FIB-4→TE

- single tests led to up to 60% indeterminate results

- simultaneous tests led to up to 93% indeterminate results

- sequential tests led to up to 13% indeterminate results

#### P-1713 (AASLD 2019) S. Harrison:

- Study of baseline data from Phase III [STELLAR 3](#) and [4](#) (N=3,202) investigating performance of single and sequential NITs

*Single NITs:* NFS, FIB-4, ELF, and FibroScan

*Sequential NITs:* FIB-4→ELF and FIB-4→FibroScan

- single tests led to up to 50% indeterminate results

- sequential tests led to up to 24% indeterminate results

# Epidemiology

Estimates of the [worldwide prevalence](#) of MASLD range from 17% to 51% depending on methodology, with an estimated mean of 24%. Approximately [20%](#) of patients with MASLD develop MASH amounting to an estimated prevalence of MASH in the general population of 1.5-6.5%; approximately 20% of MASH patients have advanced fibrosis (F3-F4) of which approximately 1/3 have compensated cirrhosis.

Unlike obesity and T2D where diagnosis is based on easy to obtain clinical measures (BMI and A1c respectively), methods for diagnosing MASLD/MASH include multiple non-invasive and invasive measures (see previous sections for details).

This section includes an overview of projected prevalence rates of MASLD, MASH, distribution of fibrosis stages, and MASLD-related mortality in the US, EU5 (France, Germany, Italy, Spain, and UK), China, and Japan based on a recent Markov Model (based on NHANES III data and meta-analyses).

According to the model:

- **424 million** people in the US, EU5, China, and Japan had **MASLD** in 2016; if trends continue, **522 million** people in the US, EU5, China, and Japan will have MASLD by 2030.
  - prevalence rates of MASLD in the general population are projected to increase from 19.7 to 23.6%.
- **66.3 million** people in the US, EU5, China, and Japan had **MASH** in 2016; if trends continue, **97.9 million** people in the US, EU5, China, and Japan will have MASH by 2030.
  - prevalence rates of MASH in the general population are projected to increase from 3.1 to 4.4%.
- For the eight countries, **F3-F4 rates are projected to increase from 10.7 million** in 2016 to **22.0 million** in 2030.

## Global Prevalence - MASLD

The prevalence of MASLD varies widely depending on the population studied and the definition used - estimates of the [worldwide prevalence](#) of MASLD range from 17% to 51%, with an estimated mean of 24% in the general population. The prevalence of MASH in MASLD patients highly depends on the comorbidity burden.

**The prevalence of MASLD is higher in patients with obesity, T2D, and/or dyslipidemia** - with obesity and T2D rates increasing, the prevalence of MASLD is also expected to increase.

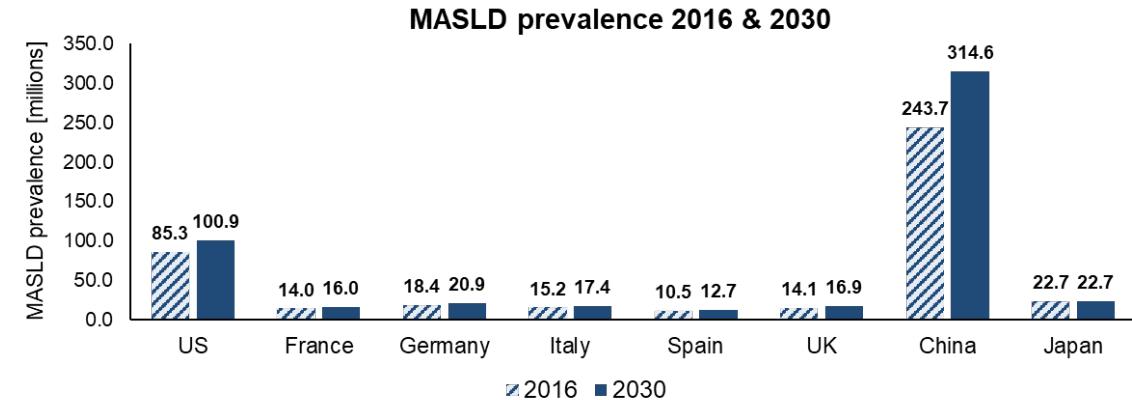
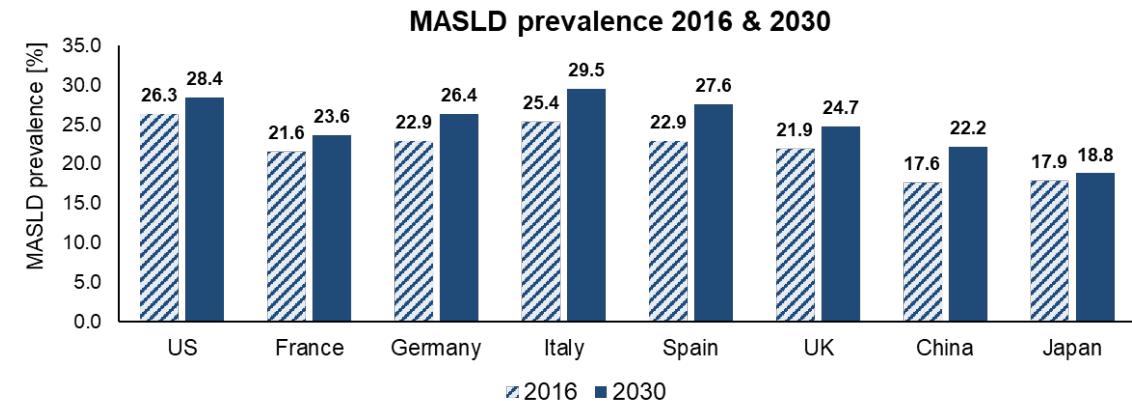
- In the US, [75-95%](#) of patients with MASLD have obesity, [25-55%](#) have T2D, and [~50%](#) have hypertriglyceridemia.
- In Europe, [up to 68%](#) of T2D patients have MASLD, and 78% of patients with obesity have MASLD

**Age, gender, and ethnicity are also associated with increased risk of MASLD.** In patients with MASLD, prevalence is significantly higher in **older** individuals, **males**, and **Hispanics**.

- When applying US Fatty Liver Index (USFLI) to [NHANES 2011-2014](#), overall MASLD prevalence was 31.3% with the lowest prevalence in non-Hispanic Blacks (18.3%) and Asians (19.6%), while the highest prevalence was seen in Mexican Americans (46.1%).

A [Markov model](#) based on the current prevalence of obesity and T2D in adults was developed to forecast future disease burden. According to the model:

- MASLD prevalence rates are projected to increase** in all geographical regions included in the model ranging from 17.6 – 26.3% in 2016 to 18.8 – 29.5% in 2030 (see upper figure).
- China is projected to have the highest number of cases followed by the US (see lower figure).

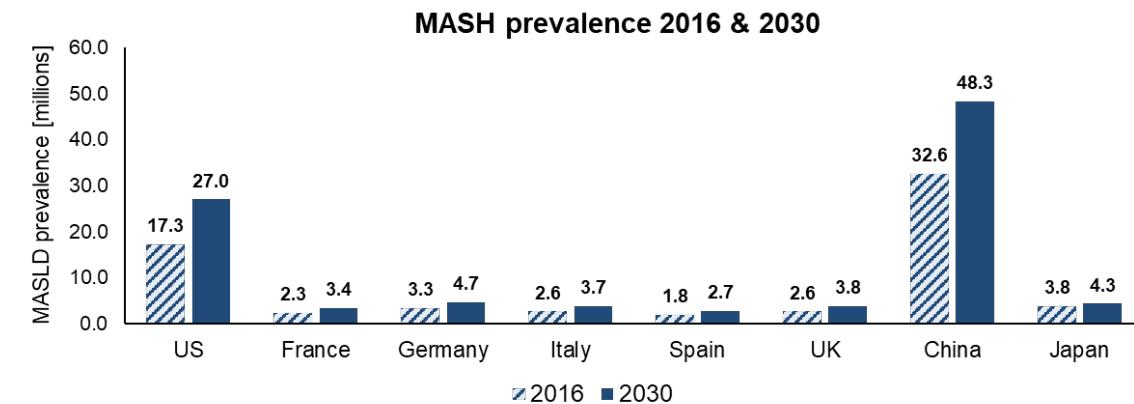
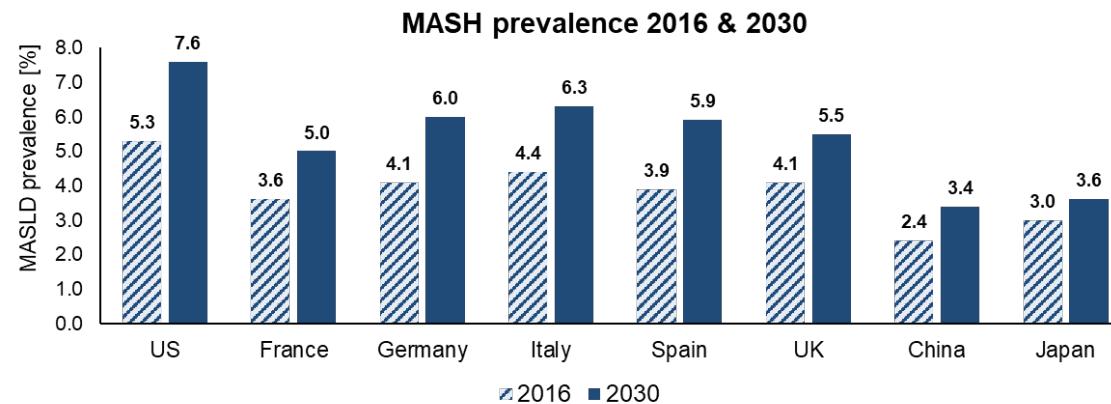


Source: [Estes et al., J Hepatology 2018](#)

## Global Prevalence - MASH

In the model it was assumed that approximately [20%](#) of patients with MASLD would be classified as MASH equating to an estimated prevalence of MASH in the general population of 1.5-6.5%. According to the model (see figures):

- **MASH prevalence rates are projected to increase** in all geographical regions included in the model ranging from 2.4 – 5.3% in 2016 to 3.4 – 7.6% in 2030.
- China is projected to have the lowest prevalence rate, but due to a population size of ~1.4 billion the highest number of cases, followed by the US.  
- US is projected to have the greatest (56%) estimated increase in cases by 2030.



Source: [Estes et al., J Hepatology 2018](#)

## MASH by fibrosis stage

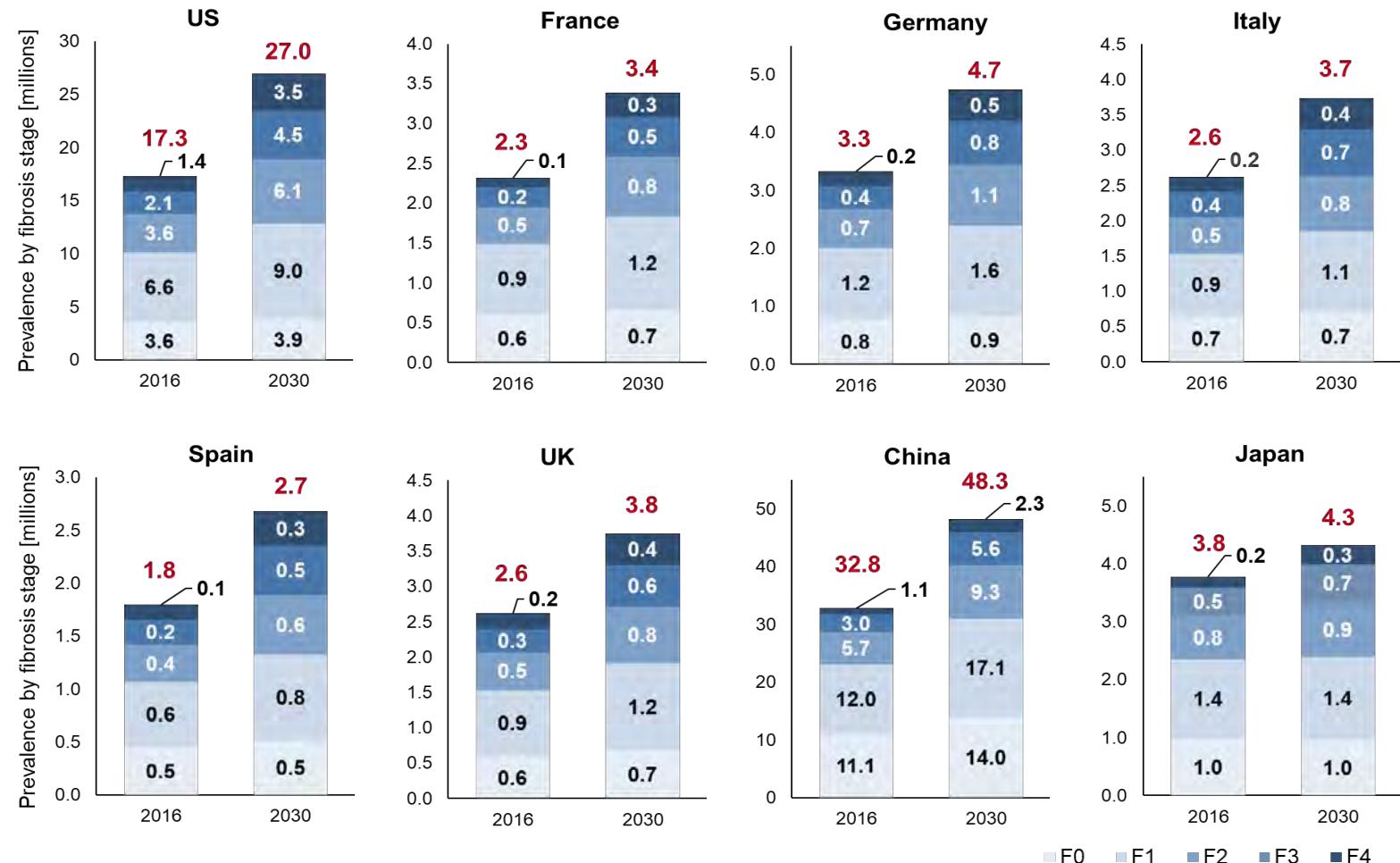
For all countries included in the [Markov model](#), increases in the number of MASH cases with advanced fibrosis from 2016 to 2030 were greater than increases in earlier fibrosis stages (see figures).

For the eight countries, F3-F4 rates are projected to increase from 10.7 million in 2016 to 22 million in 2030.

- F0-F3 rates are expected to increase from 55.9 in 2016 to 75.8 million in 2030.

Up to [7.3-11.5%](#) of adults with MASH develop cirrhosis, which can lead to liver failure, which requires transplantation.

- The number of **F4 (compensated cirrhosis)** cases are projected to increase in all included countries with the smallest increase projected for Japan (+64%) and the greatest increase projected for France (+156%).
- Incidence of decompensated cirrhosis and prevalence of HCC related to MASLD are expected to increase in all countries included in the model.



Source: [Estes et al., J Hepatology 2018](#)

## MASH-related mortality

MASLD patients have increased overall mortality compared to patients without MASLD, with the most common cause of death being cardiovascular disease. MASH patients with advanced fibrosis have an increased rate of liver-related mortality.

- Annual MASLD-related mortality is projected to increase from 2016 to 2030 in all countries included ranging from +73% (Japan) to +182% (France) (see table).

Region	Annual MASH-related mortality in 2016 and 2030 (age $\geq 15$ years)																	
	US		France		Germany		Italy		Spain		UK		China		Japan			
	2016	2030	2016	2030	2016	2030	2016	2030	2016	2030	2016	2030	2016	2030	2016	2030	2016	2030
MASH-related mortality (N)	30,240	78,310	2,490	7,030	5,180	12,510	4,870	10,490	3,260	7,590	4,870	10,390	25,280	55,740	4,720	8,130		
Increase in MASH-related mortality (%)	159		182		142		115		133		113		120		73			

Source: [Estes et al., J Hepatology 2018](#)

## MASLD in children

The rising rate of obesity among children has been accompanied by an increase in MASLD - MASLD is the most common cause of chronic liver disease among children with obesity.

An [autopsy study](#) that reviewed the records and liver histological features of 742 children aged 2 to 19 years who died from unnatural causes in San Diego County between 1993 and 2003 showed that the prevalence of MASLD was 9.6% for this age range.

A [European study](#) in 16,390 children and adolescents with overweight/obesity showed that the prevalence of MASLD was 11% with a higher prevalence in boys vs. girls (14.4 vs. 7.4%; P<0.001).

The higher rate in boys vs. girls was also found in a more [recent](#) study that evaluated 408 children aged 9-17 years old and found MASLD prevalence to be 26.0%; 29.4% in males vs. 22.6% in females. The article concludes "*In children with obesity, MASLD is present in nearly one-third of boys and one-fourth of girls*".

An [analysis](#) of adolescents aged 12-18 years included in NHANES 2017-2018 found 24.2% had any degree of steatosis (CAP  $\geq 248\text{dBm}$ ), 11.6% had S3 steatosis (CAP  $\geq 280\text{dBm}$ ), and 4.4% had significant fibrosis (liver stiffness  $\geq 7.4\text{kPa}$ ). Multivariate analysis showed that BMI (OR 1.2 [CI95% 1.2-1.4] per unit increase), sex (OR 0.5 [CI95% 0.4-0.7] for female vs. male), ethnicity (OR 4.5 [CI95% 1.7-11.8] for Hispanic vs. non-Hispanic white), and hypertension (OR 3.5 [CI95% 1.3-4.5]) were associated with S3 steatosis; BMI (OR 1.1 [CI95% 1.0-1.2] per unit increase) and ethnicity (OR 3.9 [CI95% 1.2-13.2] for non-Hispanic black vs. non-Hispanic white) were associated with significant fibrosis. One of three adolescents with significant fibrosis were normal weight and 78% had normal ALT levels.

Weight loss is the only consistently effective therapy for MASLD in children since pharmacologic intervention is more restricted than in adults with MASLD; Vitamin E has been shown to effectively improve histology in children with MASH. The growing prevalence of MASLD in children is a [concern](#).

AASLD [Practice Guidance](#) issued in 2018 emphasizes:

- **Intensive lifestyle modifications** in children with MASLD should be first in line treatment.
- Metformin (500mg BID) offers no benefit to children with MASLD and should not be prescribed to specifically treat MASLD or MASH.
- **Vitamin E** (800mg IU/day) improves histological benefits to some pediatric MASH patients. Long-term safety is unknown, and risks/benefits should be discussed with each patient.

# Marketed Products

On March 14<sup>th</sup>, 2024, Madrigal's resmetirom (marketed Rezdiffra) was the first drug to be approved for the treatment of non-cirrhotic MASH with moderate to advanced liver fibrosis (F2-F3). Guidance from medical societies on how to implement resmetirom in care for MASH patients, how to monitor treatment response, and when to stop treatment is expected in the coming months.

This section includes:

- A profile of resmetirom (Rezdiffra; Madrigal)
- A summary of regulatory Phase III trials/ongoing trials that may lead to a future extension/label change

## resmetirom (Rezdiffra) - Madrigal

Approved	Companies	MOA	ROA/Dosing	Scenarios of Use	Patent Expiry
US 2024	Roche (Originator), Madrigal (Owner)	THR $\beta$ agonist oral (QD)	oral (QD) 60, 80, or 100mg	adult MASH F2-F3	2033

### Labels/Warnings

In conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). This indication is approved under accelerated approval based on improvement of MASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Hepatotoxicity: Monitor patients during treatment with Rezdiffra for elevations in liver tests and for the development of liver-related adverse reactions. Discontinue Rezdiffra and continue to monitor the patient if hepatotoxicity is suspected.

Gallbladder-Related Adverse Reactions: Cholelithiasis and cholecystitis were observed more often in Rezdiffra-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event such as acute cholecystitis is suspected, interrupt Rezdiffra treatment until the event is resolved

[US Label](#)

### CVrg Synopsis

Data from MAESTRO-NASH released in December 2022 showed significant improvements in both primary histology endpoints, making resmetirom the first drug to show benefit on both MASH and fibrosis in a Phase III trial. Additionally, resmetirom showed improvement in atherogenic lipids, and was generally safe and well-tolerated. In July 2023, Madrigal completed a rolling submission of an NDA to the US FDA seeking accelerated approval of resmetirom for MASH with fibrosis and on March 14, 2024, resmetirom became the first drug to achieve accelerated approval for the treatment of MASH F2-F3 in conjunction with diet and exercise from the US FDA.

The EMA accepted an MAA for resmetirom in MASH F2-F3 in March 2024 making it the first drug to seek regulatory approval for this indication in the EU.

### Key News/Milestones

- **March 2024:** Rezdiffra approved for treatment of non-cirrhotic MASH F2-F3 in the US
- **March 2024:** The EMA accepts MAA for MASH with fibrosis
- **Sep. 2023:** Resmetirom (Madrigal), the US FDA accepts NDA and assigns PDUFA date of March 14, 2023
- **June 2023:** Madrigal initiates rolling NDA submission to the US FDA for MASH fibrosis
- **Dec. 2022:** Impressive topline data from Phase III MAESTRO-NASH show both histology endpoints met
- **May 2022:** Madrigal plans Phase III trial MAESTRO-NASH Outcomes in MASH with compensated cirrhosis
- **March 2019:** Madrigal initiates Global Phase III trial of resmetirom in MASH fibrosis
- **Sep. 2016:** Madrigal initiates Phase II of THR- $\beta$  agonist MGL-3196
- **Sep. 2011:** Madrigal acquires assets of VIA including MGL-3196

### 2024 Sentinels

- **March 2024:** Rezdiffra (resmetirom, Madrigal) approved for treatment of non-cirrhotic MASH F2-F3 in the US
- **March 2024:** Resmetirom (Madrigal), the EMA accepts MAA for MASH with fibrosis
- **March 2024:** Resmetirom, Madrigal delays completion of US Phase III trial MAESTRO-NASH OUTCOMES in MASH F4

## resmetirom - Clinical Trials (1 of 3)

Trial	Patients	Treatment	Endpoints
<b>MAESTRO-NASH OUTCOMES</b> Phase III - US <a href="#">NCT05500222</a> Start: Aug. 2022 1° Completion: Dec. 2026 Completion: Jan. 2027	700 MASH patients with well-compensated cirrhosis aged ≥18 years, Child-Pugh A (5 or 6) with no history of decompensation event, ≥3 metabolic risk factors, MRE ≥4.2kPa (if MRE available), ELF ≥9.8 (only if MRE unavailable or contraindicated)	resmetirom (oral 80mg QD) vs. placebo	<b>Primary Endpoint:</b> incidence of any event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, and confirmed increase of MELD from 12 to ≥15 from baseline up to 36 months
<b>MAESTRO-NAFLD-OLE</b> Phase III - US, Puerto Rico <a href="#">NCT04951219</a> Start: July 2021 1° Completion: March 2026 Completion: April 2026	1,000 MASH patients <ul style="list-style-type: none"> <li>- patients completing the 52-week visit in Phase III trial MAESTRO-NAFLD1</li> <li>- patients screen failing for biopsy-driven Phase III trial MAESTRO-NASH               <ul style="list-style-type: none"> <li>- NAS=3 (steatosis 1, ballooning 1, inflammation 1) and F1B, F2, or F3, or</li> <li>- NAS ≥4 (≥1 in each component) and F1A or F1C, PRO-C3 ≤14                   <ul style="list-style-type: none"> <li>- MASH with compensated cirrhosis, Child-Pugh A 5-6, MELD &lt;12, albumin ≥3.2, bilirubin &lt;2</li> </ul> </li> </ul> </li> <li>- patients screen failing for MAESTRO-NASH OUTCOMES and <i>de novo</i> patients with documented Child-Pugh A/B (&lt;8) NASH cirrhosis (including minimal decompensation), MELD &lt;15 (unless MELD ≥15 based on non-cirrhotic parameters)</li> </ul>	MAESTRO-NAFLD1 completers: <ul style="list-style-type: none"> <li>- double-blind resmetirom (oral 80 or 100mg for 12 weeks then 100mg for 40 weeks)</li> <li>- double-blind resmetirom (oral 100mg) for 52 weeks</li> <li>- open-label resmetirom (same dose as in MAESTRO-NAFLD1) for 52 weeks</li> </ul> MASH cirrhosis (MAESTRO-NASH screen fail): <ul style="list-style-type: none"> <li>- open-label resmetirom (oral 80mg) for 104 weeks</li> </ul> MASH non-cirrhosis (MAESTRO-NASH screen fail): <ul style="list-style-type: none"> <li>- open-label resmetirom (oral 100mg) for 52 weeks</li> </ul> MASH cirrhosis (direct enrollment in MAESTRO-NAFLD-OLE or MAESTRO-NASH-OUTCOMES screen fail): <ul style="list-style-type: none"> <li>- open-label resmetirom (oral 40mg) for 104 weeks</li> </ul>	<b>Primary Endpoint:</b> AEs up to 52 weeks

## resmetirom - Clinical Trials (2 of 3)

Trial	Patients	Treatment	Endpoints
<b>MAESTRO-NASH</b> Phase III - Global <a href="#">NCT03900429</a> Start: March 2019 1° Completion: Jan. 2028 Completion: Jan. 2028	<p>2000 MASH patients with F2-F3 fibrosis (<math>\leq 15\%</math> high risk F1 patients)</p> <p><b>Pre-screening:</b> <math>\geq 3</math> metabolic risk factors, no Hx of significant alcohol consumption, AST <math>&gt; 17</math> or 20U/L (females and males, respectively) + meet FibroScan criteria OR MASH with F1B-F3 on historic liver biopsy</p> <p><b>Inclusion:</b> biochemical test for fibrosis OR FibroScan OR MASH with F1B-F3 on historic (&lt;2 years) liver biopsy, liver fat <math>\geq 8\%</math>, eGFR <math>\geq 45</math> BL biopsy: MASH with F1B-F3 and NAS <math>\geq 4</math> (<math>\geq 1</math> for steatosis, ballooning, and lobular inflammation)</p>	resmetirom (oral 80 or 100mg QD) vs. placebo for 54 months	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- MASH resolution (<math>\geq 2</math>-pt improvement in NAS) without worsening in fibrosis at 52 weeks</li> <li>- <math>\geq 1</math> stage improvement in fibrosis without worsening in NAS at 52 weeks</li> <li>- composite clinical outcome composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events, histological progression to cirrhosis, and confirmed increase of MELD score from <math>&lt; 12</math> to <math>\geq 15</math> up to 54 months)</li> </ul> <p><u>Dec. 2022 + EASL 2023:</u></p> <ul style="list-style-type: none"> <li>- Pts without a 52-week biopsy due to early study termination or missing liver biopsy (~17% of pts across treatment arms) were included and considered as non-responders.             <ul style="list-style-type: none"> <li>- compliance to treatment was high and minimally impacted by COVID-restrictions.</li> </ul> </li> <li>- Resmetirom (both doses) met both primary histology endpoints with sign. more pts achieving MASH resolution with <math>\geq 2</math>-pt reduction in NAS and no worsening in fibrosis and <math>\geq 1</math> stage improvement in fibrosis without worsening of NAS vs. pbo.             <ul style="list-style-type: none"> <li>- histology endpoints were achieved across baseline fibrosis stages and T2D status, including similar sign. levels and magnitude of improvement in F2, F3, and F2-F3 subgroups.</li> </ul> </li> <li>- Resmetirom (both doses) showed sign. more pts achieving <math>\geq 2</math>-pt reduction in NAS and no worsening in fibrosis, <math>\geq 2</math>-pt reduction in NAS and <math>\geq 1</math>-stage improvement in fibrosis, MASH resolution (with <math>\geq 2</math>-pt reduction in NAS) and <math>\geq 1</math>-stage improvement in fibrosis, and 2-stage reduction in fibrosis without worsening of NAS.</li> <li>- Resmetirom elicited sign. improvements from BL in liver enzymes, atherogenic lipids and lipoproteins, liver fat by MRI-PDFF, CAP, and liver stiffness by FibroScan vs. pbo.</li> <li>- Resmetirom (both doses) was safe and well-tolerated.</li> <li>- Frequency of SAEs was similar between Tx arms, and the rate of study discontinuation was generally low.</li> <li>- Most common AEs were diarrhea in beginning of Tx, generally mild, transient in nature, and mild nausea.</li> </ul>

## resmetirom - Clinical Trials (3 of 3)

Trial	Patients	Treatment	Endpoints
<b>MAESTRO-NAFLD1</b> Phase III - US <a href="#">NCT04197479</a> Start: Dec. 2019 1° Completed: Jan. 2023 <b>Completed: Jan. 2023</b>	1,343 MASLD/MASH patients aged ≥18 years, liver fat ≥8%, stable dyslipidemia therapy ≥30 days prior to randomization: - FibroScan 5.5 to <8.5kPa and CAP ≥280dB/m OR - MRE >2 to 4kPa and liver fat ≥8% (MRI-PDFF) consistent with steatosis and fibrosis ≥1 stage OR - recent liver biopsy (<2 years) with NAS ≥4, steatosis ≥1, fibrosis stage 0 or 1A/1C, and PRO-C3 <14ng/mL or NAS <4, steatosis ≥1, and fibrosis ≤3 or NAS ≥4, steatosis ≥1, and fibrosis ≤3 without ballooning	resmetirom (oral 80 or 100mg QD) vs. placebo for 52 weeks; 100 patients will be enrolled in an open-label arm to receive resmetirom (oral 100mg QD) for 52 weeks	<p><b>Primary Endpoint:</b> AEs  <u>Jan. 2022 + ILC 2022 + AASLD 2022:</u>  <b>Full study cohort:</b></p> <ul style="list-style-type: none"> <li>- Resmetirom was safe and well tolerated at both dose levels.</li> <li>- AEs were generally mild to moderate in severity.</li> <li>- The frequency of SAEs was similar across treatment arms, and discontinuation rates due to AEs were low.</li> <li>- Most common reported AEs were generally mild diarrhea or increased stool frequency at the beginning of therapy, which occurred in more resmetirom treated pts compared to pbo (9 and 17%, respectively).</li> <li>- Resmetirom (both doses) sign. reduced atherogenic lipids LDL-C, ApoB, and TG vs. pbo.</li> <li>- Resmetirom (both doses) sign. reduced liver fat at 16 and 52 weeks vs. pbo. <ul style="list-style-type: none"> <li>- lipid reductions with open label resmetirom (100mg) arm were numerically greater vs. double-blind (100mg).</li> <li>- open label pts were less impacted by COVID-related dose interruption than pts in the double-blind arms.</li> </ul> </li> <li>- In pts with baseline ALT ≥30U/L, resmetirom (both doses) elicited rapid (12 wks) sign. red. in liver enzymes.</li> <li>- Most pts did not have baseline liver stiffness measures that met the criteria for analysis. <ul style="list-style-type: none"> <li>- while resmetirom (100mg) directionally showed treatment effect, changes in liver stiffness by FibroScan were not sign. different from pbo.</li> </ul> </li> <li>- A responder analysis in pts with elevated BL liver stiffness showed sign. more resmetirom-treated pts improved and fewer worsened liver stiffness by MRE and FibroScan vs. pbo.</li> </ul> <p><b>Open-label cohort - 105 + 75 pts with cirrhosis at baseline:</b></p> <ul style="list-style-type: none"> <li>- Compared to non-cirrhotic pts, cirrhotic pts had sign. higher MRE and lower liver fat.</li> <li>- 34% of cirrhotic pts had liver fat ≤5% vs. 37.8% ≥8% which was unrelated to steatosis grade on biopsy.</li> <li>- Pts with liver fat ≤5% had higher FIB-4, MELD, MRE, and lower ALT and CAP vs. patients with liver fat ≥8%.</li> <li>- Similar to non-cirrhotic pts, LV was greatly elevated in well-comp. MASH cirrhosis vs. to healthy subjects.</li> <li>- More pts improved than worsened liver stiffness by MRE and FibroScan. <ul style="list-style-type: none"> <li>- pts with more severe cirrhosis saw the greatest improvements in FibroScan.</li> </ul> </li> <li>- Pts with less severe cirrhosis and higher liver fat at baseline had greater reductions in liver fat, while reductions in liver volume were similar regardless of cirrhosis severity; 73% of pts achieved ≥15% red. in LV.</li> <li>- Changes in spleen volume (SV) were more variable compared to changes in liver fat and LV. <ul style="list-style-type: none"> <li>- among pts with ≥10% change in SV 35-37% had a decrease in SV while 5-15% had an increase.</li> </ul> </li> <li>- Strong correlation between change in LV and SV especially in pts with severe cirrhosis based on MRI-PDFF.</li> <li>- Resmetirom sign. reduced liver fat by -34%; 60% of pts achieved ≥30% reduction in relative liver fat.</li> <li>- In pts with baseline MRE ≥3.5kPa, resmetirom elicited a non-sign. MRE reduction of -0.5kPa. <ul style="list-style-type: none"> <li>- 35% of pts achieved ≥15% reduction in MRE.</li> </ul> </li> <li>- Fibrosis markers PIIINP, TIMP, and rev. T3 all reduced with resmetirom, while CK18 (M30) did not reach sign.</li> <li>- Liver enzymes GGT, ALP, and AST were sign. reduced from baseline with resmetirom.</li> <li>- At weeks 20, atherogenic lipids LDL-C, ApoB, TG, and Lp(a) were sign. reduced by resmetirom regardless of liver fat content at baseline; the magnitude of reductions were similar to that in non-cirrhotic MASH pts.</li> <li>- Resmetirom was safe and well-tolerated with an AE profile similar to pts with non-cirrhotic MASH.</li> </ul>

# Products in Development

Approximately 260 products are in active (development update within the last 3 years) clinical development for the treatment of MASLD or MASH. ~64 products are in mid-to-late stages of clinical development (Phase II+).

Several classes are being evaluated and five products are in Phase III development in the US, EU5, or Japan:

- SCD1 modulator, **aramchol** (Galmed)
- GLP-1 agonist, **semaglutide** (Novo Nordisk)
- panPPAR agonist **lanifibranor** (Inventiva)
- FGF21 analog, **efruxifermin** (Akero)
- FGF21 analog, **pegozafermin** (89bio)
- Dual GLP-1/GRA, **survotutide** (BI/Zealand)

This section includes:

- Review of late-stage clinical development in 2023 and a list of key events expected in 2024/2025.
- Timeline and Endpoints for Current Therapies in Development for MASH.
- Regulatory landscape with timepoints.
- Profiles for the products in Phase II+ along with trials for those late phase products, and trials of approved anti-diabetic drugs in the treatment of MASLD/MASH.

## 2023 Year in Review

	1Q 2023	2Q 2023	3Q 2023	4Q 2023
<b>CLINICAL TRIALS</b>	<ul style="list-style-type: none"> <li>Ph IIb <a href="#">NCT04844450</a> <b>ASC41</b> (Gannex) withdrawn</li> </ul>	<ul style="list-style-type: none"> <li>Ph IIb <a href="#">FORTUNA</a> <b>AZD2693</b> (AZ) genetic MASH F2-F3</li> <li>Ph II <a href="#">NCT05795517</a> <b>HSK31679</b> (Haisco) MASLD</li> <li>Ph IIb <a href="#">IMPACT</a> <b>pevividutide</b> (Altimmune) MASH F2-F3</li> <li>Ph IIb <a href="#">NCT05877547</a> <b>efinopegdutide</b> (Merck) MASH F2-F3</li> </ul>	<ul style="list-style-type: none"> <li>Ph II <a href="#">NCT05979779</a> <b>HU6</b> (Rivus) MASLD</li> <li>Ph II <a href="#">NCT06054815</a> <b>DA-1241</b> (DongA/NeuroBo) MASH</li> </ul>	<ul style="list-style-type: none"> <li>Ph II <a href="#">SKYLINE</a> <b>GSK4532990</b> (GSK) MASH</li> <li>Ph IIb <a href="#">MONARCH</a> <b>miricorilant</b> (Corcept) MASH F2-F3</li> <li>Ph IIb <a href="#">NCT06168383</a> <b>HSK31679</b> (Haisco) MASH F2-F3</li> <li>Ph III <a href="#">SYNCHRONY</a> Real-World <b>efruxifermin</b> (Akero) MASLD/MASH</li> </ul>
<b>DATA</b>	<ul style="list-style-type: none"> <li><b>HPG1860</b> (Hepagene) NIT data <a href="#">RISE</a></li> <li><b>VK2735</b> (Viking) WL in Phase I <a href="#">NCT05203237</a></li> <li><b>Pegozafeamin</b> (89bio) histology data <a href="#">ENLIVEN</a></li> </ul>	<ul style="list-style-type: none"> <li><b>Ervogastat/clesacostat</b> (Pfizer) NIT data <a href="#">NCT04399538</a></li> <li><b>Rencofilstat</b> (Hepion) NIT data <a href="#">ALTITUDE-NASH</a></li> <li><b>DD 01</b> (D&amp;D) NIT data <a href="#">NCT04812262</a></li> <li><b>VK2809</b> (Viking) primary endpoint met <a href="#">VOYAGE</a></li> <li><b>Aldafeamin</b> (NGM) primary endpoint met <a href="#">ALPINE 4</a></li> <li><b>Efruxifermin</b> (Akero) complementary to GLP-1 <a href="#">SYMMETRY</a></li> </ul>	<ul style="list-style-type: none"> <li><b>TERN-501/TERN-101</b> (Terns) primary endpoint met <a href="#">DUET</a></li> </ul>	<ul style="list-style-type: none"> <li><b>Efruxifermin</b> (Akero) fails to meet primary endpoint <a href="#">SYMMETRY</a></li> <li><b>Pegozafeamin</b> (89bio) 48-week NIT data <a href="#">ENLIVEN</a></li> <li><b>ASC41</b> (Gannex) NIT data <a href="#">NCT05462353</a></li> </ul>
<b>REG.</b>	<ul style="list-style-type: none"> <li><b>OCA</b> (Intercept), FDA accepts NDA and assigns PDUFA date of June 22, 2023</li> <li><b>Linafexor</b> (Cascade) Fast Track Designation from US FDA</li> <li>ICER draft evidence report favors <b>resmetirom</b> (Madrigal) over <b>OCA</b> (Intercept)</li> </ul>	<ul style="list-style-type: none"> <li><b>Resmetirom</b> (Madrigal) receives US FDA Breakthrough Therapy Designation for MASH fibrosis</li> <li><b>OCA</b> (Intercept) receives CRL from US FDA, discontinues all MASH-related investments</li> <li><b>Efinopegdutide</b> (Hanmi/Merck) Fast Track Designation from US FDA</li> <li><b>Resmetirom</b>, Madrigal rolling NDA for NASH fibrosis initiated</li> </ul>	<ul style="list-style-type: none"> <li><b>Resmetirom</b> (Madrigal), US FDA accepts NDA and assigns PDUFA date of March 14, 2023</li> <li><b>Pegozafeamin (89bio)</b> receives Breakthrough Therapy Designation for MASH</li> </ul>	<ul style="list-style-type: none"> <li><b>Pevividutide</b> (Altimmune) receives Fast Track Designation from US FDA</li> <li><b>Lanifibranor (Inventiva/Sino)</b>, receives Breakthrough Therapy Designation from NMPA</li> </ul>
<b>COMPANY NEWS</b>	<ul style="list-style-type: none"> <li><b>MK3655</b>, Merck terminates Phase IIb development due to lack of efficacy</li> <li><b>PLN-1474</b>, Novartis returns rights to Pliant</li> <li><b>ARO-PNPLA3</b>, J&amp;J returns rights to Arrowhead</li> <li><b>RES-010</b>, Resalis raises €10 million to fund development miR-22 ASO in obesity and NASH</li> <li>PathAI and GSK partner to utilize AIM-NASH in <a href="#">HORIZON</a> of <b>GSK4532990</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Cotadutide</b>, AZ discontinues development - pivoting to dual GLP-1/GRA <b>AZD9550</b> (SC QW)</li> <li><b>FIA586</b>, Novartis discontinues development for MASH</li> <li><b>Lanifibranor (Inventiva/Sino)</b> to enter clinical development in China</li> <li><b>Aligos</b> and <b>Amoytop</b> enter collaboration to develop oligonucleotide-based therapies for liver diseases in Greater China</li> </ul>	<ul style="list-style-type: none"> <li><b>JKB-122 (Biostax)</b>, FDA transfers IND for NAFLD, MASH fibrosis, and autoimmune hepatitis from TaiwanJ</li> <li><b>AMG 609</b>, Amgen discontinues development of Phase I siRNA targeting PNPLA3</li> <li><b>BMS-986263</b>, BMS discontinues development of HSP47 siRNA in MASH F4</li> <li><b>Kriya</b> acquires <b>Tramontane</b> including an AVV vector-based FGF21 lead program</li> <li><b>Inventiva</b> and <b>Hepalys</b> enter licensing agreement for <b>Ilanifibranor</b> in Japan and S. Korea</li> <li><b>PXL065</b>, Poxel seeking partnership for pivotal Phase III program in MASH</li> </ul>	<ul style="list-style-type: none"> <li><b>T3D 959</b>, T3D Therapeutics discontinues development for MASH</li> <li><b>Tesamorelin (Theratechnologies)</b>, all future development for MASH will be through partnership deals</li> <li><b>Saroglitzaz</b>, Zydus enters co-marketing deals with Lupin and Torrent in India</li> <li><b>Rencofilstat</b>, Hepion announces a strategic restructuring considering acquisition, merger and alike to fund future development in MASH</li> <li><b>Pegozafeamin</b>, 89bio raises \$172.5 million to fund continued development - planned Phase III program 2024</li> </ul>

## 2024/2025 Key Events (1 of 2)

Event	Drug (MOA, Company)	Indication	Date
Trial Starts	🇺🇸 <b>semaglutide</b> (GLP-1 agonist, Novo Nordisk) academic Phase III <a href="#">NCT05067621</a>	pediatric MASH	June 2022
	🇺🇸 <b>azemiglitazone (MSDC-0602K)</b> (mTOT modulator, Cirius) Phase III <a href="#">MMONARCH-1</a>	MASH + fibrosis + T2D	June 2022
	🇺🇸 <b>TERN-501</b> (THRβ agonist, Terns) Phase II <a href="#">DUET</a>	MASH	Discont. January 2024
	GB 1211 (galectin 3 inhibitor, Galectin) Phase II	MASH + cirrhosis	early 2024
	🇺🇸 <b>pegozafermin</b> (FGF21, 89bio) Phase III <a href="#">ENLIGHTEN-Fibrosis</a>	MASH + fibrosis	March 2024
	🇺🇸 <b>survadutide</b> (dual GLP-1/GRA, BI/Zealand) Phase III <a href="#">NCT06309992</a>	MASH	March 2024
	🇺🇸 <b>ALG-055009</b> (THRβ agonist, Aligos) Phase II <a href="#">HERALD</a>	MASH	April 2024
	🇨🇳 <b>VSA006</b> (HSD17B13 siRNA, Visirna) Phase IIb <a href="#">NCT06322628</a>	MASH	April 2024
	pegozafermin (FGF21, 89bio) Phase III ENLIGHTEN-Cirrhosis	MASH + cirrhosis	2Q 2024
	denifanstat (FASN inhibitor, Sagimet) Phase III	MASH + fibrosis	2H 2024
	🇺🇸 <b>hydronione</b> (NSAID, Gyre) Phase II	MASH + fibrosis	2024
Data Expected	🇺🇸 <b>ARO-PNPLA3</b> (PNPLA3 siRNA, Arrowhead) I <a href="#">NCT04844450</a>	genetic MASLD	January 2024
	🇺🇸 <b>denifanstat</b> (FASN inhibitor, Sagimet) Phase IIb <a href="#">FASCINATE-2</a>	MASH + fibrosis	January 2024
	🌐 <b>tirzepatide</b> (dual GLP-1/GIP, Lilly) Phase IIb <a href="#">SYNERGY-NASH</a>	MASH + fibrosis	February 2024
	🌐 <b>survadutide</b> (dual GLP-1/GRA, BI) Phase IIb <a href="#">NCT04771273</a>	MASH + fibrosis	February 2024
	🇺🇸 <b>ION224</b> (FASN inhibitor, Sagimet) Phase IIb <a href="#">NCT04932512</a>	MASH + fibrosis	March 2024
	🇺🇸 <b>efruxifermin</b> (FGF21, Akero) Phase IIb <a href="#">HARMONY</a> 96-week data	MASH + fibrosis	March 2024
	🇨🇳 <b>chiglitazar</b> (PPAR pan agonist, Chipscreen) Phase II <a href="#">CINAR</a>	MASH	March 2024
	🌐 <b>Ianifibranor/empagliflozin</b> (pan PPAR agonist, SGLT-2 inhibitor, Inventiva) Phase II <a href="#">LEGEND</a>	MASH + fibrosis	March 2024
	🌐 <b>semaglutide/cagrilintide/NN9499</b> (GLP-1/amylin/FGF21, Novo Nordisk) Phase IIb NCT05016882	MASH + cirrhosis	May 2024
	🇺🇸 <b>BOS-580</b> (FGF21, Boston Pharmaceuticals) Phase II <a href="#">NCT04880031</a> Part B, histology	MASH + fibrosis	2Q 2024
	🇺🇸 <b>VK2809</b> (THRβ agonist, Viking) Phase IIb <a href="#">VOYAGE</a> , histology	MASH + fibrosis	2Q 2024

## 2024/2025 Key Events (2 of 2)

Event	Drug (MOA, Company)	Indication	Date
Data Expected	 <b>GSK4532990</b> (HSD17B13 siRNA, GSSK) Phase IIb <a href="#">HORIZON</a>	MASH F3-F4	September 2025
	 <b>DA-1241</b> (GPR119 agonist, NeuroBo) Phase II <a href="#">NCT06054815</a>	MASH + T2D	2H 2024
	 <b>belapectin</b> (galectin-3 inhibitor, Galectin) Phase II/III <a href="#">NAVIGATE</a>	MASH + cirrhosis	4Q 2024
	 <b>semaglutide/cilofexor/firsocostat</b> (GLP-1a/FXR/ACCi, Novo Nordisk/Gilead) Phase IIb <a href="#">NCT04971785</a>	MASH + cirrhosis	November 2024
	 <b>semaglutide</b> (GLP-1 agonist, Novo Nordisk) Phase III <a href="#">ESSENCE</a>	MASH + fibrosis	Late 2024
	 <b>efruxifermin</b> (FGF21, Akero) Phase IIb <a href="#">SYMMETRY</a> 96-week data	MASH with cirrhosis	1Q 2025
	 <b>pemvidutide (ALT-801)</b> (dual GLP-1/GRA, Altimmune) Phase IIb <a href="#">IMPACT</a>	MASH + fibrosis ± T2D	1Q 2025
	 <b>efocipegtrutide</b> (triple GLP-1/GIP/GRA, Hanmi) interim analysis Phase IIb <a href="#">NCT04505436</a>	MASH + fibrosis	May 2025
	 <b>AZD2693</b> ( PNPLA3 inhibitor, AZ) Phase IIb <a href="#">FORTUNA</a>	genetic MASH + fibrosis	July 2025
	 <b>efinopegdutide</b> (dual GLP-1/GRA, Hanmi/Merck) Phase IIb <a href="#">NCT05877547</a>	MASH + fibrosis	December 2025
	 <b>miricorilant</b> (glucocorticoid antagonist, Corcept) Phase IIb <a href="#">MONARCH</a>	MASH + fibrosis	December 2025
	 <b>Ianifibranor</b> (PPAR pan agonist, Inventiva) Phase III <a href="#">NATiV3</a>	MASH + fibrosis	2H 2025
Regulatory Events	 <b>resmetirom</b> (THRβ agonist, Madrigal) FDA approved	MASH + fibrosis	March 2024
	 <b>resmetirom</b> (THRβ agonist, Madrigal) EMA submission	MASH + fibrosis	March 2024

## 2024 Key Events – Company News

Date	Company News
January	JPM 2024: TERN-501/TERN-101, Terns discontinues development for MASH to focus on obesity and cancer
January	BI and Ribo enter collaboration to develop RNAi-based therapies in MASH
January	Tebao enters licensing agreement with Suzhou Alphamab for GLP-1 agonist KN056 and KN069 (undisclosed MOA) for MASH in China
January	Novo Nordisk enters research collaborations with Omega and Cellarity in obesity and MASH
January	BI funds £30 million observational study ADVANCE to improve understanding of MASH cirrhosis
March	NGM enters merger agreement with Atlas to go private

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (1 of 8)

Phase III		Clinical Outcome	Surrogate Endpoints	Fibrosis	Advanced Liver Disease	MASH and Lipids	Liver Enzymes	Inflamm./Apoptosis	Safety	Target spec.	Non-invasive Scores	Metabolic	QOL	
Agent/MOA	Trial	Primary Endpoint	Secondary Endpoint											
aramchol (SCD1 modulator) Galmed	<a href="#">ARMOR</a>	▲	-	▲	▲	≥1-stage impr. fibrosis wo worsening of MASH	Fibrosis improvement	NAS improvement	Change in liver fat	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in CK18	Target enzyme activity
azemiglitazone (MSDC-0602K) (mTOT modulator) Cirius	<a href="#">MMONARCH-1</a>	●	-	-	-	Resolution of MASH wo worsening of fibrosis	Change in liver stiffness	Collagen proportionate area (CPA)	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in GGT	Change in inflammatory markers	Target specific biomarkers
belapectin (galectin-3 inhib.) Galectin	<a href="#">NAVIGATE</a>	-	●	-	-	≥2-point impr. in NAS wo worsening of fibrosis	≥1-stage impr. fibrosis	MASH resolution	NAS improvement	Change in plasma lipids/lipoproteins	Change in ALT	Change in GGT	AEs	ELF panel
efruxifermin (FGF21) Akero	<a href="#">SYNCHRONY Histology</a>	-	-	●	▲	-	-	-	-	-	-	-	-	<a href="#">FIB-4</a>
	<a href="#">SYNCHRONY Real-World</a>	-	-	-	-	-	-	-	-	-	-	-	-	<a href="#">Fibrotest/FibroScan</a>
	SYNCRONY Outcomes	-	-	-	-	-	-	-	-	-	-	-	-	<a href="#">NAFLD fibrosis score</a>
lanifibranor (pan PPAR agonist) Inventiva	<a href="#">NATIV3</a>	▲	-	-	-	▲	-	-	-	-	-	-	-	<a href="#">APRI</a>
pegozafermin (FGF21) 89bio	<a href="#">ENLIGHTEN Fibrosis</a>	-	●	▲	▲	-	-	-	-	-	-	-	-	<a href="#">Add. fibrosis markers</a>
	ENLIGHTEN Cirrhosis	-	-	-	-	-	-	-	-	-	-	-	-	<a href="#">Change in A1c/glucose metabolism</a>
		-	-	-	-	-	-	-	-	-	-	-	-	<a href="#">BW/BMI</a>
		-	-	-	-	-	-	-	-	-	-	-	-	<a href="#">Improvement in QOL</a>

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (2 of 8)

Phase III continued		Clinical Outcome	Surrogate Endpoints					Fibrosis		Advanced Liver Disease		MASH and Lipids		Liver Enzymes		Inflamm./Apoptosis		Safety		Target spec.		Non-invasive Scores		Metabolic		QOL											
Agent/MOA	Trial		Composite clinical endpoint/survival Progression to cirrhosis	≥1-stage impr. fibrosis w/o worsening of MASH	Resolution of MASH w/o worsening of fibrosis	≥2-point impr. in NAS w/o worsening of fibrosis	Resolution of MASH and improvement in fibrosis	Development of varices	≥2-stage impr. fibrosis	≥1-stage impr. fibrosis	Fibrosis improvement	Change in liver stiffness	Collagen proportionate area (CPA)	Change in HVPG	Improvement in MELD score	Impr. in Child-Pugh score	MASH resolution	NAS improvement	Change in liver fat	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in ASP	Change in GGT	Change in CK18	Change in inflammatory markers	AEs	Target enzyme activity	ELF panel	FIB-4	Fibrotest/FibroScan	NAFLD fibrosis score	APRI	Add. fibrosis markers	Change in A1c/glucose metabolism	BW/BMI	Improvement in QOL
resmetirom (THRβ agonist) Madigal	<a href="#">MAESTRO-NASH</a>	▲	-	▲	▲	-	-	-	-	-	-	-	-	-	-	-	-	-	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	<a href="#">MAESTRO-NAFLD1</a>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	●	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	<a href="#">MAESTRO-NAFLD-OLE</a>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	●	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	<a href="#">MAESTRO-NASH OUTCOMES</a>	▲	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
semaglutide SC (GLP-1 agonist) Novo Nordisk	<a href="#">ESSENCE</a>	▲	-	▲	▲	●	●	-	-	-	-	-	-	-	-	-	-	●	●	●	-	-	-	-	-	●	-	●	●	●	●	●	●	●	●	●	●
survotudite (dual GLP-1/GRA) BI/Zealand	<a href="#">NCT06309992</a>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	▲	-	●	-	-	-	-	-	-	-	-	-	-	-	-	-	-	●	●	▲	-	

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (3 of 8)

Phase IIb		Clinical Outcome	Surrogate Endpoints		Fibrosis		Advanced Liver Disease		NASH and Lipids		Liver Enzymes		Inflamm./Apoptosis		Safety		Target spec.		Non-invasive Scores		Metabolic		QOL												
Agent/MOA	Trial		Composite clinical endpoint/survival Progression to cirrhosis	≥1-stage impr. fibrosis w/o worsening of NASH	Resolution of NASH w/o worsening of fibrosis	≥2-point impr. in NAS w/o worsening of fibrosis	Resolution of NASH and improvement in fibrosis	Development of varices	≥2-stage impr. fibrosis	Fibrosis improvement	Change in liver stiffness	Collagen proportionate area (CPA)	Change in HVPG	Improvement in MELD score	Impr. in Child-Pugh score	MASH resolution	NAS improvement	Change in liver fat	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in ASP	Change in GGT	Change in CK18	Change in inflammatory markers	AEs	Target enzyme activity	ELF panel	FIB-4	Fibrotest/FibroScan	NAFLD fibrosis score	APRI	Add. fibrosis markers	Change in A1c/glucose metabolism	BW/BMI
aldafermin (NGM282) (FGF19) NGM	<a href="#">ALPINE 4</a>	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
ASC41 (THRβ agonist) Gannex	<a href="#">NCT05118360</a>	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -	●	- - -	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -				
AZD2693 (PNPLA3 inhibitor) AZ	<a href="#">FORTUNA</a>	- - -	●	▲	●	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
denifanstat (FASN inhibitor) Sagimet	<a href="#">FASCINATE-2</a>	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
efinopegduotide (GLP-1/GRA) Hanmi/Merck	<a href="#">NCT05877547</a>	- - -	●	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -					
efocipegduotide (triple GLP-1/GIP/GRA) Hanmi	<a href="#">NCT04505436</a>	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
efruxifermin; AKR-001 (Akero) FGF21	<a href="#">HARMONY</a>	- - -	▲	●	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	●	- - -	- - -	- - -	- - -	- - -	- - -	●	●	●	●	●	●					
	<a href="#">SYMMETRY</a>	- - -	▲	●	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	●	●	●	●	●	●					
GSK4532990 (HSD17B13 siRNA) GSK/Arrowhead	<a href="#">HORIZON</a>	- - -	▲	▲	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●				
HTD1801 (berberine/ ursodeoxycholic acid) HighTide	<a href="#">CENTRICITY</a>	- - -	●	- - -	▲	- - -	- - -	●	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	●	●	●	●	●	●	- - -	- - -	●	●	●	●	●	●				
icosabutate (enhanced omega-3 FA) NorthSea	<a href="#">ICONA</a>	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -	- - -	●	●	●	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -				
ION224 (DGAT2 inhibitor) Ionis	<a href="#">NCT04932512</a>	- - -	●	●	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (4 of 8)

**Phase IIb continued**

Agent/MOA	Trial	Clinical Outcome	Surrogate Endpoints					Fibrosis		Advanced Liver Disease		NASH and Lipids		Liver Enzymes		Inflamm./Apoptosis		Safety	Target spec.	Non-invasive Scores		Metabolic	QOL																
			Composite clinical endpoint/survival	Progression to cirrhosis	≥1-stage impr. fibrosis w/o worsening of NASH	Resolution of NASH w/o worsening of fibrosis	≥2-point impr. in NAS w/o worsening of fibrosis	Resolution of NASH and improvement in fibrosis	Development of varices	≥2-stage impr. fibrosis	≥1-stage impr. fibrosis	Fibrosis improvement	Change in liver stiffness	Collagen proportionate area (CPA)	Change in HVPG	Improvement in MELD score	Impr. in Child-Pugh score	MASH resolution	NAS improvement	Change in liver fat	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in ASP	Change in GGT	Change in CK18	Change in inflammatory markers	AEs	Target enzyme activity	Target specific biomarkers	ELF panel	FIB-4	Fibrotest/FibroScan	NAFLD fibrosis score	APRI	Add. fibrosis markers	Change in A1c/glucose metabolism	BW/BMI	Improvement in QOL
<b>miricorilant</b> (glucocorticoid RA) Corcept	<a href="#">MONARCH</a>	- -	● ● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -
<b>norursodeoxycholic acid</b> (homolog of ursodeoxycholic acid) Dr. Falk	<a href="#">EudraCT2018-003443-31</a>	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
<b>pegozafermin (BIO89-100)</b> (FGF21) 89bio	<a href="#">ENLIVEN</a>	- - -	▲ ▲	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
<b>penvidutide</b> (dual GLP-1/GRA) Altimimmune	<a href="#">IMPACT</a>	- - -	▲ ▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
<b>rapirotsiran sodium</b> (HSD17B13 RNAi), Alnylam/Regeneron	<a href="#">NASHGEN-2</a>	- - -	● ●	- - -	- - -	- - -	- - -	- - -	- - -	(1°endpoint: qFibrosis)	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
<b>rencofilstat</b> (cyclophilin inhib.) Hepion	<a href="#">ASCEND-NASH</a>	- - -	▲ ▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -
<b>saroglitazar</b> (PPAR α/γ agonist) Zydus	<a href="#">NCT05011305</a>	- - -	● ▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ● ● ● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	
<b>survotudotide</b> (dual GLP-1/GRA) Bi/Zealand	<a href="#">NCT04771273</a>	- - -	- - -	▲	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -
<b>tirzepatide</b> (dual GLP-1/GIP) Lilly	<a href="#">SYNERGY-NASH</a>	- - -	● ▲	- - -	- - -	- - -	- - -	●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	●	- - -

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (5 of 8)

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (6 of 8)

## **Phase II *continued***

- ▲ Primary Endpoint
- Secondary Endpoint

## Primary and Secondary Endpoints in Ongoing Late-stage Trials (7 of 8)

Phase II Multiple Agents																																						
Agent/MOA	Trial	Clinical Outcome	Surrogate Endpoints		Fibrosis		Advanced Liver Disease		NASH and Lipids		Liver Enzymes		Inflamm./Apoptosis		Safety		Target spec.		Non-invasive Scores		Metabolic		QOL															
			▲ Primary Endpoint	● Secondary Endpoint	Composite clinical endpoint/survival	Progression to cirrhosis	≥1-stage impr. fibrosis w/o worsening of NASH	Resolution of NASH w/o worsening of fibrosis	≥2-point impr. in NAS w/o worsening of fibrosis	Resolution of NASH and improvement in fibrosis	Development of varices	≥2-stage impr. fibrosis	≥1-stage impr. fibrosis	Fibrosis improvement	Change in liver stiffness	Collagen proportionate area (CPA)	Change in HVPG	Improvement in MELD score	Impr. in Child-Pugh score	MASH resolution	NAS improvement	Change in liver fat	Change in plasma lipids/lipoproteins	Change in ALT	Change in AST	Change in ASP	Change in GGT	Change in CK18	Change in inflammatory markers	AEs	Target enzyme activity	Target specific biomarkers	ELF panel	FIB-4	Fibrotest/FibroScan	NAFLD fibrosis score	APRI	Add. fibrosis markers
clesacostat, PF-05221304 (ACCi) ervogastat, PF-06865571 (DGAT2i)	MIRNA	- - -	▲	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
semaglutide SC (GLP-1 agonist) cilofexor (FXR agonist) firsocostat (ACC inhibitor)	NCT03987074	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
selonsertib (ASK1 inhibitor) NN9500 (FGF21 analog) cagrilintide (amylin analog)	NCT05016882	- - -	▲	● ●	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
pemafibrate (PPARα analog) tofogliflozin (SGLT-2 inhibitor)	NCT05327127	- - -	- - -	- - -	▲	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
TERN-101 (FXR agonist) TERN-501 (THRβ agonist)	DUET	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -					
Ianifibranor (pan PPAR) empagliflozin (SGLT-2i)	LEGEND	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	▲	●	- - -	- - -	- - -					

Primary and Secondary Endpoints in Ongoing Late-stage Trials (8 of 8)

## **Phase II Pediatric Trials**

- ▲ Primary Endpoint
- Secondary Endpoint

## MASH Regulatory Landscape (1 of 4)

## Phase III



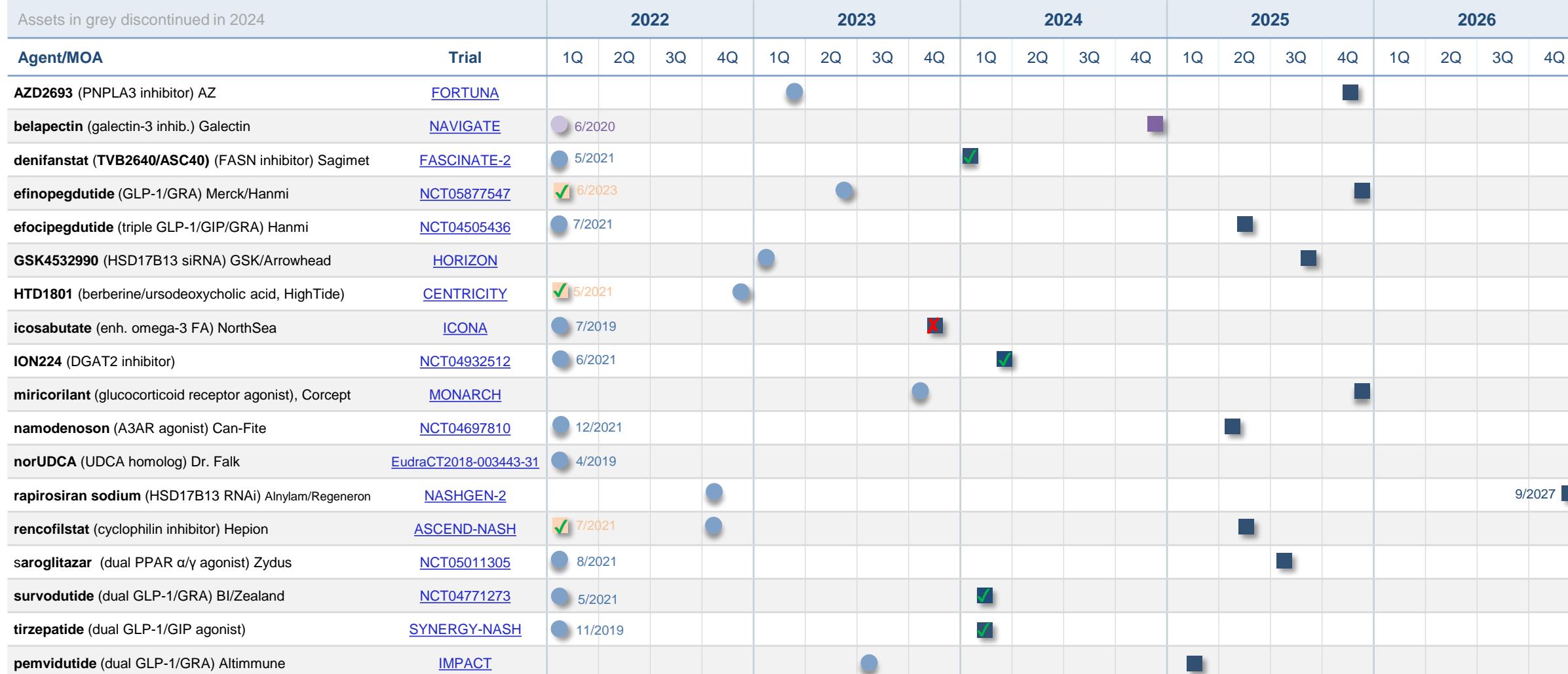
## Phase IIb

aldafermin; NGM282 (FGF19) NGM	ALPINE 4	●	12/2019		✓															
ASC41 (THRβ agonist) Gannex	NCT05118360									●				■						

■ Phase II readout  
 ● Phase IIb Start  
 ■ Phase IIb Readout  
 ● Phase III Start  
 ■ Phase III Interim Analysis  
 ● Withdrawn/terminated  
 ✓ Endpoint met  
 ✗ Endpoint missed  
 ▲/▲ NDA/MAA Submission  
 ● Approval

## MASH Regulatory Landscape (2 of 4)

## Phase IIb



■ Phase II readout   ● Phase IIb Start   ■ Phase IIb Readout   ● Phase III Start   ■ Phase III Interim Analysis   ● Withdrawn/terminated   ✓ Endpoint met   ✗ Endpoint missed   ▲/△ NDA/MAA Submission   ● Approval

## MASH Regulatory Landscape (3 of 4)

## Phase IIb

Assets in grey discontinued in 2024		2022				2023				2024				2025				2026			
Agent/MOA	Trial	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
VK2809 (THRβ agonist) Viking	<a href="#">VOYAGE</a>	<span style="background-color: #ccc; border-radius: 50%; width: 15px; height: 15px; display: inline-block;"></span>	11/2019							<span style="background-color: #333; border-radius: 5px; width: 15px; height: 15px; display: inline-block;"></span>	1H 2024										

## Phase II

ALG-055009 (THRβ agonist) Aligos	<a href="#">HERALD</a>																				
BOS-580 (FGF21) Boston Pharmac./Novartis	<a href="#">NCT04880031</a>																				
HPG 1860 (non-bile FXR agonist) Hepagene	<a href="#">RISE</a>																				
HU6 (mitochondrial uncoupler) Rivos	<a href="#">M-ACCEL</a>																				
Ieronlimab (CCR5 mAb) CytoDyn	<a href="#">NCT04521114</a>																				
linafexor (FXR agonist, Cascade)	<a href="#">NCT05591079</a>																				
LPCN 1144 (testosterone prodrug) Lipocene	<a href="#">LiFT</a>																				
mitiperstat (MPO modulator) AZ	<a href="#">COSMOS</a>																				
namodenoson (A3AR agonist) CanFite	<a href="#">NCT04697810</a>																				
ORMD 0801 (oral insulin) Oramed	<a href="#">NCT04618744</a>																				
Parmodia; pefabibrate (PPAR α agonist) Kowa	<a href="#">NCT03350165</a>																				
PXL065 (MPC inhibitor) Poxel	<a href="#">DESTINY 1</a>																				
tesamorelin (GHRF analog) Theratechnologies	<a href="#">NCT03375788</a>																				
tipelukast (5-lipoxygenase inhibitor) MediciNova	<a href="#">NCT05464784</a>																				

■ Phase II readout  
 ● Phase IIb Start  
 ■ Phase IIb Readout  
 ● Phase III Start  
 ■ Phase III Interim Analysis  
 ● Withdrawn/terminated  
 ✓ Endpoint met  
 ✗ Endpoint missed  
 ▲/▲ NDA/MAA Submission  
 ● Approval

## MASH Regulatory Landscape (4 of 4)

## Phase II Multiple Agents

Assets in grey discontinued in 2024		2022				2023				2024				2025				2026			
Agent/MOA	Trial	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q
clesacostat, PF-05221304 (ACC inhibitor) Pfizer ervogastat, PF-06865571 (DGAT2 inhibitor) Pfizer	<a href="#">MIRNA</a>	● 6/2020								■											
semaglutide SC (GLP-1 agonist) Novo Nordisk cilofexor (FXR agonist) Gilead firsocostat (ACC inhibitor) Gilead	<a href="#">NCT04971785</a>	● 8/2021											■								
semaglutide (GLP-1 agonist) Novo Nordisk NN9500 (FGF21 analog) Novo Nordisk cagrilintide (amylin analog) Novo Nordisk	<a href="#">NCT05016882</a>	● 8/2021								■											
lanifibranor (pan PPAR) Inventiva empagliflozin (SGLT-2 inhibitor) BI/Lilly	<a href="#">LEGEND</a>									✓											
pemafibrate (PPAR $\alpha$ analog) Kowa tofogliflozin (SGLT-2 inhibitor) Kowa	<a href="#">NCT05327127</a>			●									■								
TERN-101 (FXR agonist) Terns TERN-501 (THR $\beta$ agonist) Terns	<a href="#">DUET</a>							✓		●											

■ Phase II readout  
 ● Phase IIb Start  
 ■ Phase IIb Readout  
 ● Phase III Start  
 ■ Phase III Interim Analysis  
 ● Withdrawn/terminated  
 ✓ Endpoint met  
 ✗ Endpoint missed  
 △/▲ NDA/MAA Submission  
 ● Approval

## Phase II+ Development Pipeline - by Phase (1 of 4)

Product	Companies	Non-cirrhotic MASH	Cirrhotic MASH	MOA
Lipaglyn (saroglitazar)	Zydus Cadila	IIb - US Approved - India		dual PPARα/γ agonist
Rezdifra; resmetirom	Roche/ Madrigal	Prereg - EU III - JP, ROW US Fast Track, Breakthrough Therapy	III - US	THRβ agonist
aramchol	Galmed/ Samil	III - Global US Fast Track		SCD1 modulator
efruxifermin	Akero	III - US US Fast Track	IIb - US	FGF21 analog
Ianifibranor	Inventiva/Sino/Hepalys	III - Global US Fast Track Breakthrough Therapy	III - Location undisclosed US Fast Track	PPAR pan agonist
pegozafermin	TEVA/ 89bio	III - US	III - US	FGF21 analog
semaglutide SC	Novo Nordisk	III - Global US Breakthrough Therapy	II - US	GLP-1 agonist
survotudotide	Zealand Pharma/ Boehringer Ingelheim	III - US US Fast Track		dual GLP-1/GRA
aldafermin	NGM Biopharmaceuticals	Discont. - US, Australia	IIb - US, Australia	recombinant variant of FGF19
ASC41	Asclexis	IIb - China		THRβ agonist
AZD2693	AZ	IIb - EU, Jp, ROW		PNPLA3 inhibitor
azemiglitazone	Metabolic Solutions/ Cirius Therapeutics	IIb - US		mTOT modulator
belapectin	Galectin	Discont. - US US Fast Track	IIb - US	galectin 3 inhibitor
cagrilintide/ NN9500/ semaglutide	Novo Nordisk	IIb - Global		amylin analog/ FGF21 analog/ GLP-1 agonist
cilofexor/ firsocostat/ semaglutide	Gilead/ Novo Nordisk		IIb - Global	non-bile FXR agonist/ ACC inhibitor/ GLP-1 agonist

## Phase II+ Development Pipeline - by Phase (2 of 4)

Product	Companies	Non-cirrhotic MASH	Cirrhotic MASH	MOA
<b>clesacostat/ ervogastat</b>	Pfizer	IIb - Global US Fast Track		ACC inhibitor/ DGAT2 inhibitor
<b>denifanstat</b>	Sagimet Biosciences/ Ascletis	IIb - US II - China US Fast Track		FASN inhibitor
<b>efinopegdutide</b>	Hanmi/ Merck & Co.	II - Global US Fast Track		dual GLP-1/GRA
<b>efocipegrutide</b>	Hanmi	IIb - US I - S. Korea US Fast Track		GLP-1/GRA/GIP triple agonist
<b>ervogastat</b>	Pfizer	IIb - US		DGAT2 inhibitor
<b>GSK4532990</b>	GSK/Arrowhead	IIb - US I/II - NZ	IIb - US	HSD17B13 siRNA
<b>HSK31679</b>	Haisco	IIb - China		THRβ agonist
<b>HTD1801</b>	HighTide Therapeutics	IIb - US US Fast Track		berberine/ursodeoxycholic acid
<b>icosabutate</b>	BASF/ NorthSea Therapeutics	IIb - US		structurally enhanced omega-3 fatty acid
<b>ION224</b>	Ionis	IIb - US		DGAT2 inhibitor
<b>miricorilant</b>	Corcept	IIb - US I - UK		glucocorticoid receptor antagonist
<b>namodenoson</b>	NIH/ Can-Fite/ Chong Kun Dang/ Ewopharma	Preclin - US IIb - Israel		A3AR agonist
<b>norursodeoxycholic acid</b>	Dr. Falk Pharma	IIb - EU		homolog of ursodeoxycholic acid
<b>pemafibrate/ tofogliflozin</b>	Kowa	IIb - US		PPARα agonist/ SGLT-2 inhibitor
<b>pemvidutide</b>	Altimmune	IIb - US I - Australia		dual GLP-1/GRA
<b>rapirotsiran sodium (ALN-HSD)</b>	Alnylam/Regeneron	IIb - US, Japan		HSD17B13 RNAi

## Phase II+ Development Pipeline - by Phase (3 of 4)

Product	Companies	Non-cirrhotic MASH	Cirrhotic MASH	MOA
rencofilstat	Hepion/ Isotechnika	IIb - US US Fast Track		cyclophilin inhibitor
tirzepatide	Lilly	IIb - Global		dual GLP-1/GIP agonist
VK2809	Ligand/ Viking	IIb - US		THRβ agonist
VSA006	Visirna	IIb - China		HSD17B13 siRNA
ZSP1601	Guangdong Raynovent	IIb - China		PDE inhibitor
ALG-055009	Aligos	II - France		THRβ agonist
ALS-L1023	Angiolab/ Hanmi	II - S. Korea		ethyl acetate extract
avenciguat	Boehringer Ingelheim		II - Canada	sGC activator
BOS-580	Boston Pharmaceuticals/ Novartis	II - US		FGF21
chiglitazar	Chipscreen	II - China		PPAR pan agonist
DA-1241	Dong A/NeuroBo	II - US Preclin – S. Korea		GPR119 agonist
EYP651	Enyo	II - France		FXR agonist
FM101	Future Medicine	II - EU I - S. Korea		A3AR agonist
FXR314	Metacrine/Organovo	II - US US Fast Track		non-bile FXR agonist
HEC96719	Sunshine Lake	II - China		FXR agonist
HPG 1860	Hepagene	II - US		non-bile FXR agonist
HU6	Rivus	II - US		mitochondrial uncoupler
IVB001	VGI Health	II - Australia		delta tocotrienol
JKB-122	Jenken Biosciences/ TaiwanJ / Newsoara Biopharma/Biostax	II - Taiwan		TLR4 antagonist
J2H 1702	J2H	II - S. Korea		11β-HSD1 inhibitor

## Phase II+ Development Pipeline - by Phase (4 of 4)

Product	Companies	Non-cirrhotic MASH	Cirrhotic MASH	MOA
<b>Ieronymab</b>	Progenics/ CytoDyn	II - US		CCR5 antagonist
<b>linafexor</b>	Cascade	II - US		non-bile FXR agonist
<b>LPCN-1144</b>	Lipocine	II - US US Fast Track		testosterone prodrug
<b>MBK-01</b>	Academic	II - Portugal		fecal transplant
<b>mitiperstat</b>	AstraZeneca	II - Global		myeloperoxidase inhibitor
<b>ORMD 0801</b>	Oramed Pharmaceuticals Inc.	II - US, EU, Israel		prandial insulin
<b>pegargimimase; ADI-PEG20</b>	Polaris	II - Taiwan		arginine deiminase replacement
<b>PXL065</b>	DeuteRx/ Poxel	II - US		MPC inhibitor
<b>SNP-610</b>	Sinew Pharma	II - US, Taiwan		CYP2E1/DGAT1 inhibitor
<b>TERN-101/ TERN-501</b>	Lilly/ Terns Pharmaceutical	II - US I - EU, China		non-bile FXR agonist/ THRβ agonist
<b>TERN-501</b>	Terns Pharmaceutical	II - US Fast Track		THRβ agonist
<b>Egrifta (tesamorelin)</b>	Theratechnologies	II - US		growth hormone releasing factor analog
<b>tipelukast</b>	Kyorin/ MedicNova	II - US US Fast Track		5-lipoxygenase inhibitor
<b>ZED1227</b>	Dr. Falk Pharma	II - EU		transglutaminase 2 blocker

## Phase II+ Development Pipeline - by MOA (1 of 4)

MOA	Product	Specific MOA	Non-cirrhotic MASH	Cirrhotic MASH
Angiogenic Therapies	<b>ALS-L1023:</b> Angiolab/Hanmi	ethyl acetate extract	II - S. Korea	
	<b>belapectin:</b> Galectin	galectin 3 inhibitor	Discont. - US	IIb - US
	<b>namodenoson:</b> NIH/ Can-Fite/ Chong Kun Dang/ Ewopharma	A3AR agonist	Preclin - US IIb - Israel	
	<b>rencofilstat:</b> Hepion/ Isotechnika	cyclophilin inhibitor	IIb - US, EU US Fast Track	
Antifibrotic and/or Antiinflammatory Agents	<b>avenciguat:</b> Boehringer Ingelheim	sGC activator		II - Canada
	<b>FM101:</b> Future Medicine	A3AR agonist	II - EU I - S. Korea	
	<b>IVB001:</b> VGI Health	delta tocotrienol	II - Australia	
	<b>mitiperstat:</b> AstraZeneca	myeloperoxidase inhibitor	II - Global	
	<b>tipelukast:</b> Kyorin/ MediciNova	5-lipoxygenase inhibitor	II - US US Fast Track	
	<b>cagrilintide/ NN9500/ semaglutide:</b> Novo Nordisk	amylin analog/ FGF21 analog/ GLP-1 agonist	IIb - Global	
Combinations/Multi-MOA	<b>cilofexor/ firsocostat/ semaglutide:</b> Gilead/ Novo Nordisk	non-bile FXR agonist/ ACC inhibitor/ GLP-1 agonist		IIb - Global
	<b>clesacostat/ ervogastat:</b> Pfizer	ACC inhibitor / DGAT2 inhibitor	IIb - Global	
	<b>pemafibrate/ tofoglitlozin:</b> Kowa	PPAR $\alpha$ agonist/ SGLT-2 inhibitor	IIb - US II - Japan	
	<b>TERN-101/ TERN-501:</b> Lilly/ Terns Pharmaceutical	non-bile FXR agonist/ THR $\beta$ agonist	Discont. - US	
Immune Modulators	<b>JKB-122:</b> Jenken Biosciences/ TaiwanJ / Newsoara Biopharma/Biotax	TLR4 antagonist	II - Taiwan	
	<b>leronlimab:</b> Progenics/ CytoDyn	CCR5 antagonist	II - US	
Incretin-based Therapies	<b>semaglutide SC:</b> Novo Nordisk	GLP-1 agonist	III - Global	
Incretin Combinations	<b>survadutide:</b> Zealand Pharma/ Boehringer Ingelheim	dual GLP-1/GRA	III - US US Fast Track	
	<b>efinopegdutide:</b> Hanmi/ Merck & Co.	dual GLP-1/GRA	IIb - Global US Fast Track	

## Phase II+ Development Pipeline - by MOA (2 of 4)

MOA	Product	Specific MOA	Non-cirrhotic MASH	Cirrhotic MASH
Incretin Combinations <i>continued</i>	<b>efcipegtrutide:</b> Hanmi	GLP-1/GRA/GIP triple agonist	IIb - US US Fast Track I - S. Korea	
	<b>pemvidutide:</b> Altimmune	dual GLP-1/GRA	IIb - US I - Australia	
	<b>tirzepatide:</b> Lilly	dual GLP-1/GIP agonist	IIb - Global	
Insulins	<b>ORMD 0801:</b> Oramed Pharmaceuticals Inc.	prandial insulin	II - US, EU , Israel	
Lipid Modulators	<b>Rezdiffra; resmetirom:</b> Madrigal	THRβ agonist	Preg - EU III - Jp, ROW US Fast Track, Breakthrough	III - US
	<b>aramchol:</b> Galmed/ Samil	SCD1 modulator	III - Global US Fast Track	
	<b>ASC41:</b> Ascletis	THRβ agonist	IIb - China	
	<b>AZD2693:</b> AZ/Ionis	PNPLA3 inhibitor	IIb - Global	
	<b>denifanstat:</b> Sagimet Biosciences/ Ascletis	FASN inhibitor	IIb - US II - China US Fast Track	
	<b>ervogastat:</b> Pfizer	DGAT2 inhibitor	IIb - US	
	<b>GSK4532990:</b> GSK/Arrowhead	HSD17B13 siRNA	IIb - US	IIb - US
	<b>HSK31679:</b> Haisco	THRβ agonist	IIb - China	
	<b>icosabutate:</b> BASF/ NorthSea Therapeutics	structurally enhanced omega-3 fatty acid	IIb - US	
	<b>ION224:</b> Ionis	DGAT2 inhibitor	IIb - US	
	<b>norursodeoxycholic acid:</b> Dr. Falk Pharma	homolog of ursodeoxycholic acid	IIb - EU	
	<b>rapirosiran sodium (ALN-HSD):</b> Alnylam/Regeneron	HSD17B13 RNAi	IIb - US, Japan	
	<b>VK2809:</b> Ligand/ Viking	THRβ agonist	IIb - US	
	<b>VSA006:</b> Visirna	HSD17B13 siRNA	IIb - China	
	<b>ALG-055009:</b> Aligos	THRβ agonist	II - France	
	<b>SNP-610:</b> Sinew Pharma	CYP2E1/DGAT1 inhibitor	II - US, Taiwan	

## Phase II+ Development Pipeline - by MOA (3 of 4)

MOA	Product	Specific MOA	Non-cirrhotic MASH	Cirrhotic MASH
Lipid Modulators <i>continued</i>	<b>TERN-501:</b> Terns Pharmaceutical	THRβ agonist	II - US US Fast Track	
	<b>efruxifermin:</b> Akero	FGF21 analog	III - US US Fast Track	IIb - US
	<b>pegozafermin:</b> TEVA/ 89bio	FGF21 analog	III - US	III - US
	<b>aldafermin:</b> NGM Biopharmaceuticals	recombinant variant of FGF19	Discont. - US, Australia	IIb - US, Australia
	<b>azemiglitazone:</b> Metabolic Solutions/ Cirius Therapeutics	mTOT modulator	IIb - US	
	<b>BOS-580:</b> Boston Pharmaceuticals/ Novartis	FGF21	II - US	
	<b>EYP651:</b> Enyo	FXR agonist	II - France	
Metabolism Modulators	<b>FXR314:</b> Metacrine/Organovo	non-bile FXR agonist	II - US	
	<b>HEC96719:</b> Sunshine Lake	FXR agonist	II - China	
	<b>HPG 1860:</b> Hepagene	non-bile FXR agonist	II - US	
	<b>HU6:</b> Rivus	mitochondrial uncoupler	II - US	
	<b>J2H 1702:</b> J2H	11β-HSD1 inhibitor	II - S. Korea	
	<b>linafexor:</b> Cascade	non-bile FXR agonist	II - US US Fast Track	
	<b>HTD1801:</b> HighTide Therapeutics	berberine/ursodeoxycholic acid	IIb - US US Fast Track	
	<b>miricorilant:</b> Corcept	glucocorticoid receptor antagonist	IIb - US I - UK	
Other	<b>ZSP1601:</b> Guangdong Raynovent	PDE inhibitor	IIb - China	
	<b>DA-1241:</b> Dong-A/NeuroBo	GPR119 agonist	II - US Preclin – S. Korea	
	<b>Egrifta (tesamorelin) :</b> Theratechnologies	growth hormone releasing factor analog	II - US	
	<b>LPCN-1144:</b> Lipocene	testosterone prodrug	II - US US Fast Track Breakthrough Designation	

## Phase II+ Development Pipeline - by MOA (4 of 4)

MOA	Product	Specific MOA	Non-cirrhotic MASH	Cirrhotic MASH
Other	<b>MBK-01:</b> Academic	fecal transplant	II - Portugal	
	<b>pegarginase (ADI-PEG20):</b> Polaris	arginine deiminase replacement=	II - Taiwan	
	<b>ZED1227:</b> Dr. Falk Pharma	transglutaminase 2 blocker	II - EU	
PPAR Modulators	<b>Lipaglyn (saroglitazar):</b> Zydus Cadila	dual PPAR $\alpha/\gamma$ agonist	IIb - US Approved - India	
	<b>Ianifibranor:</b> Inventiva	PPAR pan agonist	III - Global US Fast Track	III - Location undisclosed
	<b>chiglitazar:</b> Chipscreen	PPAR pan agonist	II - China	
	<b>PXL065:</b> DeuteRx/ Poxel	MPC inhibitor	II - US	

## Early Phase Development Pipeline - by MOA (1 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Antifibrotic and/or Antiinflammatory Agents	AZD2389: AZ	undisclosed	I - US	Feb. 2024: AZD2389 (AZ) in Phase I development for MASH
	ECC 0509: Eccogene	SSAO inhibitor	I - Australia	Nov. 2021: AASLD 2021: Anti-fibrotic/Anti-inflammatory Agents: TPL2i and SSAO 2
	GB1211: Galecto	Galectin 3 inhibitor	I - UK	Aug. 2023: GB 1211, Galecto plans Phase II trial in NASH with decompensated cirrhosis
	HPN-01: Hepanova	IκB kinase inhibitor	I - US	July 2020: HPN-01, Hepanova plans US Phase I PK trial
	hydrionone: Gyre	NSAID derived from perfenidone	I - US	Nov. 2023: Hydronione, Gyre plans US Phase II development for NASH with fibrosis in 2024
	lixudebart: INSERM/ Alentis	CLDN1 mAb	I - EU	Jan. 2022: ALE-F02, Alentis initiates Phase I FIH trial
	LR20056: TransThera/ LG Chem Life Sciences	SSAO inhibitor	I - US Preclin - China	March 2022: LG203003 and LR20056, LG Chem provides update on clinical programs
	NN6561: Novo Nordisk	VAP-1 inhibitor	I - EU	Jan. 2024: NN6561 (Novo Nordisk) in Phase I development for MASH
	NP011: NEXEL	integrin αVβ3 /αVβ5 modulator	I - S. Korea	June 2022: NP 011, NEXEL plans S. Korean Phase I trial mid 2022
	OA-235i: Oasis	PAR2 inhibitor	I - US	Sep. 2023: OA-235i, Oasis updates US Phase I trial adding MAD cohort
	ontamalimab: Takeda	MADCAM1 mAb	I - undisclosed	
	PLN-1474: Pliant Therapeutics	integrin inhibitor	I - US	Jan. 2024: NASH-TAG 2024: PLN-1474 (Pliant) safe and well-tolerated in FIH study
	SFA001: SFA Therapeutics	microbiome derived agent targeting GPR43, GPR441, down-regulating NFκB	I - undisclosed	Jan. 2023: SFA001, SFA Therapeutics plans academic US Phase I study in NASH
	SYN-020: Synthetic Biologics	alkaline phosphatase	I - US	May 2022: SYN-020 (Synthetic Biologics) safe and well-tolerated in Phase I MAD study
	ZSP1603: Guangdong Zhongsheng Pharmaceutical	undisclosed	I - China	
	AMP 945: Cytopia/ Amplia Therapeutics	FAK inhibitor	Preclin - Australia	
	BLD 3051: Blade	calpain inhibitor	Preclin - US	Sep. 2021: BLD 3051, Blade initiates preclinical development in hepatic and pulmonary fibrosis

## Early Phase Development Pipeline - by MOA (2 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Antifibrotic and/or Antiinflammatory Agents <i>continued</i>	<b>BTT 105:</b> Biotoxtech	hydroquinone derivative	Preclin - S. Korea	
	<b>CB5138:</b> CohBar	analog of mitochondrially encoded peptide	Preclin - US	
	<b>CRB A4:</b> Celros	SH3YL1 modulator	Preclin – S. Korea	
	<b>EPGN 696:</b> Epigen/ Novo Nordisk	LPA1 receptor antagonist	Preclin - US	May 2018: Epigen enters agreement with Novo Nordisk for oral LPA1 receptor antagonist EPGN696 in fibrotic diseases including NASH
	<b>EPGN2154:</b> Epigen	LPA1 receptor antagonist	Preclin - US	Jan. 2024: NASH-TAG 2024: EPGN2154 (Epigen) shows anti-fibrotic activity independent of weight loss in murine MASH models
	<b>FRTX 10:</b> Carna Biosciences/ Fresh Tracks	MPYS inhibitor	Preclin - US	
	<b>GB2064:</b> PharmAkea/ Galecto	LOXL2 inhibitor	Preclin - US	
	<b>HPP 3033:</b> vTv Therapeutics	NRF2 activator	Preclin - US	
	<b>ID 11905:</b> Ildong Pharmaceutical	ENPP2 inhibitor	Preclin - S. Korea	Sep. 2022: ID11905, Ildong plans clinical development for the treatment of NASH in 2023
	<b>IOA-289:</b> iOnctura	autotaxin inhibitor	Preclin - Switzerland	June 2023: (EASL) Novel Preclinical data on Anti-fibrotic Agents
	<b>IVB002:</b> VGI Health	tocotrienol prodrug	Preclin - Australia	
	<b>LABP-111:</b> Nlmmune	LANCL2 activator	Preclin - US	
	<b>LAE 104:</b> Laekna Therapeutics	NK cell stimulant	Preclin - China	
	<b>LAE 105:</b> Laekna Therapeutics	NK cell stimulant	Preclin - China	
	<b>METI 201:</b> Metimedi	undisclosed	Preclin - S. Korea	
	<b>NMX 2:</b> NovoMedix	IL-11 inhibitor	Preclin - US	
	<b>PLN-169:</b> Pliant	integrin inhibitor	Preclin - US	
	<b>Research program:</b> adenosine analogs Purnovate: Adial	adenosine analog	Preclin - US	Jan. 2020: BI acquires exclusive global rights to Enleofen's anti-IL-11 platform

## Early Phase Development Pipeline - by MOA (3 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Antifibrotic and/or Antiinflammatory Agents <i>continued</i>	<b>Research Program: antibodies:</b> Enleofen/Boehringer Ingelheim	IL11 inhibitors	Preclin - Germany, Singapore	Jan. 2020: BI acquires exclusive global rights to Enleofen's anti-IL-11 platform
	<b>SRN 001:</b> siRNAgen	AREG siRNA	Preclin - S. Korea	
	<b>TES 1025:</b> Tes Pharma	ACMSD inhibitor	Preclin - Italy	
	<b>TLC-065:</b> Orsobio	SSAO inhibitor	Preclin - US	
	<b>VB-601:</b> VBL Therapeutics	MOSPD2 mAb	Preclin - Israel	Nov. 2021: VB 601, VBL Therapeutics plans first-in-human study in 2H 2021
	<b>YHC 1102:</b> Yuhan/ Gilead	undisclosed	Preclin - S. Korea	June 2021: YHC 1102, YHC 1108 (Yuhan/Gilead) to enter preclinical development
	<b>YHC 1108:</b> Yuhan/ Gilead	undisclosed	Preclin - S. Korea	June 2021: YHC 1102, YHC 1108 (Yuhan/Gilead) to enter preclinical development
	<b>ZED 3269:</b> Zedira	transglutaminase inhibitor	Preclin - Germany	
	<b>ZMC001:</b> Zymedi	KARS1 inhibitor	Preclin - US	
Apoptosis Modulators	<b>GST-HG151:</b> Fujian	JNK inhibitor	I - China	May 2022: GST-HG151, Fujian Cosunter initiated Chinese Phase I SAD/MAD trial
	<b>HRX-0215:</b> HepaRegenix	MKK4 inhibitor	I - EU	Aug. 2021: HRX-0215, HepaRegenix initiates FIH Phase I trial
	<b>SRT 015:</b> Seal Rock Therapeutics	ASK-1 inhibitor	I - Australia	Nov 2022: (AASLD) SRT-015, safe and well-tolerated in FIH SAD/MAD study
	<b>TLY012:</b> Theraly	TRAILR2 agonist	I - US	Dec. 2021: TLY012 (Theraly) in US Phase I development for NASH with fibrosis, chronic pancreatitis, and systemic sclerosis
Cell Therapies	<b>HepaStem:</b> Cellaion	derived from human adult liver-derived progenitor cells	I/II - EU	June 2023: (EASL) PANASH: HepaStem cell therapy shows favorable safety profile and preliminary efficacy in NASH F3-F4
Combinations (multi-class) <i>continued</i>	<b>ASC43F:</b> Asclexis	dual FASN inhibitor/FXR agonist	I - US Preclin - China	
	<b>BAR 502:</b> Bar Pharmaceuticals	dual FXR/GPBAR1 agonist	I - Portugal	Sep. 2022: BAR 502, Bar delays Portuguese Phase I trial by 9 months

## Early Phase Development Pipeline - by MOA (4 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Combinations (multi-class)	<b>ASC44F:</b> Ascleitis	dual FASN inhibitor/FXR agonist	Preclin - China	
	<b>ASC45F:</b> Ascleitis	dual FASN inhibitor/THRβ agonist	Preclin - China	
	<b>HMSFDC-5688:</b> Hua Medicine	GKA/PPAR $\gamma$ agonist	Preclin - China	
	<b>i2o-110:</b> i2obio	undisclosed combination	Preclin - US	
Devices	<b>Gelesis300:</b> Gelesis	carboxymethylcellulose crosslinked with citric acid	Preclin - US	April 2019: (ILC 2019) Gel-B: improves gut barrier function; mitigates diet induced weight gain and lipid accumulation
	<b>APX-311:</b> Aptabio	NOX inhibitor	I - S. Korea	June 2022: APX-311, Aptabio plans Phase II trial in 2022
	<b>mosedipimod:</b> Enzychem	TLR4 inhibitor	I - S. Korea	
	<b>NXC 736:</b> NextGen	NLRP3 inflammasome inhibitor	I - S. Korea	Oct. 2021: NXC 736, NextGen initiates S. Korean Phase I FIH trial
	<b>pegipanermin:</b> INmune Bio	TNF inhibitor	I - US	Jan. 2021: LIVNate, Inmune plans open-label Phase IIa trial in patients with presumed NASH and F2-F3
Immune Modulators	<b>tolimidone:</b> Pfizer/ Bukwang/ Melior Discovery/ Adhera	Lyn kinase stimulant	I - US	Oct. 2021: Tolimidone, Adhera expands agreement with Melior to include NASH and pulmonary inflammation
	<b>adalimumab:</b> 180 Life Sciences	TNF mAb	Preclin - UK	
	<b>COYA 205:</b> Coya	allogeneic Treg-derived exosome	Preclin - US	
	<b>KINE 101D:</b> Kine Sciences	Treg modulator	Preclin - S. Korea	
	<b>PVT 201:</b> Parvus	Treg stimulant	Preclin - Canada	
	<b>VENT-01:</b> Ventus/ Novo Nordisk	NLRP3 inflammasome inhibitor	Preclin - US	
	<b>AZD9550</b> AstraZeneca	dual GLP-1/GRA	I/II - UK	Dec. 2023: AZ9550, AZ conducting US Phase I/II trial CONTEMPO in T2D with overweight/obesity
Incretin Combinations	<b>AP 026:</b> Sino	dual FGF21/GLP-1 agonist	I - China	
	<b>DD 01:</b> D&D/ Shenzhen Salubris Pharmaceuticals	dual GLP-1/GRA	I - US, S. Korea	June 2023: (EASL) DD01 improves liver fat, glycemic control, and body weight
	<b>DR 10624:</b> Zhejiang Doer	triple GLP-1/GRA/FGF21	I - China	
	<b>DR 10627:</b> Zhejiang Doer	dual GLP-1/GIP agonist	I - China	

## Early Phase Development Pipeline - by MOA (5 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Incretin Combinations <i>continued</i>	<b>DR 10628:</b> Zhejiang Doer	dual GLP-1/GIP agonist	I - China	Aug. 2023: DR10628 (Zhejiang Doer Biologics) in Phase I development for T2D and NASH in China
	<b>GMA106:</b> Gmax Biopharm	dual GLP-1 agonist/GIP antagonist	I - Australia	Sep. 2021: GMA 106, Gmax plans Australian Phase I FIH trial
	<b>HEC88473:</b> HEC Pharm	dual FGF21/GLP-1 agonist	I - China	Nov. 2023: AASLD 2023: HEC88473 reduces liver fat and A1c at 5 weeks
	<b>PB-718:</b> PegBio	dual GLP-1/GRA	I - US Preclin - China	Aug. 2021: PB-718, PegBio finally discloses US Phase I FIH trial two years after initiation
	<b>SCO-094:</b> Takeda/ Scobia Pharma/ Huangdong Medicine	dual GLP-1/GIP agonist	I - EU	June 2021: SCO-094, Huadong Medicine licenses dual GLP-1/GIP agonist SCO-094
	<b>VK2735:</b> Viking	dual GLP-1/GIP agonist	I - Australia	Oct 2023: Obesity Week 2023: VK2735 (Viking) improves liver fat and atherogenic lipids in Australian Phase I trial
	<b>YH25724:</b> Yuhan/BI	dual GLP-1/FGF21	I - EU	
	<b>DD 03:</b> D&D	oral triple GLP-1/GIP/GRA	Preclin - S. Korea	
	<b>DD 15:</b> D&D	triple GLP-1/GIP/GRA	Preclin - S. Korea	March 2024: DD 15 (D&D) in preclinical development for obesity – included under MetSera collaboration
	<b>GMA107:</b> Gmax Biopharm	likely triple GLP-1/GRA/GIP agonist	Preclin - China	
Incretin-based Therapies	<b>mazdutide:</b> Innovent/ Lilly	dual GLP-1/GRA	Preclin - China	
	<b>OBG21502:</b> Onogene	tetra GLP-11/GRA/FGF21/anti-cytokine agonist	Preclin - S. Korea	Sep. 2023: OGB 21502, Onogene plans to enter clinical development for NASH F4 in 2024
	<b>AZD5004:</b> Eccogene	GLP-1 agonist	I - US	Dec. 2022: ECC5004, Eccogene initiates clinical development of oral GLP-1 agonist in NASH and obesity
	<b>ecnoglutide:</b> Sciwind	GLP-1 agonist	I - Australia	June 2022: (ILC) Sciwind's early incretins show promise in mouse models
	<b>KN 056:</b> Alphamab/ Tebao	GLP-1 agonist	I - China	Jan. 2024: Tebao enters licensing agreement with Suzhou Alphamab for GLP-1 agonist KN056 and KN069 (undisclosed MOA) for MASH in China
	<b>oral ecnoglutide:</b> Sciwind	GLP-1 agonist	I - Australia	
	<b>CYRS-MD02:</b> Cyrus	oral GLP-1 agonist	Preclin - S. Korea	
	<b>hyglutide:</b> Genexine/CSPC Pharma	GLP-1 agonist	Preclin - China	Sep. 2022: Hyglutide (CSPC) to enter clinical development for NASH in China

## Early Phase Development Pipeline - by MOA (6 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Incretin-based Therapies <i>continued</i>	<b>i2o-105s:</b> i2obio	GLP-1 agonist	Preclin – US	
	<b>i2o-130:</b> i2obio	glucagon analog	Preclin – US	
	<b>Research program: small molecule GLP-1:</b> Eccogene	GLP-1 agonist	Preclin - China	
	<b>RGT-028:</b> Regor	oral GLP-1 agonist	Preclin - US	
	<b>XW014:</b> Sciwind	GLP-1 agonist	Preclin - China	June 2022: (ILC) Sciwind's early incretins show promise in mouse models
	<b>XW017:</b> Sciwind	GIP agonist	Preclin - China	June 2022: (ILC) Sciwind's early incretins show promise in mouse models
Lipid Modulators	<b>YGX 1:</b> Youngene	oral GLP-1 agonist	Preclin - China	Jan. 2023: YGX 1 (Youngene) in preclinical development for NASH and obesity
	<b>ALN-PNP:</b> Alnylam/ Regeneron	PNPLA3 RNAi	I - US	March 2024: Regeneron adds MASLD cohorts and delays completion of US Phase I trial
	<b>ARO-PNPLA3:</b> Arrowhead	siRNA against PNPLA3	I - US	Feb 2023: JNJ-0795/ARO-PNPLA3, J&J returns rights to Arrowhead
	<b>AZD7503:</b> Ionis/AstraZeneca	HSD17B13 RNAi	I - US	Oct. 2023: AZD7503, AZ plans Japanese Phase I study
	<b>ECC4703:</b> Eccogene	THRβ agonist	I - US Preclin - China	June 2023: ECC4703, Eccogene raises ~\$25 million in a Series B financing to support development pipeline
	<b>INI 822:</b> Inipharm	HSD17B13 inhibitor	I - US	July 2023: INI-822, Inipharm initiates FIH Phase I trial
	<b>LG203003:</b> LG Chem	DGAT2 inhibitor	I - US, S. Korea	Aug. 2022: LG203003, LG Chem initiates US Phase I FIH trial
	<b>LY3849891:</b> Lilly	PNPLA3 siRNA	I - US	May 2022: LY3849891, Lilly plans US/Japanese Phase I trial in NAFLD with PNPLA3 L148 genotype
	<b>LY3885125:</b> Lilly	SCAP siRNA	I - US	Oct. 2023: LY3885125, Lilly accelerates completion of US Phase SAD/MAD trial in dyslipidemia and NAFLD
	<b>PF-07853578:</b> Pfizer	PNPLA3 modulator	I - US	Sep. 2023: PF-07853578, Pfizer initiates US FIH SAD Phase I trial
	<b>RJ4287:</b> Nanjing Ruijie	THRβ agonist	I - China	Aug. 2023: RJ4287, Nanjing Ruijie initiates Chinese Phase I SAD/MAD FIH trial

## Early Phase Development Pipeline - by MOA (7 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Lipid Modulators <i>continued</i>	<b>CIDEB targeting siRNA:</b> Argo	CIDEB siRNA	Preclin - China	Jan. 2024: Three preclinical siRNA therapies targeting PNPLA3, HSD17B13, and CIDEB in development for MASH with Argo
	<b>CVI-301:</b> CVI Pharma	THRβ agonist	Preclin - China	June 2023: (EASL) Novel THRβ agonists show potential in preclinical models
	<b>Cyta-001:</b> CytaTx	THRβ agonist	Preclin - US	
	<b>GNV069:</b> Genevant	HSD17B13 siRNA	Preclin - Canada	
	<b>HP 515:</b> Hinova	THRβ agonist	Preclin - China	
	<b>HPG 7233:</b> Hepagene	THRβ agonist	Preclin - China	Sep. 2023: HPG 7233, Hepagene plans to enter clinical development for NASH and dyslipidemia
	<b>HSD17B13 targeting siRNA:</b> Argo	HSD17B13 siRNA	Preclin - China	Jan. 2024: Three preclinical siRNA therapies targeting PNPLA3, HSD17B13, and CIDEB in development for MASH with Argo
	<b>INI 678:</b> Inipharm	HSD17B13 inhibitor	Preclin - US	June 2022: (ILC) Lipid Modulators: HSD17B13 improved features of NASH in a human hepatocyte system
	<b>PNPLA3 targeting siRNA:</b> Argo	PNPLA3 siRNA	Preclin - China	Jan. 2024: Three preclinical siRNA therapies targeting PNPLA3, HSD17B13, and CIDEB in development for MASH with Argo
	<b>Preclinical program:</b> Esperion	ACL inhibitor	Preclin - US	
Metabolism Modulators	<b>RBD 1073:</b> Suzhou Ribo	HSD17B13 RNAi	Preclin - China	
	<b>idebenone:</b> Santhera Pharmaceuticals	Coenzyme Q10	I/II - US	Dec. 2020: Idebenone, academic US Phase I/II trial planned in NASH
	<b>ASC42:</b> Ascletis	non-bile FXR agonist	I - US Preclin - China US Fast Track Designation	Nov. 2021: ASC42F, Ascletis initiates global Phase I development of fixed dose combination of THRβ agonist ASC41 and non-bile FXR agonist ASC42
	<b>ATX304:</b> Amplifier Tx	AMPK activator	I - EU	Aug. 2020: O304, Betagenon initiates Swedish Phase I trial of novel formulation
	<b>B1344:</b> Tasly	FGF21	I - US	Dec. 2022: B1344, Tasly initiates FIH Phase I trial
	<b>CB4211:</b> Albert Einstein College of Medicine/ CohBar	MOTSc analog	I - US	Sep. 2021: CB4211, CohBar granted patent from USPTO for treatment of NASH

## Early Phase Development Pipeline - by MOA (8 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Metabolism Modulators <i>continued</i>	ID11903: Ildong Pharmaceutical	FXR agonist	I - US	Nov. 2022: ID119031166M, Ildong initiated US Phase I SAD/MAD trial
	MT 2004: Shaanxi Micot	non-bile FXR agonist	I - US	Feb. 2020: MT 2004, Zi'an Biocare initiates US Phase I SAD/MAD trial in healthy subjects
	NN6581: Novo Nordisk	LXR $\alpha$ siRNA	I - UK	March 2023: NN6581, Novo Nordisk initiates enrollment of UK Phase I FIH trial
	NN6582: Novo Nordisk	MARC1 siRNA	I - Austria	March 2023: NN6582, Novo Nordisk initiates enrollment of Austrian Phase I FIH trial
	TLC-2716: Phenex/ Orsobio	LXR inverse agonist	I - NZ	Nov. 2022: (AASLD) TLC-2716, a potent, liver- targeted, inverse agonist of LXR, demonstrates profound reductions in hepatic and plasma lipids in dysmetabolic rodent models
	TLC-3595: Shionogi/Orsobio	ACC2 inhibitor	I - Japan	June 2023: (EASL) ACC2 inhibition improves steatosis and fibrosis with no hypertriglyceridemia in preclinical models
	vutiglabridin (HSG4112): Glaceum	leptin sensitizer	I - S. Korea	Nov. 2019: (AASLD 2019) Novel Preclinical Metabolism Modulators
	XZP-5610: Xuanzhu	FXR agonist	I - China	June 2021: XZP-5610, Xuanzhu initiates Chinese FIH Phase I SAD/MAD trial
	XZP-6019: Xuanzhu	FXR agonist	I - China	Oct. 2021: XZP-6019, Xuanzhu plans Chinese Phase I FIH trial
	GF-1002: Genflow	SIRT6 AVV	Preclin - Belgium, UK	Sep. 2023: GF-1002, Genflow to initiate clinical development of SIRT6 AVV in 2025
	i20-107:i2obio	amylin analog	Preclin - US	
	IOT022: InorbitTx	FXR agonist	Preclin - EU	
	IOT038: InorbitTx	ketohexokinase inhibitor	Preclin - EU	July 2022: IOT038, InorbitTx to initiate IND enabling studies in 3Q 2022
	KRIYA 497: Kriya	FGF21 geneTx	Preclin - US	
Neurotransmitter Modulators	Research program: mitochondrial uncouplers: MITO Biopharma	mitochondrial uncouplers	Preclin - US	
	GM 60106: JD Bioscience	5-HT2A agonist	I - Australia	Aug. 2022: GM-60106, JD Bioscience initiates Australian Phase I FIH trial

## Early Phase Development Pipeline - by MOA (9 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Neurotransmitter Modulators <i>continued</i>	<b>INV-347:</b> Inversago/ Novo Nordisk	CB1R blocker	I - Canada	Jan. 2024: INV-347 (Novo Nordisk) in Phase I development
	<b>monlunabant:</b> Inversago/Novo Nordisk	CB1 antagonist	I - Canada	Sep. 2021: INV-202, Inversago initiates Canadian FIH Phase I trial
	<b>SCO 267:</b> Takeda/ Scobia Pharma	GPR40 agonist	I - Japan	Feb. 2022: SCO267, Scobia looks for partners to continue development
	<b>AGTX-2003:</b> Agentix	CB1R inverse agonist	Preclin - US	
	<b>GM 60186:</b> JD Bioscience	5-HT2A agonist	Preclin - S. Korea	
Other	<b>GH509:</b> 1Globe	undisclosed	I/II - China	March 2023: GH509, 1Globe initiates Chinese Phase I/II trial in NASH F2-F3 with T2D
	<b>GDD 3898:</b> Lipidio	undisclosed	Ib - US	
	<b>A 4368:</b> Autophagy Sciences	autophagy activator	I - S. Korea	July 2021: A 4368, Autophagy Sciences plans S. Korean Phase I FIH trial
	<b>ALY688:</b> Allysta	adiponectin receptor agonist	Preclin - US I - Australia	April 2021: ALY688, Allysta initiates Australian Phase I FIH trial
	<b>BI 3006337:</b> BI	undisclosed	I - US	Aug. 2023: BI 3006337, BI initiates Phase I MAD trial in NAFLD with overweight/obesity
	<b>EA 3571:</b> EA Pharma	undisclosed	I - Japan	May 2022: EA3571 (EA Pharma) in Phase I development in Japan
	<b>HS 10356:</b> Jiangsu Hansoh	undisclosed antiviral	I - China	Dec. 2020: HS 10356, Jiangsu Hansoh initiates Chinese Phase I SAD/MAD trial
	<b>IMM-H014:</b> Tianjin Chase Sun	undisclosed	I - China	Jan. 2024: IMM-H014, Tianjin Chase Sun initiates Chinese Phase I FIH trial
	<b>LB P8:</b> LIScure	microbiome modulator	I - Australia	Sep. 2021: LB-P6 & LB-P8, LIScure plans Australian Phase I MAD trial
	<b>LPCN-1148:</b> Lipocene	testosterone prodrug	I - US	Sep. 2022: LPCN-1144, LPCN-1148, Lipocene to focus on CNS conditions - seeking partners for NASH assets
	<b>OLX75016:</b> OliX Pharmaceuticals	siRNA against undisclosed target	I - Australia	Dec. 2023: OLX75016, OliX cleared to enter Phase I development in NASH

## Early Phase Development Pipeline - by MOA (10 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Other continued	<b>SNP-630:</b> Sinew Pharma	enzyme inhibitor targeting P450 2E1 (CYP2E1)	I - Taiwan	March 2021: SNP-630, Sinew plans Taiwanese FIH Phase I trial
	<b>SYHA 1805:</b> CSPC Pharma	undisclosed	I - China	July 2021: SYHA 1805, CSPC ZhongQi initiates Chinese MAD trial
	<b>TB-840:</b> Therasid	undisclosed	I - S. Korea	Sep. 2021: TB-840, Therasid initiates S. Korean FIH Phase I trial
	<b>ZSP0678:</b> Guangdong Zhongsheng	undisclosed	I - China	
	<b>ADC-001:</b> NovoBiome	live biotherapeutic	Preclin - France	May 2021: ADC-001, NovoBiome launched to target microbiome-liver-gut axis
	<b>BEBT 508:</b> BeBetter Med	undisclosed siRNA	Preclin - US	
	<b>CKR 334:</b> CK Regeon	CXXC5 inhibitor	Preclin - S. Korea	
	<b>CS27186:</b> Shenzhen Chipscreen	undisclosed nuclear receptor agonist	Preclin - China	
	<b>DCR-LIV2:</b> Dicerna/ Boehringer Ingelheim	undisclosed RNAi	Preclin - US	May 2021: DCR-LIV2, BI accepts GalXC RNAi candidate for advancement under R&D agreement with Dicerna
	<b>DT-109:</b> Diapin	three amino acid peptide	Preclin - US	Dec. 2020: DT-109 (Diapin), early preclinical data show beneficial effects of tri-peptide in NASH
	<b>GTX-011:</b> GAT Therapeutics	NR3C modulator	Preclin - Spain	
	<b>i2o-120:</b> i2obio	PPY analog	Preclin - US	
	<b>KN 069:</b> Alphamab/ Tebao	undisclosed	Preclin - China	Jan. 2024: Tebao enters licensing agreement with Suzhou Alphamab for GLP-1 agonist KN056 and KN069 (undisclosed MOA) for MASH in China
	<b>LB P7:</b> LISCure	microbiome modulator	Preclin - S. Korea	
	<b>LDN 072:</b> Ladon	undisclosed	Preclin - Hungary	
	<b>LR19131:</b> LG Chem	undisclosed	Preclin - S. Korea	
	<b>M008:</b> MRM Health	microbiome based therapy	Preclin - Belgium	
	<b>MT-001:</b> Mitotherapeutix	siRNA against undisclosed target	Preclin - US	
	<b>NASH therapeutic:</b> Viscient	undisclosed	Preclin - US	

## Early Phase Development Pipeline - by MOA (11 of 11)

MOA	Product	Specific MOA	Dev. Stage	Last milestone
Other <i>continued</i>	<b>PN 101 RS:</b> Paean	mitochondria-based therapeutic	Preclin - S. Korea	
	<b>QBT 002:</b> Qing Bile Therapeutics	tetrahydroxylated bile acid	Preclin - Canada	
	<b>QBT 006:</b> Qing Bile Therapeutics	tetrahydroxylated bile acid	Preclin - Canada	
	<b>RBD5083:</b> Suzhou Ribo	undisclosed RNAi	Preclin - China	
	<b>RCYM 001:</b> Guangdong Zhongsheng	undisclosed	Preclin - China	
	<b>RES-010:</b> Resalis	ASO against MiR-22	Preclin - Italy	Nov. 2023: AASLD 2023: Novel ASO RES-010 additive to GLP-1 weight loss in mice
	<b>Research program: GaINAc conjugated siRNA therapeutics:</b> e-Therapeutics	undisclosed siRNA	Preclin - UK	
	<b>Research program: oligonucleotide therapies:</b> Aligos/ Merck	undisclosed	Preclin - EU	
	<b>RJ 7183:</b> Nanjing Ruijie	undisclosed	Preclin - China	
	<b>RSVI 301:</b> Rosvivo	miRNA based therapeutic	Preclin - US	
	<b>SAL 0125:</b> Shenzhen	undisclosed	Preclin - China	
	<b>TU 5113:</b> TiumBio	undisclosed	Preclin - S. Korea	
	<b>TXR 611:</b> Aria	undisclosed	Preclin - US	
	<b>TXR 612:</b> Aria	undisclosed	Preclin - US	
Proliferation Modulators	<b>VB 0004:</b> Vectus	vasodilator	Preclin - Australia	
	<b>YGX 2:</b> Youngene	undisclosed	Preclin - China	
PPAR modulators	<b>ZSYM 008:</b> Guangdong Zhongsheng	undisclosed	Preclin - China	
	<b>Oxy 210:</b> MAX BioPharma	dual TGFβ/Hedgehog inhibitor	Preclin - US	
PPAR modulators	<b>TGF beta1 isoform specific antisense oligonucleotide:</b> Isarna	TGF β RNAi	Preclin - Germany	
	<b>BEBT 503:</b> BeBetter Med	pan PPAR agonist	I - Australia	
	<b>T3D 980:</b> T3D Therapeutics/Bayer	PPARδ/γ agonist	Preclin - US	

## Agents with Special Regulatory Status (1 of 2)

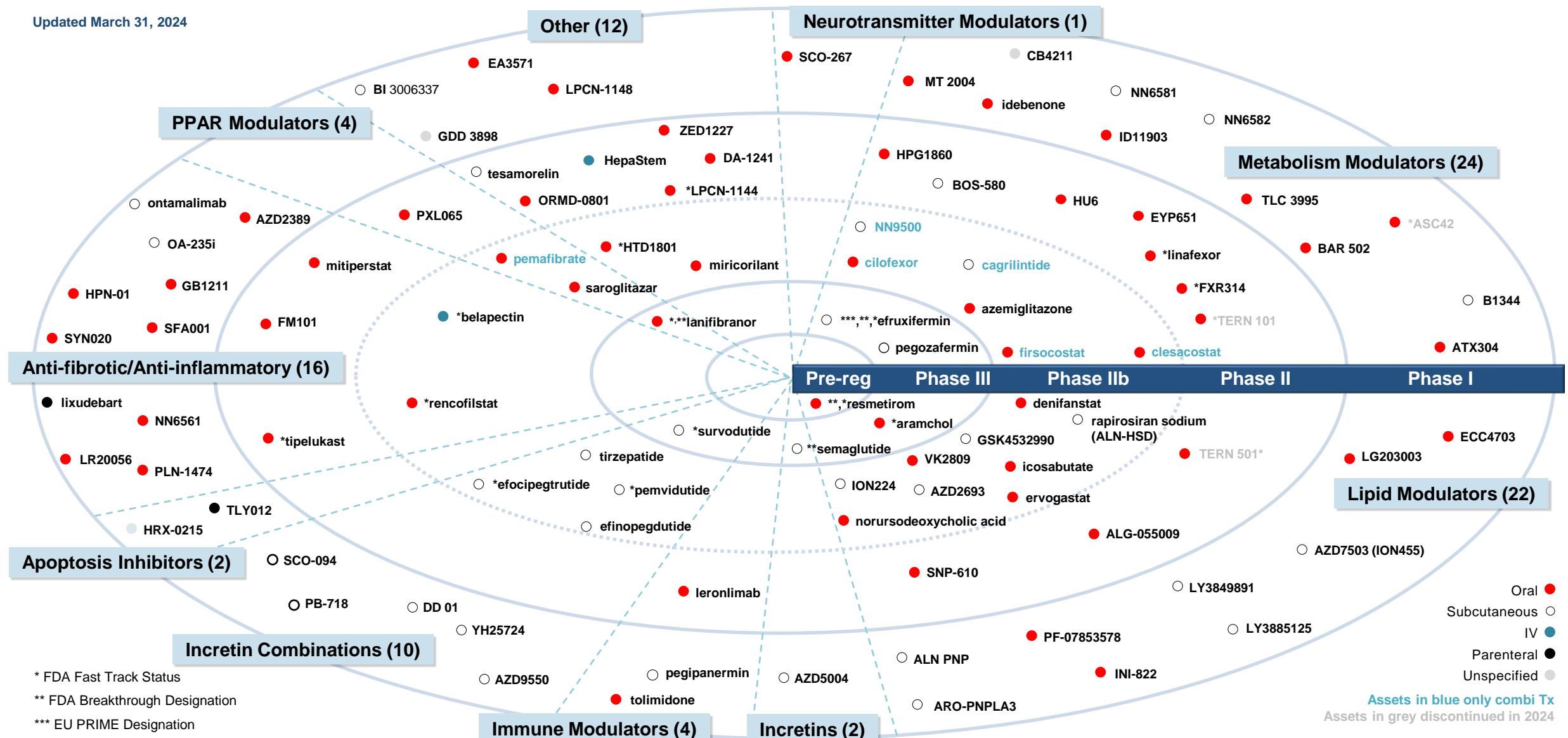
Product		Originator/Licensee	Phase	Status	Region	MOA
<b>MASH</b>	<b>aramchol</b>	Galmed	III	Fast Track Designation	US	bile acid resorption inhibitor
	<b>ASC42</b>	Ascletis	I	Fast Track Designation	US	non-bile FXR agonist
	<b>BI 1467335</b>	BI	disc.	Fast Track Designation	US	AOC3 inhibitor
	<b>cotadutide</b>	AZ	disc.	Fast Track Designation	US	dual GLP-1/GRA
	<b>efinopegdutide</b>	Hanmi/Merck	IIb	Fast Track Designation	US	dual GLP-1/GRA
	<b>efocipegtrutide</b>	Hanmi	IIb	Fast Track Designation	US	triple GLP-1/GRA/GIP agonist
	<b>efruxifermin</b>	Akero	III	PRIME Designation	EU	FGF21
	<b>efruxifermin</b>	Akero	III	Fast Track Designation	US	FGF21
	<b>efruxifermin</b>	Akero	III	Breakthrough Therapy Designation	US	FGF21
	<b>elafibranor</b>	Genfit	disc.	Fast Track Designation	US	dual PPARα/δ agonist
	<b>firsocostat</b>	Gilead	II	Fast Track Designation	US	ACC inhibitor
	<b>fluasterone</b>	Stero	Preclin	Orphan Drug Status	US	glucose-6-P dehydrogenase inhibitor
	<b>HTD1801</b>	Hightide	II	Fast Track Designation	US	undisclosed
	<b>lanifibranor</b>	Inventiva	III	Fast Track Designation	US	PPAR pan agonist
	<b>lanifibranor</b>	Inventiva	III	Breakthrough Therapy Designation	US	PPAR pan agonist
	<b>linafexor</b>	Cascade	II	Fast Track Designation	US	non-bile FXR
	<b>LPCN 1144</b>	Lipocene	II	Fast Track Designation	US	testosterone prodrug
	<b>MET409</b>	Metacrine	disc.	Fast Track Designation	US	non-bile FXR
	<b>MET642</b>	Metacrine	disc.	Fast Track Designation	US	non-bile FXR
	<b>pegozafermin</b>	89bio	III	Breakthrough Therapy Designation	US	FGF21
	<b>pemvidutide</b>	Altimmune	IIb	Fast Track Designation	US	dual GLP-1/GRA
	<b>clesacostat</b>	Pfizer	II	Fast Track Designation	US	ACC inhibitor
	<b>rencofilstat</b>	Hepion	IIb	Fast Track Designation	US	cyclophilin inhibitor

## Agents with Special Regulatory Status (2 of 2)

Product		Originator/Licensee	Phase	Status	Region	MOA
<b>MASH</b>	<b>resmetirom</b>	Madrigal	Approved	Fast Track Designation	US	THRβ agonist
	<b>resmetirom</b>	Madrigal	Approved	Breakthrough Therapy Designation	US	THRβ agonist
	<b>semaglutide SC</b>	Novo Nordisk	III	Breakthrough Therapy Designation	US	GLP-1 agonist
	<b>survotudide</b>	BI	III	Fast Track Designation	US	dual GLP-1/GRA
	<b>TERN-101</b>	Terns	disc.	Fast Track Designation	US	non-bile FXR
	<b>TERN-201</b>	Terns	disc.	Fast Track Designation	US	SSAO inhibitor
	<b>TERN-501</b>	Terns	disc.	Fast Track Designation	US	THRβ agonist
<b>MASH + fibrosis</b>	<b>AXA1125</b>	Axcella	disc.	Fast Track Designation	US	designed amino acid composition
	<b>BMS-986263 (ND-L02-s0201)</b>	Nitto Denko	disc.	Fast Track Designation	US	siRNA against HSP47
	<b>cenicriviroc</b>	Takeda/Allergan/Dong-A	disc.	Fast Track Designation	US	CCR2/CCR5 dual receptor antagonist
	<b>clesacostat/ervogastat</b>	Pfizer	IIb	Fast Track Designation	US	ACC inhibitor/DGAT2 inhibitor
	<b>epeleuton (DS102)</b>	Afimmune	disc.	Fast Track Designation	US	omega 6 fatty acid
	<b>EDP-305</b>	Enanta	disc.	Fast Track Designation	US	non-bile FXR agonist
	<b>belapectin</b>	Galectin	IIb/III	Fast Track Designation	US	galectin-3 inhibitor
	<b>obeticholic acid</b>	Intercept	disc.	Breakthrough Therapy Designation	US	FXR agonist
	<b>pegozafermin</b>	89bio	III	PRIME Designation	EU	FGF21
	<b>tipelukast</b>	MediciNova	II	Fast Track Designation	US	5-lipoxygenase inhibitor
	<b>tropifexor</b>	Novartis	disc.	Fast Track Designation	US	non-bile FXR agonist
	<b>volixibat</b>	Sanofi/Shire/Mirum	disc.	Fast Track Designation	US	bile acid resorption inhibitor
	<b>emricasan</b>	Conatus/Novartis	disc.	Fast Track Designation	US	caspase inhibitor
	<b>lanifibranor</b>	Inventiva	III	Fast Track Designation	US	PPAR pan agonist
<b>MASLD</b>	<b>NS-0200</b>	NuSirt	disc.	Fast Track Designation	US	SIRT-1 activator

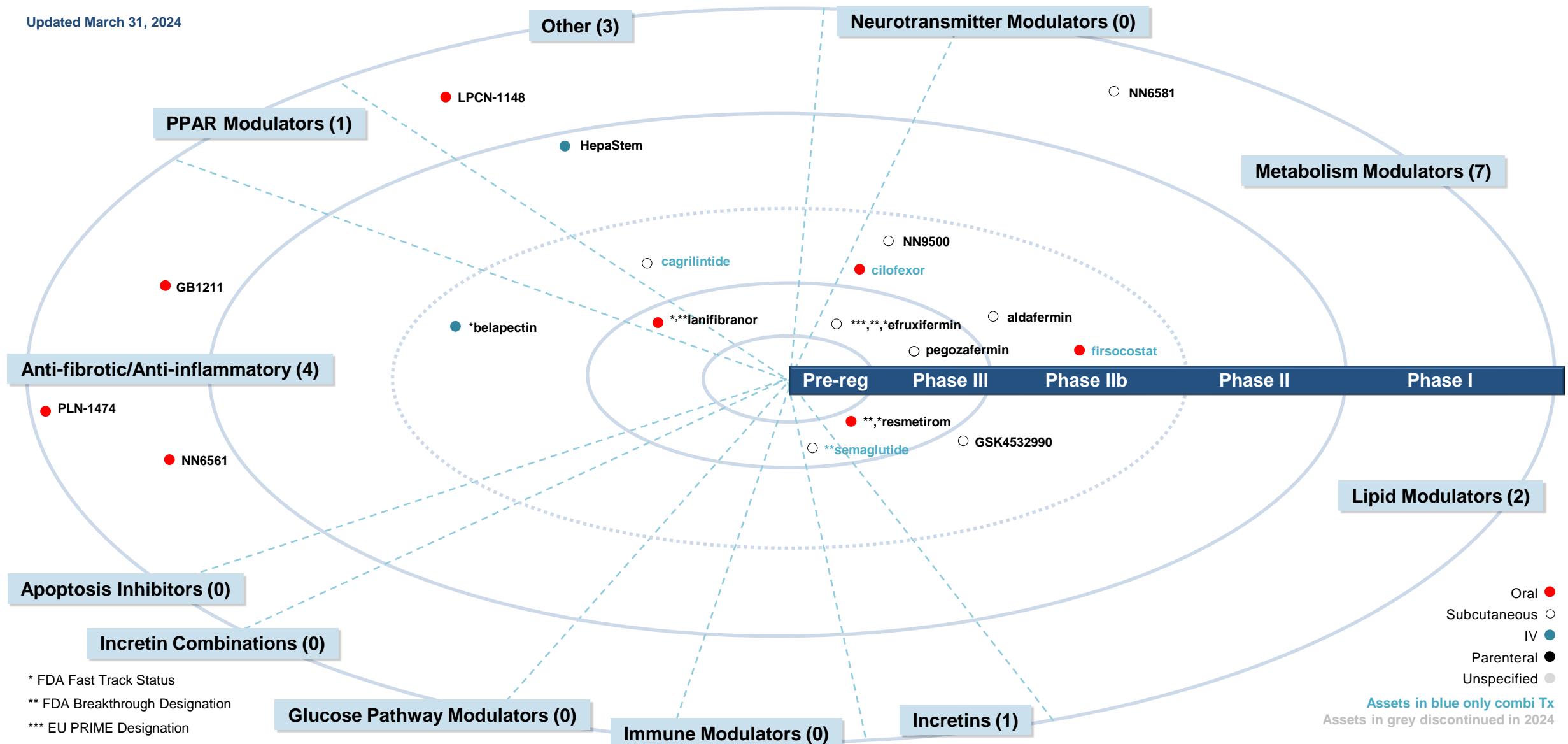
# Agents in development for MASH in US, EU, and Japan – Phase I-III

Updated March 31, 2024



# Agents in development for MASH with compensated cirrhosis (F4)† in US, EU, and Japan – Phase I-III

Updated March 31, 2024



# Agents in Global Development for MASH – Phase I

## Phase I – Global Development

Assets in grey discontinued in 2024; In blue new in 2024

<b>AXD2389</b> 2/2024 (AZ) US undisclosed	<b>SYN-020</b> (Synthetic Biologics) - US alkaline phosphatase	<b>AZD9550</b> (AZ) - UK dual GLP-1/GRA	<b>VK2735</b> (Viking) - Australia dual GLP-1/GIP	<b>ASC42</b> 4/2024 (Gannex) - US non-bile FXR	<b>vutiglabridin</b> (HSG4112) (Glaceum) - S. Korea leptin sensitizer	<b>IMM-H014</b> 1/2024 (Tianjin Chase Sun) - China undisclosed
<b>ECC 0509</b> (Eccogene) - Australia SSAO inhibitor	<b>ZSP1603</b> (Guangdong) - China undisclosed	<b>DD 01</b> (D&D) - S. Korea, US dual GLP-1/GRA	<b>YH25724</b> (Yuhan/Bi) - EU dual GLP-1/FGF21	<b>ATX-304</b> (Amnplifier Tx) - EU AMPK activator	<b>XZP-5610</b> (Xuanzhu) - China FXR agonist	<b>INV-347</b> 1/2024 (Novo Nordisk) - Canada CB1 receptor blocker
<b>GB1211</b> (Galecto) - UK galectin-3 inhibitor	<b>GST-HG151</b> (Fujian Cosunter) - China JNK inhibitor	<b>DR 10624</b> (Zhejiang Doer) - China triple GLP-1/GIP/FGF21	<b>ALN PNP</b> (Alnylam/Regeneron) - US. PNPLA3 RNAi	<b>B1344</b> (Tasly) - US FGF21	<b>XZP-6019</b> (Xuanzhu) - China FXR agonist	<b>monlunabant</b> (INV-202) (Novo Nordisk) - Canada CB1 receptor inv. agonist
<b>HPN-01</b> (Hepanova) - US IkB kinase inhibitor	<b>HRX-0215</b> (HepaRegenix) MKK4 inhibitor	<b>DR 10627</b> (Zhejiang Doer) - China dual GLP-1/GIP	<b>ARO-PNPLA3</b> (Arrowhead) - US siRNA against PNPLA3	<b>BAR 502</b> (Bar Pharma) - Portugal dual FXR/GPBAR1 agonist	<b>BEBT 503</b> (BeBetter Med) - Australia pan PPAR agonist	<b>LB P8</b> (LISCure) - Australia microbiome modulator
<b>lixudebart</b> (Inserm/Alentis) - Switzerland CLDN1 mAb	<b>SRT-015</b> (Seal Rock) - Australia ASK-1 inhibitor	<b>DR 10628</b> (Zhejiang Doer) - China dual GLP-1/GIP	<b>AZD7503</b> (Ionis/AZ) - US HSD17B13 RNAi	<b>CB4211</b> (CohBar) - US MOTSc analog	<b>A 4368</b> (Autophagy Sci.) - S. Korea autophagy activator	<b>LPCN-1148</b> (Lipocine) - US testosterone prodrug
<b>LR20056 (TT-01025)</b> (LG Chem/TransThera) - US SSAO inhibitor	<b>TLY012</b> (Theraly) - US TRAILR2 agonist	<b>AZD5004</b> (AZ) - US oral GLP-1	<b>ECC4703</b> (Eccogene) - US THRβ agonist	<b>ID11903</b> (Ildong) - US non-bile FXR	<b>ALY688</b> (Allysta) - Australia adiponectin RA	<b>OLX75016</b> 2/2024 (OliX) – Australia undisclosed siRNA
<b>NN6561</b> 1/2024 (Novo Nordisk) – EU VAP-1 inhibitor	<b>APX-311</b> (AptaBio) - S. Korea (NOX inhibitor)	<b>ecnoglutide</b> (Sciwind) - Australia GLP-1 agonist	<b>INI-822</b> (Inipharm) HSD17B13 inhibitor	<b>idebenone</b> (Santhera) - US Coenzyme Q10	<b>BI 3006337</b> (Bi) - US undisclosed	<b>SCO-267</b> (Scobia) - Japan GPR40 agonist
<b>NP011</b> (NEXEL) - S. Korea TGF-β inhibitor	<b>mosedipimod</b> (Enzychem) - S. Korea TLR4 inhibitor	<b>GMA 106</b> (Gmax) - Australia dual GLP-1agonist/GIP ant.	<b>LG203003</b> (LG Chem) - US DGAT2 inhibitor	<b>MT 2004</b> (Xi'an Biocare) - US non-bile FXR	<b>EA3571</b> (EA Pharma) - Japan undisclosed	<b>SNP-630</b> (Sinew) - Taiwan CYP2E1 inhibitor
<b>OA-235i</b> (Oasis) - US PAR2 inhibitor	<b>NXC 736</b> (NextGen) - S. Korea NLRP3 inflammasome inhib	<b>HEC88473</b> (HEC Pharm) - China dual FGF21/GLP-1	<b>LY3849891</b> (Lilly) PNPLA3 siRNA	<b>NN6581</b> (Novo Nordisk) - UK MARC1 siRNA	<b>GDD 3898</b> (Lipidio) - US undisclosed	<b>SYHA 1805</b> (CSPC) - China undisclosed
<b>ontamalimab</b> (Takeda) – undisclosed MADCAM1 mAb	<b>pegipanermin (LIVNate)</b> (INmune) - US TNF inhibitor	<b>KN 056</b> 1/2024 (Alphamab/Tebao) – China GLP-1	<b>LY3885125</b> (Lilly) – US SCAP siRNA	<b>NN6582</b> (Novo Nordisk) - Austria LXRx siRNA	<b>GH509</b> (1Globe) - China undisclosed	<b>TB-840</b> (Therasid) - S. Korea undisclosed
<b>PLN-1474</b> (Pliant) - US integrin inhibitor	<b>tolimidone</b> (Melior) - US Lyn kinase stimulant	<b>PB-718</b> (PegBio) - US dual GLP-1/GRA	<b>PF-07853578</b> (Pfizer) – US PNPLA3 modulator	<b>TLC-2712</b> (Orsobio) - NZ LXR inverse agonist	<b>GM-60106</b> (JD Bioscience) - Australia 5-HT2A agonist	<b>ZSP0678</b> (Guangdong) - China undisclosed
<b>SFA001</b> (SFA Therapeutics) - US microbiome derived agent	<b>AP 026</b> (Sino) - China dual GLP-1/FGF21	<b>SCO-094</b> (Scochia) - Japan dual GLP-1/GIP	<b>RJ4287</b> (Nanjing Ruijie) – China THRβ agonist	<b>TLC 3995</b> (Shionogi/Orsobio) - Japan ACC2 inhibitor	<b>HS 10356</b> (Jiangsu Hansoh) - China undisclosed antiviral	

Anti-fibrotic/Anti-inflam.

Apoptosis Inhibitors

Immune Modulators

Incretins/Glucose Mod.

Lipid Modulator

Metabolism Modulator

PPAR Modulator

Other

## Agents in Global Development for MASH – Phase IIa

### Phase IIa – Global Development

<b>FM101</b> (Future Medicine) <a href="#">NCT04710524</a> - Hungary A3AR agonist	<b>BOS-580</b> (Boston Ph./Novartis) <a href="#">NCT04880031</a> - US FGF21	<b>ALS-L1023</b> (AngioLab) <a href="#">NCT04342793</a> S. Korea MMP inhibitor
<b>IVB001</b> (VGI Health) - Australia tocotrienol	<b>EYP651</b> (Enyo) - France non-bile FXR	<b>DA-1241</b> (DongA/NeuroBo) <a href="#">NCT06054815</a> – US GPR119 agonist
<b>mitiperstat</b> (AZ) <a href="#">COSMOS</a> - US, EU myeloperoxidase modulator	<b>FXR314</b> (was MET642) (Organovo) - US non-bile FXR	<b>HepaStem</b> (Cellaion) - <a href="#">PANASH</a> EU cell-based therapy
<b>tipelukast</b> (MediciNova) <a href="#">NCT05464784</a> - US 5-LO/LTC4	<b>HEC96719</b> (Sunshine Lake) <a href="#">NCT05397379</a> - China FXR agonist	<b>LPCN-1144</b> (Lipocene) <a href="#">LiFT</a> - US testosterone prodrug
<b>JKB-122</b> (Jenken, Taiwan) <a href="#">NCT04255069</a> - Taiwan TLR4 antagonist	<b>HPG 1860</b> (Hepagene) <a href="#">RISE</a> - US non-bile FXR	<b>pegarginimase</b> (Polaris) <a href="#">NCT05842512</a> – Taiwan arginine deiminase replacement
<b>leronlimab</b> (CytoDyn) – <a href="#">NCT04521114</a> US CCR5 antagonist	<b>HU6</b> (Rivus) <a href="#">NCT04874233</a> - US mitochondrial uncoupler	<b>tesmorelin</b> (Theratechnologies) <a href="#">NCT03375788</a> - US GHRF analog
<b>ORMD-0801</b> (Oramed) <a href="#">NCT02653300</a> - Israel oral insulin	<b>J2H 1702</b> (J2H) <a href="#">NCT06297434</a> - S. Korea 11β-HSD1 inhibitor	<b>ZED1227</b> (Dr. Falk) <a href="#">EudraCT2021-002253-29</a> - EU transglutaminase 2 blocker
<b>ALG-055009 3/2024</b> (Aligos) <a href="#">HERALD</a> - US THR $\beta$ agonist	<b>linafexor</b> (Cascade) <a href="#">NCT05591079</a> - US non-bile FXR	
<b>SNP610</b> (Microbio) <a href="#">NCT03468556</a> - US, Taiwan CYP2E1/DGAT1	<b>chiglitazar</b> (Chipscreen) <a href="#">NCT05193916</a> - China PPAR $\delta/\gamma$ agonist	
<b>TERN-501 1/2024</b> (Terns) <a href="#">DUET</a> - US THR $\beta$ agonist	<b>PXL065</b> (Poxel) <a href="#">DESTINY 1</a> - US MPC inhibitor	

Anti-fibrotic/Anti-inflam.

Apoptosis Inhibitors

Immune Modulators

Incretins/Glucose Mod.

Lipid Modulator

Metabolism Modulator

PPAR Modulator

Other

Assets in grey discontinued (mono Tx) in 2023  
In blue new in 2023

## Agents in Global Development for MASH – Phase IIb

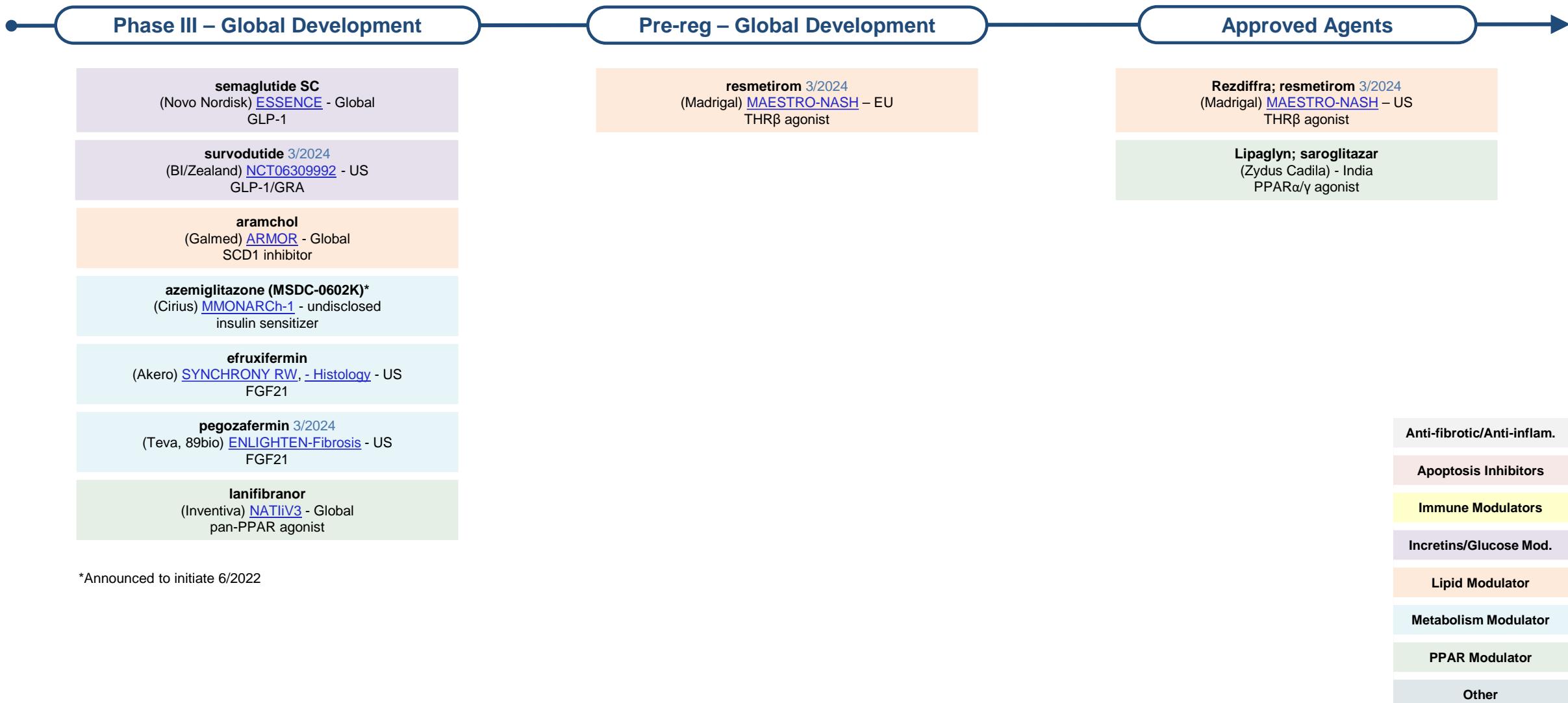
### Phase IIb – Global Development

<b>belapectin</b> (Galectin) <a href="#">NAVIGATE</a> - US galectin-3 inhibitor	<b>ervogastat (PF-06865571)</b> (Pfizer) <a href="#">MIRNA</a> - US DGAT2 inhibitor	<b>azemiglitazone (MSDC-0602K)*</b> (Cirius) <a href="#">EMMINENCE</a> - US Insulin sensitizer
<b>namodenoson</b> (Can-Fite) <a href="#">NCT04697810</a> - Israel A3 agonist	<b>GSK-4532990 (ARO-HSD)</b> (Arrowhead, GSK) <a href="#">HORIZON</a> - US HSD17B13 siRNA	<b>Lipaglyn, saro glitazar</b> (Zydus Cadila) <a href="#">NCT05011305</a> - US PPAR $\alpha/\gamma$ agonist
<b>rencofilstat</b> (Hepion) <a href="#">ASCEND-NASH</a> - US cyclophilin inhibitor	<b>HSK31679</b> (Haisco) <a href="#">NCT06168383</a> - China THR $\beta$ agonist	<b>HTD1801</b> (HighTide) <a href="#">MONARCH</a> - undisclosed glucocorticoid receptor antagonist
<b>efinopegdutide</b> (Hanmi/Merck) <a href="#">NCT05877547</a> - Global GLP-1/GRA	<b>icosabutate</b> (NorthSea) <a href="#">ICONA</a> - US structurally enhanced omega-3 FA	<b>miricorilant</b> (Corcept) <a href="#">CENTRICITY</a> - US berberine/ursodeoxycholic acid
<b>efocipegrutide (HM15211)</b> (Hanmi) <a href="#">NCT04505436</a> - US/S. Korea GLP-1/GIP/GRA	<b>ION224</b> (Ionis) <a href="#">NCT04932512</a> - US DGAT2 inhibitor	<b>ZSP1601</b> (Guangdong Raynovent) <a href="#">NCT05692492</a> - China PDE inhibitor
<b>pemvidutide</b> (Altimmune) <a href="#">IMPACT</a> - US dual GLP-1/GRA	<b>norursodeoxycholic acid</b> (Dr. Falk) <a href="#">EudraCT2018-003443-31</a> - EU homolog of ursodeoxycholic acid	Anti-fibrotic/Anti-inflam.
<b>tirzepatide</b> (Lilly) <a href="#">SYNERGY-NASH</a> - Global dual GLP-1/GIP	<b>rapirostiran sodium</b> (Alnylam, Regeneron) <a href="#">NCT05519475</a> - US, Japan HSD17B13 siRNA	Apoptosis Inhibitors
<b>ASC41</b> (Asclexis) <a href="#">NCT05118360</a> - China THR $\beta$ agonist	<b>VK2809</b> (Viking) <a href="#">NCT02927184</a> - US THR $\beta$ agonist	Immune Modulators
<b>AZD2693</b> (Ionis/AZ) - Global <a href="#">FORTUNA</a> PNPLA3 inhibitor	<b>VSA006 4/2024</b> (Visirna) <a href="#">NCT06322628</a> - China HSD17B13 siRNA	Incretins/Glucose Mod.
<b>denifanstat</b> (Sagimet) <a href="#">FASCINATE-2</a> - US, ROW FASN inhibitor	<b>aldafermin F4</b> (NGM) <a href="#">NCT02443116</a> - Australia, US FGF-19	Lipid Modulator
		Metabolism Modulator
		PPAR Modulator
		Other

\*Phase III announced to initiate 6/2022

Assets in grey discontinued (mono Tx) in 2024  
In blue new in 2024

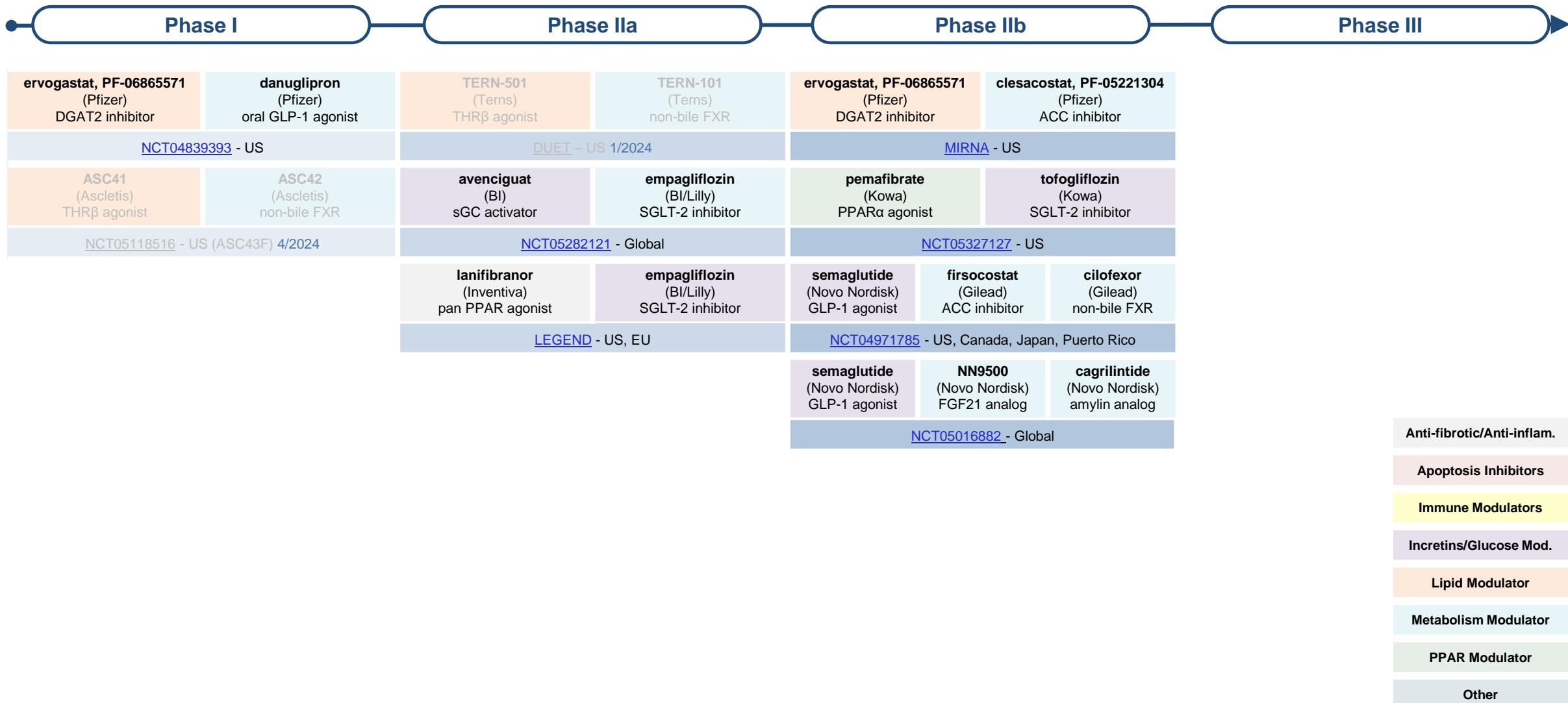
## Agents in Global Development for MASH – Phase III



\*Announced to initiate 6/2022

Assets in grey discontinued (mono Tx) in 2024  
In blue new in 2024

# Agents in Global Development for MASH – Combination Therapy



Assets in grey discontinued (mono Tx) in 2024  
In blue new in 2024

## Profiled products ranked by number in subclass

Class	Subclass	Phase II	Phase IIb	Phase III	PreReg	Marketed	Total
Lipid Modulators	Other	0	5	0	0	0	5
Antifibrotic/Antiinflammatory	Other	3	1	0	0	0	4
Combinations/Multi-MOA	Other	0	4	0	0	0	4
Metabolism Modulators	FGF19 and FGF21	1	1	2	0	0	4
Other	Other	2	2	0	0	0	4
Incretin Combinations	dual GLP-1/GRA	0	2	1	0	0	3
Lipid Modulators	THR beta agonists	1	2	0	0	0	3
Lipid Modulators	DGAT1 or DGAT2 inhibitors	0	2	0	0	0	2
Metabolism Modulators	FXR or LXR Modulators	2	0	0	0	0	2
Metabolism Modulators	Other	1	1	0	0	0	2
Antifibrotic/Antiinflammatory	Galectin 3 inhibitors	0	1	0	0	0	1
Immune Modulators	Chemokine Modulators	1	0	0	0	0	1
Incretins	GLP-1 agonists	0	0	1	0	0	1
Incretin Combinations	dual GLP-1/GIP agonist	0	1	0	0	0	1
Incretin Combinations	triple GLP-1/GIP/GRA	0	1	0	0	0	1
Insulins	Prandial Insulin	1	0	0	0	0	1
Lipid Modulators	Omega-3 Fatty Acids	0	1	0	0	0	1
Lipid Modulators	SCD1 Modulators	0	0	1	0	0	1
PPAR Modulators	Pan Agonists	0	0	1	0	0	1
PPAR Modulators	$\alpha/\gamma$ Agonists	1	0	0	0	1 (India)	1
PPAR Modulators	MPC inhibitor	1	0	0	0	0	1

# Anti-fibrotic/Anti-inflammatory Agents

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# belapectin

Status	Companies	MOA/ROA	Target Population	Next Milestone		
Phase IIb cirrhotic MASH (US June 2015) discontinued non-cirrhotic MASH (US Sep. 2016)	Galectin (Originator)	galectin 3 inhibitor IV (Q2W)	MASH with cirrhosis	• 4Q 2024: Expected interim analysis from Phase IIb part of NAVIGATE		
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels		
<ul style="list-style-type: none"> <li>Purported to reverse fibrosis</li> <li>Every other week dosing</li> <li>US Fast Track Designation for MASH with fibrosis</li> </ul>		<ul style="list-style-type: none"> <li>Injectable</li> <li>Failed to improve fibrosis (by LiverMultiScan, FibroScan, MRE) in Phase II NASH-FX</li> <li>Development by a small biopharmaceutical company</li> </ul>				
Key Milestones				CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>April 2020:</b> Galectin releases details of Phase II/III trial NASH-RX in MASH cirrhosis patients with no baseline varices</li> <li><b>Aug. 2019:</b> Galectin submits Type C Written Response to the FDA; expecting to initiate Phase III NASH-RX of belapectin in MASH patients with cirrhosis in Q4 2019</li> <li><b>May 2018:</b> Galectin continues Phase III plans for belapectin, not granted Breakthrough Therapy Designation by the US FDA</li> <li><b>Feb. 2018:</b> Galectin completes US Phase IIb, NASH-CX, of belapectin in MASH patients with cirrhosis</li> <li><b>Dec. 2017:</b> Galectin fails to meet primary endpoint of Phase IIb, NASH-CX, of belapectin, positive data in subgroup of cirrhotic patients without varices</li> <li><b>Sep. 2016:</b> Belapectin fails Phase II NASH-FX in MASH with fibrosis</li> <li><b>June 2015:</b> Phase II NASH-CX of belapectin in MASH with cirrhosis initiated</li> <li><b>May 2015:</b> FDA does not grant Special Protocol Assessment (SPA) for Phase II NASH-CX</li> <li><b>Aug. 2013:</b> Belapectin receives FDA Fast Track Designation in MASH with fibrosis</li> </ul>				<p>Preclinical evidence suggests galectin-3 is essential for development of liver fibrosis, hence belapectin is thought to prevent fibrosis by inhibiting galectin-3. While the FDA did not grant a Special Protocol Assessment (SPA) for Phase III NAVIGATE (was NASH-RX), Galectin opted to take the FDA's feedback and proceed with this trial as a Phase IIb trial, rather than resubmit the SPA in an attempt to obtain Phase III status for NAVIGATE.</p> <p>After failing NASH-FX in MASH patients with fibrosis in 2016, Galectin stated that belapectin's primary indication is MASH with cirrhosis, hoping NASH-CX in cirrhosis could have been registrational. Although NASH-CX did not meet its primary endpoint of improving HVPG, a distinct patient population with well-compensated cirrhosis and no esophageal varices who may benefit from belapectin treatment was identified. Since more than 90% of cirrhotic patients develop esophageal varices, the reduction in development of new esophageal varices in patients with no baseline varices with belapectin seems promising.</p> <p>In May 2018, Galectin met with the US FDA to seek an agreement on a plan for a Phase III trial of belapectin in cirrhotic MASH patients without varices. The company announced to be moving forward with Phase III plans despite the FDA rejecting Breakthrough Therapy Designation for belapectin for MASH with cirrhosis without esophageal varices. In April 2020, Galectin released the protocol for Phase IIb/III trial NAVIGATE and the first patient was enrolled in June 2020. Further details regarding the adaptive trial design were presented at AASLD 2021.</p>		

## belapectin - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>NAVIGATE</b> Phase II/III - Global <a href="#">NCT04365868</a> Start: June 2020 1° Completion: Dec. 2024 Completion: Dec. 2024	1010 MASH patients with cirrhosis without esophageal gastroesophageal, or isolated gastric varices aged 15-75 years with portal hypertension and ≥2 of the following: platelet count <150,000/mm <sup>3</sup> , spleen size ≥15cm, or collateral vessels, histological MASH F4 or MASH with ≥1 of the following: obesity: BMI ≥30kg/m <sup>2</sup> or waist circumference ≥102cm (men) or ≥88cm (women), hypertension: use of anti-hypertensive drug for ≥1 year or sBP/dBP >140/80mmHg, T2D: use of anti-diabetic medication for ≥1 year or A1c 6.5-9.5%, or dyslipidemia: treatment for hypertriglyceridemia for ≥6 months or TG ≥150mg/dL, HDL ≤40mg/dL (men) or ≤50mg/dL (women), if treated with vitamin E, pioglitazone, and/or statin on stable dose ≥3 months 357 of 1,010 patients will be enrolled in the Phase IIb part of the trial	belapectin (2 or 4mg/kg lean body mass IV Q2W) vs. placebo for 78 weeks	<b>Primary Endpoint:</b> proportion of patients developing new esophageal varices from baseline at 78 weeks
<b>NASH-CX</b> Phase II - US <a href="#">NCT02462967</a> Start: June 2015 1° Completed: Oct. 2017 <b>Completed:</b> Oct. 2017	162 MASH patients aged 18-75 years with hepatic venous pressure gradient (HVPG) ≥6 mmHg, biopsy confirmed cirrhosis (Ishak stage 5-6)	belapectin (2 or 8 mg/kg, IV infusion) vs. placebo every other week for 1 year (26 doses)	<b>Primary Endpoint:</b> change in hepatic venous pressure gradient (HVPG) vs. placebo at 1 year <u>Press release December 2017 and ILC 2018:</u> <b>All patients:</b> <ul style="list-style-type: none"><li>- belapectin did not meet primary endpoint of absolute reduction of HVPG at 1 year vs. pbo.</li><li>- belapectin sign. improved hepatocyte ballooning vs. pbo.</li></ul> <b>Patients with no baseline varices:</b> <ul style="list-style-type: none"><li>- belapectin 2mg/kg sign. reduced HVPG in pts with no baseline esophageal varices.</li><li>- Development of new esophageal varices in pts with no BL varices was sign. reduced with belapectin.</li><li>- In pts with mild BL portal hypertension (mean HVPG 7.8mmHg) HVPG increased by 25% in the pbo group, while belapectin reduced HVPG relative to BL (-4 and -3% for 2mg/kg and 8mg/kg doses, respectively).</li><li>- In pts with sign. portal hypertension at baseline (mean HVPG 13.4mmHg), absolute HVPG was reduced sign. in the 2mg/kg belapectin group vs. pbo.</li><li>- No effect on fibrosis or NAS, but there was a statistically sign. improvement in hepatocyte ballooning with 2mg/kg belapectin and a trend with 8mg/kg belapectin vs. pbo.</li></ul> <b>Responder analysis, pts with an absolute reduction of ≥2mmHg or ≥20% of HPVG from BL:</b> <ul style="list-style-type: none"><li>- In responder pts without esophageal varices, 2mg/kg dose belapectin reduced of HPVG ≥2mmHg in more pts vs. pbo (44 vs. 15%) and ≥20% HVPG reduction (40 vs. 15%).</li><li>- belapectin was well-tolerated and no safety concerns were identified; ten pts discontinued the trial before end of treatment.</li></ul>

FM101

FM101				Next Milestone
Status	Companies	MOA/ROA	Target Population	Aug. 2023: Expected completion of Phase II <a href="#">NCT04710524</a>
Phase II non-cirrhotic MASH (EU May 2021)	Future Medicine (Originator)	A3AR agonist oral	MASH with fibrosis	
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Anti-inflammatory and antifibrotic activity in MASH animal models</li> <li>Also in development for glaucoma, diabetic nephropathies, ocular hypertension, and PBC</li> </ul>		<ul style="list-style-type: none"> <li>Other A3AR agonists namodenoson (CanFite) and PBF-1650 (Palobiofarma)</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Jan. 2021:</b> Future Medicine plans a Phase II trial in MASLD/MASH patients</li> </ul>		<p>FM101 is a potent modulator of human A3 adenosine receptor (A3AR) over-expressed in inflammatory cells. Data from a first-in-human study presented at ILC 2020 (FRI096) showed FM101 was well-tolerated in healthy subjects.</p>		
2024 Sentinels				

## FM101 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - Hungary, Poland, Spain  <a href="#">NCT04710524</a>          Start: June 2021          1° Completion: May 2023          Completion: Aug. 2023</p>	<p>60 patients aged ≥18 years, MASH (≥1 point in steatosis, ballooning, and inflammation score) with F1-F3 OR MASLD with ≥3 of: FPG ≥100mg/dL, HDL-C &lt;40 or 50mg/dL, waist circumference &gt;102 or 88cm (men and women, respectively), TG ≥150mg/dL or on TG lowering medication, SBP ≥130mmHg or DBP ≥85mmHg or on anti-hypertensive medication, ALT &gt;1xULN, liver fat ≥8%, MRE ≥2.9kPa</p>	<p>FM101 (oral 150 or 300mg BID) vs. placebo for 13 weeks (was 28 days); on day 91 (final day) only single dose</p>	<p><b>Primary Endpoints:</b>          - TEAEs up to day 106          - change in ALT from baseline at 91 days</p>

mitiperstat				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US Oct. 2022)	AstraZeneca (Originator)	myeloperoxidase inhibitor oral	MASH with fibrosis	• 1H 2024: Expected data from Phase II trial COSMOS
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>In development for the treatment of pulmonary hypertension and HF</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Dec. 2022:</b> AZ has initiated a Phase II trial in MASH F2-F3</li> </ul>		<p>Myeloperoxidase is an enzyme stored in azurophilic granules of polymorphonuclear neutrophils and macrophages and released into the extracellular fluid during inflammation. Mitiperstat shows potent target engagement, and in 4Q 2022, AZ initiated a Phase I trial in MASH patients with F2-F3.</p>		

## mitiperstat - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>COSMOS</b> Phase II - US, Argentina, Denmark, Italy, Mexico, Norway, Portugal, Spain, Sweden <a href="#">NCT05638737</a> Start: Oct. 2022 1° Completion: April 2024 <b>Completed:</b> April 2024	122 MASH patients aged 18-75 years, NAS ≥4 (≥1 in each of steatosis, lobular inflammation, and ballooning), F2-F3, ALT >ULN to <200U/L, stable body weight (≤5% change for 3 months prior to screening)	mitiperstat (oral 5mg dosing frequency not disclosed) vs. placebo	<b>Primary Endpoint:</b> change in ALT from baseline at 12 weeks

rencofilstat				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (Global Sep. 2022)	Hepion (Owner, Global), Isotechnika (Originator)	cyclophilin inhibitor oral (QD)	MASH with fibrosis	• Sep. 2025: Expected completion of Phase IIb trial ASCEND-NASH
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Marked in vivo anti-fibrotic effects in a wide range of animal models</li> <li>Fast Track Designation from the US FDA</li> <li>In Phase II development for HCC</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Dec. 2023:</b> Hepion announced a strategic restructuring considering acquisition, merger and alike to fund future development in MASH</li> <li><b>Nov. 2021:</b> Rencofilstat receives Fast Track Designation from the US FDA</li> <li><b>Sep. 2021:</b> Hepion plans Phase IIb trial ASCEND-NASH in MASH F2-F3</li> <li><b>Dec. 2020:</b> Topline data from Phase IIa AMBITION show improvement in liver enzymes</li> <li><b>Oct. 2020:</b> Hepion rolls out proprietary AI machine learning platform AI-POWR</li> <li><b>May 2020:</b> Hepion plans US Phase IIa trial in presumed MASH F2-F3</li> </ul>		<p>Rencofilstat is a cyclophilin inhibitor in development for MASH, HCC, and viral hepatitis by Hepion. Data from Phase IIa trial AMBITION, showed beneficial effects of rencofilstat on liver enzymes after 4 weeks of treatment; further outcome measures include non-invasive markers of fibrosis. Data from Phase I and II trials of rencofilstat as well as pre-clinical data were analyzed using Hepion's artificial intelligence platform AI-POWR to enrich design of Phase IIb trial ASCEND-NASH initiated in August 2022.</p> <p>In December 2023, Hepion announced a strategic restructuring plan considering acquisition, merger, reverse merger, other business combination, sale of assets, licensing, and other strategic transactions. ASCEND-NASH thus far has enrolled 131 patients, and the Company intends to complete treatment of these patients and enroll additional patients once the trial is fully funded, or a strategic transaction entered.</p>		

## rencofilstat - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>ASCEND-NASH</b> Phase IIb - US, Germany, France, Italy, Spain, Mexico, Hungary <a href="#">NCT05402371</a> Start: Oct. 2022 1° Completion: May 2025 Completion: Sep. 2025	336 MASH patients with F2-F3 aged ≥18 years, NAS ≥4 (≥1 point in each of lobular inflammation and ballooning)	rencofilstat (oral 75, 150, or 225mg QD) vs. placebo for 12 months	<b>Primary Endpoints:</b> - ≥1 stage improvement in fibrosis without worsening in MASH OR - MASH resolution without worsening in fibrosis from baseline at 12 months
<b>ALTITUDE-NASH</b> Phase IIb - US <a href="#">NCT05402371</a> Start: Sep. 2022 1° Completion: June 2023 Completion: Sep. 2023	61 patients aged 18-75 years with presumed MASH F3 based on Agile 3+ (≥0.53) or historic biopsy, BMI >25kg/m <sup>2</sup>	rencofilstat (oral 75, 150, or 225mg QD) vs. placebo for 4 months	<b>Primary Endpoints:</b> - hepatic function from baseline at 4 months by HepQuant SHUNT from baseline at 120 days - TEAEs up to 120 days <u>May 2023:</u> - Rencofilstat met the primary endpoint showing improved physiologic liver function at 4. - in 34 pts with the most advanced functional impairment at baseline (DSI >17), rencofilstat showed even greater improvements in physiologic liver function. - Rencofilstat improved ALT and AST as well as fibrosis markers PRO-C3, PIIINP, TIMP1, HA, and ELF score (composite of PIIINP, TIMP1, and HA).
<b>AMBITION</b> Phase II - US <a href="#">NCT04480710</a> Start: June 2020 1° Completed: June 2021 <b>Completed:</b> Oct. 2021	49 adult patients with presumed MASH and F2-F3	rencofilstat (oral 75 or 225mg QD) vs. placebo for 28 days	<b>Primary Endpoint:</b> safety, tolerability, and PK from baseline at 28 days <u>Press release Dec. 2020 + July 2021 + Sep. 2021:</u> - Rencofilstat (both doses) was generally safe and well-tolerated with no SAEs and few AEs, which were mostly mild and unrelated to study drug. - Rencofilstat reached max concentrations within two hours after dosing with an effective half-life of approximately 30h, supporting QD dosing. - Rencofilstat (both doses) reduced ALT, which achieved statistical sign. when pooling the two dose-groups vs. pbo. - ALT reduction with rencofilstat (both doses) was lowered up to 10-15%. - In pts with BL PRO-C3 levels >17.5ng/mL, rencofilstat (225mg; N=7) decreased PRO-C3 by -7.9% (-2.1ng/mL) and -22.4% (-11.6ng/mL) vs. +3.5% (+0.7ng/mL) and -4.7% (-1.6ng/mL) for pbo (N=9) at days 28 and 42, respectively. - rencofilstat (75mg; N=11) decreased PRO-C3 by -9.1% at day 42, indicating dose-dependent effect. - In pts with baseline PRO-C3 levels >15.0ng/mL, rencofilstat (225mg; N=9) decreased PRO-C3 levels by -4.1% and -14.3% vs. +1.5% and -8.8% for placebo (N=9) at days 28 and 42, respectively. - The reductions in PRO-C3 mirror previously reported dose-dependent improvements in ALT. - Based on rencofilstat exposure, baseline ALT, PRO-C3, and additional demographic/clinical measures, PK/PD analyses using Hepion's AI-POWR predicted individual pt ALT and PRO-C3 responses. - Analysis of full-genome RNA transcriptomics showed rencofilstat elicited changes in gene-expression in six collagen isoforms, and multiple structural and enzymatic elements of the fibrotic matrix. - Rencofilstat (75mg) was generally safe and well-tolerated. - Drug exposure was similar to previous findings in healthy individuals.

# tipelukast

## Next Milestone

- Dec. 2024: Expected completion of US Phase II trial

Status	Companies	MOA/ROA	Target Population
Phase II non-cirrhotic MASH (US Nov. 2015)	Kyorin (Originator), MediciNova (ex-JP, China, Taiwan, S. Korea)	5-lipoxygenase inhibitor oral	MASH with fibrosis

### Strengths/Opportunities

- Safe and well-tolerated in MediciNova's asthma program (more than 600 patients exposed)
- Fast Track Designation for MASH with fibrosis
- Also in development for idiopathic pulmonary fibrosis (Phase II, with Orphan Drug status and granted US Fast Track status in Sep. 2015)

### Weaknesses/Threats

- Development in asthma was discontinued after testing showed that multiple doses per day were required for therapeutic effect
- Development by a small biopharmaceutical company

## 2024 Sentinels

### Key Milestones

- April 2022:** MediciNova announces US Phase II trial in MASLD with T2D and hypertriglyceridemia
- May 2021:** MediciNova is planning a Phase II trial in MASH
- April 2018:** Tipelukast reduces triglyceride levels in patients with MASLD and MASH
- April 2018:** MediciNova terminates US Phase II trial of tipelukast based on positive interim results
- July 2016:** MediciNova relaxes enrollment criteria, increases patient numbers in newly initiated Phase II of tipelukast
- March 2016:** MediciNova initiates Phase II trial of tipelukast in MASH with hypertriglyceridemia
- Nov. 2015:** Phase IIa of tipelukast in MASH with hypertriglyceridemia initiated

### CVrg Synopsis

Since licensing tipelukast from Kyorin in 2002, MediciNova holds exclusive global development and commercialization rights for tipelukast. In March 2015, tipelukast entered Phase II development in MASH patients with fibrosis with expected completion in December 2018. In April 2018, interim results showing tipelukast meeting the primary endpoint of reducing serum triglycerides were met, and MediciNova decided to discontinue enrollment and terminate the study to further accelerate development of tipelukast; more detailed interim results were presented at ILC 2018. In their 2Q 2021 earnings call, MediciNova stated to be working with collaborators planning a larger Phase II trial of tipelukast in MASH, and in July 2022 a US Phase II trial of tipelukast in patients with MASLD, T2D, and hypertriglyceridemia was initiated.

## tipelukast - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II – US  <a href="#">NCT05464784</a>          Start: Aug. 2022          1° Completion: June 2024          Completion: Dec. 2024</p>	<p>40 MASLD patients with T2D aged 21-75 years, A1c &gt;6.55% to ≤10%, TG &gt;150mg/dL, liver fat ≥8% by MRI-PDFF, taking OAD for 3 months, without advanced fibrosis</p>	<p>tipelukast (oral 500mg QD) vs. placebo for 24 weeks</p>	<p><b>Primary Endpoints:</b>          - change in CAP by FibroScan from baseline at 24 weeks          - change in fasting serum TG from baseline at 24 weeks</p>
<p>Phase II - US  <a href="#">NCT02681055</a>          Start: March 2016          1° Completed: May 2018  <b>Completed:</b> Oct. 2019</p>	<p>19 MASLD/MASH patients aged ≥18 years with fasting TG &gt;150mg/dL, BMI ≤45kg/m<sup>2</sup>, +/- stable (≥ 4 months) dose of anti-diabetic medications, fibrates, statins, niacin, or ezetimibe</p>	<p>tipelukast (oral 250mg) QD for the first 4 weeks, then BID for the next 8 weeks</p>	<p><b>Primary Endpoint:</b> change in triglyceride levels and cholesterol efflux capacity from baseline at 12 weeks  <u>Press release April 2018 + ILC 2018:</u>          Interim analysis of 15 pts:          - At 4 weeks, tipelukast sign. reduced serum TG in 14 of 15 pts by -135.7mg/dL (-41.3%).          - When excluding one pt with BL TG of 1,288mg/dL (300mg/dL at 8 weeks), tipelukast reduced serum TG by -74.9mg/dL (-28.8%).          - No clinically sign. safety or tolerability issues were observed during the study.  <u>IDF 2022:</u>          - The lipid profile in pts was generally worse at BL in pts with T2D, showing higher TG, total cholesterol, and LDL-C, and lower HDL-C vs. non-T2D.          - A trend towards greater reduction of TG was seen in T2D vs. non-T2D (<math>P=0.098</math>), while improvements in HDL-C were sign. greater in T2D pts vs. non-T2D (<math>P&lt;0.0002</math>).          - No difference between T2D and non-T2D was seen for improvements in total cholesterol and LDL-C.</p>

# Combinations/Multi-MOA

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cagrilintide/ NN9500/ semaglutide				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (Global Sep. 2021)	Novo Nordisk (Originator)	amylin analog/ FGF21/ GLP-1 agonist SC (QW)	MASH with fibrosis, obesity	<ul style="list-style-type: none"> <li>2Q 2024: Expected primary completion of Phase IIb trial</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Complimentary MOAs targeting different aspects of the disease</li> <li>Potent weight loss</li> </ul>		<ul style="list-style-type: none"> <li>SC administration</li> <li>GI upset</li> <li>Other late-stage mono/combination therapies in development for the treatment of MASH</li> </ul>		2024 Sentinels
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Aug. 2021:</b> Novo Nordisk plans global Phase IIb trial in MASH with F2-F4</li> </ul>		<p>Long-acting amylin analog cagrilintide is in Phase III development in combination with semaglutide (CagriSema) for the treatment of obesity and T2D. In Phase I, the combination has shown more potent weight loss than semaglutide alone. In August 2021, Novo Nordisk initiated a Phase IIb trial of cagrilintide, semaglutide, and FGF21 analog NN9500 as combination therapy for the treatment of MASH with fibrosis.</p>		

## cagrilintide/ NN9500/ semaglutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - Global  <a href="#">NCT05016882</a>            Start: Aug. 2021            1° Completion: May 2024            Completion: March 2025</p>	<p>672 MASH patients aged ≥18 years (≥19 years in S. Korea, ≥20 years in Japan, and ≥21 years in Singapore), F2-4 fibrosis, NAS ≥4 for patients with F2-F3 and ≥3 for patients with F4 (≥1 in each of steatosis, lobular inflammation, and ballooning)</p>	<p>NN9500 (SC 7.5, 15, or 30mg QW) ± semaglutide (SC 2.4mg QW) vs. cagrilintide (SC 2.4mg QW) + semaglutide (SC 2.4mg QW) vs. semaglutide (SC 2.4mg QW) vs. placebo for 19 months</p>	<p><b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 52 weeks</p>

cilofexor/ firsocostat/ semaglutide				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb cirrhotic MASH (US Aug. 2021)	Gilead (Collaborator), Novo Nordisk (Collaborator)	non-bile FXR agonist/ ACC inhibitor/ GLP-1 agonist oral (QD)/ oral (QD)/ SC (QW)	MASH F4	<ul style="list-style-type: none"> <li>Dec. 2024: Expected completion of Phase IIb trial of cilofexor + firsocostat + semaglutide SC</li> </ul>
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<ul style="list-style-type: none"> <li>Complimentary MOAs targeting different aspects of the disease</li> </ul>	<ul style="list-style-type: none"> <li>Combination of daily oral therapies with a weekly injectable therapy might pose a challenge in regard to patient compliance</li> <li>Other late-stage mono/combination therapies in development for the treatment of MASH F4</li> </ul>			<ul style="list-style-type: none"> <li><b>Feb. 2024:</b> Semaglutide/cilofexor/firsocostat, Novo Nordisk/Gilead removes MASH endpoint of Phase IIb combination trial in MASH F4</li> </ul>
Key Milestones	CVrg Synopsis			
<ul style="list-style-type: none"> <li><b>July 2021:</b> Semaglutide SC/cilofexor/firsocostat, Novo Nordisk and Gilead plan Phase IIb combination trial in MASH F4</li> <li><b>Nov. 2020:</b> Semaglutide/cilofexor/firsocostat, combi Tx safe - additive effects in non-invasive markers of efficacy</li> <li><b>June 2019:</b> Novo Nordisk and Gilead plan Phase II combination trial of semaglutide SC, firsocostat, and cilofexor in MASH with fibrosis</li> </ul>	<p>In April 2019, Novo Nordisk and Gilead announced a collaboration to investigate Novo Nordisk's GLP-1 agonist semaglutide in combination with cilofexor and ACC inhibitor firsocostat in MASH patients with F2-F3. Data from a 24-week Phase II trial presented at AASLD 2020 revealed no new safety concerns and showed additive effects of combination Tx on liver fat and liver enzymes. In March 2021, Novo Nordisk and Gilead announced an expansion to their collaboration to conduct a Phase IIb trial investigating safety and efficacy of semaglutide SC alone and in combination with a fixed-dose combination of firsocostat and non-bile FXR agonist cilofexor. The trial will be conducted in MASH patients with compensated cirrhosis (F4) and will enroll ~440 patients into 4 treatment arms evaluating impact on improvement in fibrosis and MASH resolution.</p> <p>While Gilead's cilofexor and firsocostat are solely in development for MASH in this combination, Novo Nordisk's semaglutide remains in Phase III development for MASH F2-F3.</p>			

## cilofexor/ firsocostat/ semaglutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>WAYFIND</b> Phase IIb - US, Canada, Japan, Puerto Rico <a href="#">NCT04971785</a> Start: Aug. 2021 1° Completion: Nov. 2024 Completion: Dec. 2024	457 MASH patients with compensated cirrhosis (F4) aged 18-80 years, eGFR ≥30mL/min/1.73m <sup>2</sup> , A1c ≤10%, BMI ≥23kg/m <sup>2</sup>	semaglutide (SC 2.4mg QW) ± cilofexor/firsocostat fixed-dose combination (oral 30/20mg QD) vs. cilofexor/firsocostat fixed-dose combination (oral 30/20mg QD) vs. placebo for 72 weeks semaglutide dose escalation every 4 weeks from 0.24mg	<b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 72 weeks
Phase II - US <a href="#">NCT03987074</a> Start: July 2019 1° Completed: July 2020 <b>Completed: July 2020</b>	109 patients aged 18-75 years with MASH and F2-3 on historical biopsy OR MASLD with FibroTest, MRI-PDFF, and FibroScan, ALT ≤5xULN, eGFR ≥30mL/min/1.73m <sup>2</sup> , A1c ≤9.5%, BMI >23kg/m <sup>2</sup>	- semaglutide (0.24-2.4mg SC QW), semaglutide dose escalated every 4 weeks for all treatment arms vs. - semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) vs. - semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 30mg QD) vs. - semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 100mg QD) vs. - semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) + cilofexor (oral 30mg QD)	<b>Primary Endpoint:</b> number of patients with TEAEs up to 24 weeks plus 30 days <b>AASLD 2020 Oral LO2:</b> <ul style="list-style-type: none"> <li>- All treatment regimens were safe and well-tolerated.</li> <li>- Two SAEs occurred, one with semaglutide (grade 3 diarrhea) and one with sema + cilo (100mg) (grade 3 pancreatitis); both led to discontinuation of study drug.</li> <li>- Most common AEs were GI related, consistent with GLP-1 agonism.</li> <li>- Minimal (5-10%) pruritus was observed in cilofexor groups only; all grade 1 and none leading to discontinuation.</li> <li>- 5-14% of pts discontinued any study drug due to AEs. <ul style="list-style-type: none"> <li>- of 8 pts with AEs leading to discontinuation of study drug, 6 GI related, 1 skin burning sensation, 1 hyperesthesia.</li> <li>- Few grade 3 and 4 lab abnormalities were observed.</li> </ul> </li> <li>- one event of hypertriglyceridemia (577mg/dL) was reported in a pt in the sema + fir arm (baseline TG 487mg/dL).</li> <li>- CPK elevations in two pts in the sema + cilo (100mg) arm; both deemed unrelated to study drug.</li> <li>- LDL-C increased in the sema + cilo (100mg) arm, but not in the sema + cilo (30mg) and sema + fir + cilo (30mg) arms.</li> <li>- Mild TG increases were observed in arms containing ACC inhibitor firsocostat.</li> <li>- Weight loss at 24 weeks was similar across treatment groups ranging -7.0 to -9.6%.</li> <li>- Absolute liver fat was reduced in all treatment groups with the greatest reductions in arms containing firsocostat. <ul style="list-style-type: none"> <li>- similar findings to MRI-PDFF data were observed with CAP.</li> </ul> </li> <li>- A large proportion of pts (≥80%) achieved ≥30% reduction in relative liver fat, and more pts in combination Tx groups achieved ≥30, 50, and 70% reduction in relative liver fat vs. semaglutide mono Tx.</li> <li>- Reductions in ALT were potentiated in all combination arms vs. semaglutide.</li> <li>- At 24 weeks, AST, GGT, CK18-M30, and ELF were significantly improved in all treatment arms from baseline, but no additive effect of combination Tx was observed.</li> <li>- Similar reductions in Liver stiffness by VCTE was observed across treatment arms, and no inter-group differences were observed with liver stiffness by MRE.</li> <li>- Liver stiffness was improved in all treatment arms, and to a greater extent with combination Tx.</li> <li>- More pts on combination therapy achieved ≥25% reduction in liver stiffness (53-60%) vs. semaglutide (36%).</li> <li>- FAST score was improved by all treatments and to a significant greater extent with all combinations except sema + cilo (100mg) vs. semaglutide mono Tx.</li> <li>- Glycemic parameters were improved to a similar degree in all treatment arms.</li> </ul>

# clesacostat/ ervogastat

## Next Milestone

Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US June 2020)	Pfizer (Originator)	ACC inhibitor/ DGAT2 inhibitor oral	MASH	
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<ul style="list-style-type: none"> <li>• Complementary MOAs</li> <li>• Fast Track Designation in the US</li> </ul>		<ul style="list-style-type: none"> <li>• Other late-stage mono/combination therapies in development for the treatment of MASH</li> </ul>		
Key Milestones	CVrg Synopsis			
<ul style="list-style-type: none"> <li>• <b>Aug. 2020:</b> Pfizer initiates US Phase II dose-finding trial in MASLD</li> <li>• <b>Nov. 2019:</b> (AASLD 2019) PF-05221341 + PF-06865571: no increased toxicity or meaningful PK interactions with co-administration</li> </ul>	<p>Clesacostat mono-therapy rapidly elicited dose-dependent reductions in liver fat which was sustained for 16 weeks. This was associated with increased plasma TG levels that returned to baseline levels 1-2 weeks after end of treatment. Development of clesacostat as monotherapy was discontinued in October 2020.</p> <p>DGAT2 inhibition has shown to mitigate ACCi induced increases in plasma TG and Pfizer is investigating those two MOAs in a combination dubbed PF-07055341. Phase II data presented at ILC 2020 showed potent reductions in liver fat with clesacostat and ervogastat monotherapies, while no additive effect was seen of combination; ervogastat fully mitigated the ACCi induced increase in TG.</p> <p>A Phase IIb trial, MIRNA, investigating the effect of ervogastat monotherapy or combination treatment on histological endpoints in 450 MASH patients with F2-F3 fibrosis was initiated in June 2020. The trial completed in April 2024 – no data have yet been released.</p> <p>Ervogastat remains in Phase II development as monotherapy for MASH.</p>			

## clesacostat/ ervogastat - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>MIRNA</b> Phase IIb - Global <a href="#">NCT04321031</a> Start: June 2020 1° Completion: Jan. 2024 <b>Completed:</b> April 2024	258 MASH patients aged 18-75 years, F2-F3 fibrosis, BMI $\geq 22.5\text{kg/m}^2$	<ul style="list-style-type: none"> <li>- ervogastat (oral 25, 75, 150, or 300mg BID or 150 or 300mg QD vs.</li> <li>- ervogastat + clesacostat (oral 150mg/5mg or 300mg/10mg BID) vs.</li> <li>- placebo for 48 weeks</li> </ul>	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- resolution of MASH without worsening of fibrosis from baseline at 48 weeks AND/OR</li> <li>- <math>\geq 1</math> stage improvement in fibrosis without worsening in MASH from baseline at 48 weeks</li> </ul>
Phase II - US <a href="#">NCT03776175</a> Start: Jan. 2019 1° Completed: Sep. 2019 <b>Completed: Oct. 2019</b>	99 MASLD patients with overweight/obesity aged 18-70 years, BMI $\geq 25\text{kg/m}^2$ , body weight $>50\text{kg}$ liver fat $\geq 8\%$ by MRI-PDFF, T2D on $\leq 1$ OAD OR metabolic syndrome with $\geq 2$ of FPG $\geq 10\text{mg/dL}$ , $\geq 1$ stage hypertension, HDL $<40\text{mg/dL}$ (males) $<50\text{mg/dL}$ (females), TG $\geq 150\text{mg/dL}$ , or waist circumference $>102\text{cm}$ (males) $>89\text{cm}$ (females)	clesacostat (oral 15mg BID) or ervogastat (oral 300mg BID) or clesacostat + ervogastat (oral 15mg and 300mg BID, respectively) vs. placebo for 6 weeks	<p><b>Primary Endpoint:</b> relative change in liver fat (by MRI-PDFF) from baseline at 6 weeks</p> <p><b>ILC 2020:</b></p> <ul style="list-style-type: none"> <li>- Improvements in liver fat were sign. greater with all active treatments vs. pbo; ACCi monoTx and ACCi+DGAT2i combiTx showed numerically greater reduction vs. DGAT2i monoTx.</li> <li>- More ACCi and ACCi+DGAT2i treated patients achieved <math>\geq 30</math> and <math>\geq 50\%</math> relative reduction in liver fat vs. DGAT2i.</li> <li>- TEAE occurrence was low and similar across treatment groups.</li> <li>- Most common TEAEs were diarrhea, UTI, and rash; all TEAEs were mild to moderate except for one severe TEAE of TG increase which was considered treatment related (on ACCi, resolved and patient discontinued Tx).</li> <li>- ALT and AST transiently increased with all active treatments, and after day 14, levels trended down ending below and near baseline for ALT and AST, respectively.</li> <li>- ACCi monoTx and ACCi+DGAT2i combiTX elicited an increase in GGT, while DGAT2i monoTx significantly reduced GGT.</li> <li>- ACCi monoTx sign. increased ALP, while DGAT2i monoTx significantly reduced ALP vs. pbo, both trending back to baseline in follow-up; ALP for ACCi+DGAT2i combiTX was similar to pbo.</li> <li>- In the ACCi monoTx arm, triglycerides were sign. increase vs. pbo starting at day 14, which was mitigated by combination treatment with DGAT2i.</li> <li>- HDL-C was significantly reduced in all active treatment arms vs. pbo.</li> <li>- Patients receiving ACCi and DGAT2i combination treatment experienced a significant decrease in total cholesterol at day 42 vs. pbo (<math>-9.6\%</math> [90% CI: <math>-16.3</math>, <math>-2.4</math>]), as well as sign. greater reductions in PCSK9 vs. pbo.</li> <li>- Changes in ApoB100 were not significantly different from placebo in any active treatment group.</li> <li>- ACCi treated patients experienced sign. increases in ApoC3 vs. pbo (<math>P &lt; 0.001</math>), while ApoC3 levels in the combination group were no different than pbo indicating DGAT2i mitigated the ACCi induced increase.</li> </ul>

pemafibrate/ tofogliflozin				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US June 2022)	Kowa (Originator)	PPAR $\alpha$ agonist/ SGLT-2 inhibitor oral (BID)	MASLD with high TG	<ul style="list-style-type: none"> <li>May 2025: Expected completion of US Phase IIb trial</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Pemafibrate approved in 2017 in Japan for hypercholesterolemia; in Phase III development for hypercholesterolemia in US, EU, and Russia</li> <li>Tofogliflozin approved in 2014 in Japan for T2D.</li> </ul>		<ul style="list-style-type: none"> <li>General negative perception of PPAR modulators by both patients and physicians due to AEs seen in diabetes trials.</li> <li>Other late-stage mono/combination therapies in development for the treatment of MASH</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>April 2022:</b> Kowa plans US Phase II trial</li> </ul>		<p>Pemafibrate (marketed as Parmodia) is approved for hyperlipidemia in Japan, and while it failed to improve liver fat in MASLD patients, pemafibrate significantly improved liver stiffness by MRE, liver enzymes, and plasma lipids. Tofogliflozin (marketed Apleway) is approved in Japan for treatment of T2D. In June 2022, Kowa initiated a US Phase IIb trial of pemafibrate in combination with in-house SGLT-2 inhibitor tofogliflozin to evaluate histology endpoints at 48 weeks.</p>		

## pemafibrate/ tofogliflozin - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II - US <a href="#">NCT05327127</a> Start: Nov. 2022 1° Completion: May 2025 Completion: June 2025	300 MASH patients aged ≥18 years, NAS ≥4 (score of ≥1 in each component of NAS), F1-F3	pemafibrate (oral QD) vs. tofogliflozin (oral QD) vs. pemafibrate + tofogliflozin (oral QD) vs. placebo	<b>Primary Endpoint:</b> ≥2-point improvement in NAS with no worsening in fibrosis from baseline at 48 weeks

## TERN-101/ TERN-501 discontinued

Status	Companies	MOA/ROA	Target Population
Discont. non-cirrhotic MASH (US Jan. 2024)	Terns Pharmaceutical (Owner)	non-bile FXR agonist/ THRβ agonist oral (QD)	MASH
Strengths/Opportunities	Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Complimentary MOAs targeting different aspects of the disease</li> </ul>	<ul style="list-style-type: none"> <li>Other late-stage mono/combination therapies in development for the treatment of NASH</li> </ul>		
Key Milestones	CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> Terns discontinues development for MASH to focus on obesity and cancer</li> <li><b>Aug. 2023:</b> TERN-501/TERN-101 meet primary endpoint in Phase II trial DUET</li> <li><b>May 2022:</b> Terns plans a Phase II trial of combination therapy in MASH with fibrosis</li> </ul>	<p>Terns' non-bile FXR agonist TERN-101 showed efficacy findings consistent with the FXR class with only mild to moderate pruritus in US Phase II trial LIFT. Preclinical data showed efficacy of both TERN-101 and THRβ agonist TERN-501 on measures of MASH, lipids, and liver enzymes, and while no additive effect on these measures were seen with combination therapy, differential expression of significantly more genes associated with biological processes relevant to MASH was seen with combination therapy than treatment with each asset alone.</p> <p>Phase II trial DUET evaluating TERN-501 alone and in combination with in-house non-bile FXR agonist TERN-101 was initiated in July 2022, and data released in August 2023 showed significant improvements in liver fat and cT1 with TERN-501 already at 12 weeks. Combination therapy with in-house FXR agonist TERN-101 showed only minor improvements in efficacy without any need for dose-adjustment or unexpected safety findings.</p> <p>In a J.P. Morgan presentation January 2024, Terns provided an update on its pipeline and strategic priorities for 2024, and despite reporting positive data from Phase II trial DUET the Company will be prioritizing capital allocation towards oncology and obesity programs, while limiting near-term development spend on TERN-501 in MASH.</p>		

### Next Milestone

- Development discontinued due to strategic pipeline considerations

### 2024 Sentinels

- Jan. 2024:** Terns discontinues development for MASH to focus on obesity and cancer

## TERN-101/ TERN-501 - Clinical Trials *discontinued*

Trial	Patients	Treatment	Endpoints
<b>DUET</b> Phase II - US <a href="#">NCT05415722</a> Start: July 2022 1° Completed: July 2023 <b>Completed: July 2023</b>	162 MASH patients with fibrosis aged 18-75 years, BMI $\geq 25\text{kg}/\text{m}^2$ , liver fat $\geq 10\%$ by MRI-PDFF, cT1 $\geq 800\text{ms}$	TERN-501 (oral 1, 3, 6, or 10mg QD) vs. TERN-101 (oral 10mg QD) vs. TERN-501 + TERN-101 (oral 3mg/10mg or 6mg/10mg QD) vs. placebo for 12 weeks plus follow-up at 16 weeks	<p><b>Primary Endpoint:</b> %change in liver fat from baseline at 12 weeks (TERN-501 monoTx)</p> <p>Secondary endpoints include: change in liver fat of combination Tx and change in cT1 for TERN-501 alone and in combination with TERN-101</p> <p><u>Aug. 2023 + AASLD 2023:</u></p> <ul style="list-style-type: none"> <li>- TERN-501 monoTx (3 and 6mg) sign. reduced liver fat vs. pbo.</li> <li>- Sign. more TERN-501-treated pts achieved <math>\geq 30\%</math> reduction in liver fat vs. pbo.</li> <li>- TERN-501 (6mg) sign. reduced cT1 vs. pbo.</li> <li>- TERN-501 showed a trend toward improvement in LDL-C, HDL-C, and TG, and sign. improved ApoB.</li> <li>- TERN-501 dose-dependently increased SHBG.</li> <li>- Changes in thyroid axis hormones and liver enzymes with TERN-501 were similar to pbo.</li> <li>- TERN-501/TERN-101 combination Tx elicited modest improvements in liver fat reduction and responder rate vs. TERN-501 monoTx.</li> <li>- Combination Tx did not increase LDL-C, and no treatment emergent safety signals were reported.</li> <li>- TERN-501 was safe and well-tolerated with AEs generally being mild; no drug-related SAEs were reported.</li> <li>- Drug-related AEs of interest were similar across all arms with similar rates of GI events, including nausea, diarrhea and vomiting; no drug-related CV AEs were reported.</li> <li>- Changes in thyroid axis hormones and liver enzymes with TERN-501 were similar to pbo.</li> </ul>

# Immune Modulators

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leronlimab				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US June 2020)	Progenics (Originator), CytoDyn (Owner, Global)	CCR5 antagonist SC (QW)	MASH with fibrosis	
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Nov. 2021:</b> Leronlimab improves liver fat and cT1 on first patients from open-label cohort</li> <li><b>June 2020:</b> CytoDyn initiates US Phase II trial in MASH</li> </ul>		<p>Leronlimab is a humanized mAb that blocks CCR5 and is in development for the treatment and prevention of HIV-1 infections, graft-versus-host disease, cancer, and COVID-19; leronlimab has been administered to &gt;700 patients without signs of hepatotoxicity. CCR5 antagonism has shown anti-inflammatory and anti-fibrotic effects in models of MASH, and early data from a Phase II open-label cohort showed improvements in liver fat and cT1. CytoDyn intends to file for Fast Track Designation for leronlimab in MASLD and MASH, and in early November disclosed to be working on a Phase IIb/III protocol including liver biopsy that was intended to initiate in January 2022, while in a later statement CytoDyn CEO Nader Pourhassan stated “we may proceed to file a Phase III protocol with the FDA and request accelerated approval”.</p>		

## leronlimab - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - US  <a href="#">NCT04521114</a>            Start: Dec. 2020            1° Completed: Dec. 2021  <b>Completed: Dec. 2021</b></p>	<p>60 MASH patients aged 18-75 years, histological MASH or FibroScan with FAST score &gt;0.67 and CAP ≥260, liver fat ≥8%, BMI &gt;28kg/m<sup>2</sup> (stable body weight ±5% within 6 months of screening), eGFR ≥60mL/min/1.73m<sup>2</sup>, A1c &lt;9%, if prediabetes/T2D on stable dose of anti-diabetic medication ≥3 months</p>	<p>leronlimab (SC 750mg QW) vs. placebo for 13 weeks</p>	<p><b>Primary Endpoint:</b> change in liver fat from baseline at 14 weeks  <b>Nov. 2021:</b>            Data from the first five leronlimab treated patients were released in early November:            - Liver fat was reduced in all five patients by up to 45% from baseline.            - Fibrosis was reduced in four of five patients by up to 10% from baseline.            - one patient had no change in fibrosis.            - patients achieving reduction in fibrosis had mild, moderate, or severe fibrosis at baseline.            - The cT1 reduction was ~40ms from baseline.            Data from the first 15 leronlimab treated patients were released late November:            - Liver fat was reduced by up to 45% and fibrosis assessed by cT1 was reduced by up to 8%; patients achieving reduction in fibrosis had mild, moderate, or severe fibrosis at baseline.            - Mean cT1 reduction was 24ms with reductions as high as 93ms.</p>

# Incretin Combinations

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tirzepatide				Next Milestone			
Status	Companies	MOA/ROA	Target Population				
Phase IIb non-cirrhotic MASH (Global Nov. 2019)	Lilly (Originator)	dual GLP-1/GIP agonist SC (QW)	MASH, T2D, and obesity				
Strengths/Opportunities		Weaknesses/Threats					
<ul style="list-style-type: none"> <li>Potent weight loss and A1c reduction</li> <li>Approved for T2D and obesity</li> </ul>		<ul style="list-style-type: none"> <li>GI AEs</li> <li>Other GLP-1 based therapies including semaglutide (Novo Nordisk), dual GLP-1/GRAs, pemvidutide (Altimmune), survodutide (BI), and efinopegdutide (Merck), and triple GLP-1/GIP/GRA efocipegtrutide (Hanmi)</li> </ul>					
Key Milestones		CVrg Synopsis					
<ul style="list-style-type: none"> <li><b>Feb. 2024:</b> Tirzepatide meets primary histology endpoint in Phase IIb SYNERGY-NASH</li> <li><b>Nov. 2019:</b> Lilly initiates Global Phase II trial SYNERGY-NASH of tirzepatide in overweight/obese MASH F2-F3 patients</li> <li><b>June 2019:</b> Tirzepatide shows improvement of MASH biomarkers in post-hoc analysis of T2D study</li> </ul>		<p>Tirzepatide is a weekly GLP-1/GIP dual agonist approved for the treatment of T2D and obesity. In <i>post hoc</i> analyses of a Phase IIb trial in obese T2D patients presented at ADA and AASLD 2019, tirzepatide improved MASH and fibrosis related biomarkers and to a greater extent in patients with more severe baseline disease. Additionally, data from a sub-study (SURPASS-MRI) of Phase III trial SURPASS 3 in T2D patients showed tirzepatide elicited significant and clinically meaningful reductions in liver fat content, abdominal SAT, VAT, and liver enzymes. In November 2019, Lilly initiated a Phase IIb trial, SYNERGY-NASH, in overweight/obese MASH F2-F3 patients. Topline data released in February 2024 showed the primary endpoint in SYNERGY-NASH was met with up to 73.9% of tirzepatide-treated patients achieving MASH resolution without worsening in fibrosis. No details regarding future development of tirzepatide for the treatment of MASH have yet been disclosed.</p>					
2024 Sentinels							
<ul style="list-style-type: none"> <li><b>Feb. 2024:</b> Tirzepatide (Lilly) meets primary histology endpoint in Phase IIb SYNERGY-NASH</li> </ul>							

## tirzepatide - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>SYNERGY-NASH</b> Phase II - Global <a href="#">NCT04166773</a> Start: Nov. 2019 1° Completion: Dec. 2023 Completed: Jan. 2024	196 MASH patients with overweight/obesity, BMI 27-50kg/m <sup>2</sup> , if T2D A1c ≤9.5%; F2-F3 fibrosis	tirzepatide (SC 5, 10, or 15mg QW) vs. placebo for 52 weeks; dose escalation from 2.5mg QW by 2.5mg every four weeks until target dose	<b>Primary Endpoint:</b> MASH resolution without worsening of fibrosis from baseline at 52 weeks <u>Feb. 2024:</u> <ul style="list-style-type: none"> <li>- Tirzepatide (all doses) met the primary endpoint with sign. more pts achieving MASH resolution without worsening in fibrosis vs. pbo.</li> <li>- The proportion of tirzepatide-treated pts achieving ≥1 stage improvement in fibrosis without worsening in MASH was clinically meaningful across doses.</li> <li>- Adverse events were consistent with previous studies of tirzepatide in pts with obesity or T2D.</li> </ul>

survotudide				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase III non-cirrhotic MASH (US March 2024)	Zealand Pharma (Originator, Scandinavia), Boehringer Ingelheim (ROW)	dual GLP-1/GRA SC (QW)	MASH, T2D, Obesity	<ul style="list-style-type: none"> <li>Feb. 2026: Data from Phase III trial expected</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Also in development for T2D and obesity</li> <li>Fast Track Designation for MASH from US FDA</li> <li>PRIME designation in the EU</li> </ul>		<ul style="list-style-type: none"> <li>Other GLP-1 based therapies including semaglutide (Novo Nordisk), dual GLP-1/GIP agonist tirzepatide (Lilly), dual GLP-1/GRAs pemvidutide (Altimimmune) and efinopegdutide (Merck), and triple GLP-1/GIP/GRA efocipegrutide (Hanmi)</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>March 2024:</b> BI initiates Phase III trial in non-cirrhotic MASH</li> <li><b>Feb. 2024:</b> Survotudide shows impressive histological improvements in Phase IIb</li> <li><b>Feb. 2021:</b> BI/Zealand plan global Phase II trial in MASH F1-F3</li> </ul>		<p>Survotudide, derived from oxyntomodulin activating both GLP-1 and glucagon receptors, emerged from a research collaboration between Zealand and BI. Survotudide was the second dual GLP-1/GRA to enter late-stage development for MASH and is in Phase III development for the treatment of obesity and T2D. In February 2024, data from a global Phase IIb trial showed up to 83% of survotudide-treated patients achieving improvement in MASH, and survotudide met all secondary endpoints. BI intends to “move forward as quickly as possible in MASH” and initiated a small Phase III trial in non-cirrhotic MASH in March 2024.</p>		

## survodutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase III – US  <a href="#">NCT06309992</a>          Start: March 2024          1<sup>o</sup> Completion: Feb. 2026          Completion: March 2026</p>	<p>160 non-cirrhotic MASH patients with overweight/obesity aged ≥18 years, BMI ≥30kg/m<sup>2</sup> or BMI ≥27kg/m<sup>2</sup> with ≥1 weight-related comorbidity (hypertension [SBP ≥140mmHg and/or DBP ≥90mmHg], dyslipidemia [LDL-C ≥160mg/dL, TG ≥150mg/dL, or HDL-C &lt;50mg/dL], obstructive sleep apnea, CVD [HF with NYHA II-III, Hx of stroke or cerebrovascular revascularization procedure], T2D [A1c 6.5 to &lt;10%])</p>	<p>survodutide (SC QW) vs. placebo</p>	<p><b>Primary Endpoints:</b>          - proportion of patients achieving ≥30% reduction in liver fat from baseline at 48 weeks          - change in body weight from baseline at 48 weeks</p>
<p>Phase II - Global  <a href="#">NCT04771273</a>          Start: April 2021          1<sup>o</sup> Completed: Nov. 2023  <b>Completed: Dec. 2023</b></p>	<p>295 MASH patients aged 18-80 years, NAS ≥4 (≥1 in each of lobular inflammation and ballooning), F1-F3, liver fat ≥8%, liver stiffness ≥6.0kPa (by FibroScan), BMI ≥25kg/m<sup>2</sup>, body weight ≥70kg</p>	<p>survodutide (SC 2.4, 4.8, or 6.0mg QW) vs. placebo for 48 weeks; dose-titration from 0.3mg bi-weekly to target (2.4mg dose at 16 weeks, 4.8mg dose at 20 weeks, 6.0mg dose at 24 weeks)</p>	<p><b>Primary Endpoint:</b> ≥2 point improvement in NAS (≥1 point in each of lobular inflammation and ballooning) without worsening in fibrosis from baseline at 48 weeks  <u>Feb. 2024:</u>          - At 48 weeks, up to 83% of survodutide-treated pts achieved significant improvement in MASH vs. pbo.          - The primary endpoint was met with survodutide showing improvement in MASH without worsening of fibrosis.          - Survodutide met all secondary endpoints including ≥30% reduction in liver fat, greater reduction in liver fat, ≥1 stage improvement in fibrosis, and greater changes in NAS vs. pbo.          - Survodutide did not show unexpected safety or tolerability issues at any dose level.</p>

efinopegdutide				Next Milestone		
Status	Companies	MOA/ROA	Target Population			
Phase IIb non-cirrhotic MASH (Global June 2023)	Hanmi (Originator, Asia), Merck & Co. (Global)	dual GLP-1/GRA SC (QW)	MASLD with obesity	<ul style="list-style-type: none"> <li>Dec. 2025: Expected completion of Phase IIb trial <a href="#">NCT05877547</a></li> </ul>		
Strengths/Opportunities	Weaknesses/Threats		2024 Sentinels			
<ul style="list-style-type: none"> <li>Fast Track Designation</li> </ul>	<ul style="list-style-type: none"> <li>SC administration may deter some patients</li> <li>GLP-1 agonist semaglutide (Novo Nordisk) and incretin combinations including dual GLP-1/GIP agonist tirzepatide (Lilly), GLP-1/GRA's pemvidutide (Altimmune) and survadutide (BI), and triple GLP-1/GIP/GRA efocipegtrutide (Hanmi)</li> </ul>		2024 Sentinels			
Key Milestones	CVrg Synopsis					
<ul style="list-style-type: none"> <li><b>May 2023:</b> Merck plans Phase IIb trial in MASH F2-F3</li> <li><b>July 2021:</b> Merck plans Phase II trial in MASLD patients with obesity</li> <li><b>Aug. 2020:</b> Hanmi and Merck enter exclusive licensing agreement for the treatment of MASH</li> </ul>	<p>In August 2020, Merck obtained exclusive rights to dual GLP-1/GRA efinopegdutide from Hanmi for the treatment of MASH. The asset was previously in development for obesity and T2D with Hanmi in collaboration with J&amp;J, but in July 2019 J&amp;J returned the rights to Hanmi due to lack of A1c lowering efficacy. An open-label Phase II trial initiated in August 2021 evaluated efficacy on liver fat in comparison to Novo Nordisk's GLP-1 agonist semaglutide (SC 1.0mg QW; Ozempic) and showed greater improvements in liver fat despite similar weight loss magnitude, indicating a specific contribution from glucagon receptor agonism. In June 2023, Merck initiated a Phase IIb trial in patients with MASH F2-F3.</p>					

## efinopegdutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II - US, Puerto Rico <a href="#">NCT05877547</a> Start: June 2023 1° Completion: Dec. 2025 Completion: Dec. 2025	<b>Patients:</b> 300 MASH patients aged 18-80 years (19-70 years in S. Korea), NAS ≥4, F2-F3, no T2D Hx and A1c ≤9% or T2D Hx controlled by diet or stable doses of antihyperglycemic agents	efinopegdutide (SC 4, 7, or 10mg QW) vs. semaglutide (SC 2.4mg QW) vs. placebo for 52 weeks; efinopegdutide dose-escalation every 4 weeks from 2, 4, 7, to 10mg (or 4 or 7mg), dose-escalation for semaglutide every 4 weeks from 0.25, 0.5, 1.0, 1.7, to 2.4mg	<b>Primary Endpoints:</b> - MASH resolution without worsening in fibrosis from baseline at 52 weeks - safety up to 60 weeks - Tx discontinuation up to 52 weeks
Phase II - Global <a href="#">NCT04944992</a> Start: Aug. 2021 1° Completed: Oct. 2022 <b>Completed: Oct. 2022</b>	130 MASLD patients with obesity aged 18-70 years (20-70 in Taiwan; 19-70 in S. Korea), liver fat ≥10%, BMI 25-50kg/m <sup>2</sup> , weight stable (<5% weight loss/gain within 3 months), non-diabetic or A1c ≤8.5% controlled on diet or stable dose of metformin	efinopegdutide (SC 2.4mg weeks 1-3, 5.0mg weeks 4-7, and 10.0mg weeks 8-24 QW) vs. semaglutide (SC 0.25mg weeks 1-3, 0.5mg weeks 4-7, and 1.0mg weeks 8-24) for 24 weeks	<b>Primary Endpoints:</b> - change in relative liver fat from baseline at 24 weeks - AEs up to 28 weeks - study discontinuations up to 24 weeks <b>EASL 2023:</b> - At 24 weeks, efinopegdutide elicited sign. greater reduction in liver fat vs. semaglutide (SC 1mg QW). - More efinopegdutide-treated pts achieved ≥30, 50, and 70% reduction in liver fat vs. semaglutide. - 2/3 of efinopegdutide-treated pts achieved normalization in liver fat vs. ~1/5 for semaglutide. - Efinopegdutide elicited slightly greater weight loss vs. semaglutide; baseline body weight was 100.2 vs. 94.5kg for efinopegdutide and semaglutide, respectively. - Reduction in liver fat was greater in pts achieving greater weight loss for both drugs, and consistently greater for efinopegdutide vs. semaglutide for all weight loss categories. - Efinopegdutide improved atherogenic lipids to a greater extent vs. semaglutide. - efinopegdutide-treated pts saw a reduction in HDL-C vs. an increase in semaglutide-treated pts. - Efinopegdutide and semaglutide both elicited rapid reductions in ALT and AST, which were sustained over 24 weeks. - Efinopegdutide was generally safe and well-tolerated. - The incidence of overall AEs and drug-related AEs was slightly higher for efinopegdutide vs. semaglutide; incidence of SAEs was similar for efinopegdutide and semaglutide. - No drug-related SAEs or deaths were reported. - Discontinuation of drug due to AEs and drug-related AEs was ~5% for both among efinopegdutide-treated pts while no semaglutide-treated pts discontinued study drug due to AEs. - AEs were predominantly GI-related with slightly greater incidence for efinopegdutide vs. semaglutide. - incidence of abdominal pain, upper abdominal pain, and constipation was higher among efinopegdutide-treated pts vs. semaglutide. - Efinopegdutide elicited a transient reduction in systolic and diastolic blood pressure and increase in heart rate, which all trended back to baseline levels at 24 weeks. - No change in A1c was seen with efinopegdutide compared to a -0.5% reduction with semaglutide. - Efinopegdutide decreased hemoglobin by -0.6mmol/L vs -0.1mmol/L for semaglutide.

pemvidutide				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US July 2023)	Altimmune (Originator)	dual GLP-1/GRA SC	MASH with obesity/T2D	• 1Q 2025: Expected interim analysis of Phase IIb trial
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Also in development for T2D and obesity</li> <li>Fast Track Designation from the US FDA</li> </ul>		<ul style="list-style-type: none"> <li>Other GLP-1 based assets including semaglutide SC (Novo Nordisk), dual GLP-1/GIP agonist tirzepatide (Lilly), and dual GLP-1/GRAs survadutide (BI), and efinopegdutide (Merck)</li> </ul>		2024 Sentinels
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>May 2023:</b> Altimmune plans US Phase IIb trial IMPACT in MASH ± T2D</li> <li><b>June 2021:</b> Altimmune releases interim Phase I data showing significant early weight loss</li> </ul>		<p>Pemvidutide is a dual GLP-1/GRA in development for the treatment of MASH, obesity, and T2D. Data from a Phase I trial showed significant reductions in liver fat, liver volume, and liver enzymes, which was accompanied by weight loss of up to ~7%. In May 2023, Altimmune announced Phase IIb trial IMPACT in MASH F2-F3; topline data are expected early 2025.</p> <p>In November 2023, after announcing positive weight loss data from Phase II trial MOMENTUM, Altimmune will advance ongoing partnering discussions with emphasis on a partner with interest in both obesity and MASH.</p>		

## pemvidutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>IMPACT</b> Phase II - US <a href="#">NCT05989711</a> Start: July 2023 1° Completion: Feb. 2025 Completion: Sep. 2025	190 MASH patients with/without T2D aged 18-75 years, NAS ≥ 4, F2-F3, BMI ≥27kg/m <sup>2</sup> , liver fat ≥8%, A1c ≤9.5%	pemvidutide (SC 1.2 or 1.8mg QW) vs. placebo for 48 weeks; randomized 1:2:2 - dose reduction will be allowed for patients experiencing GI intolerance	<b>Primary Endpoints:</b> - MASH resolution (≥2-pt improvement in NAS) without worsening in fibrosis from baseline at 24 weeks - ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 24 week
Phase I - US <a href="#">NCT05006885</a> Start: Sep. 2021 1° Completed: Aug. 2022 <b>Completed: Aug. 2022</b>	95 MASLD patients aged 18-65 years, BMI 28-40kg/m <sup>2</sup> , liver fat ≥10%, if T2D A1c <10% and FPG <200mg/dL on stable regimen of diet and exercise, metformin, and/or SGLT-2i	pemvidutide (SC 1.2, 1.8, or 2.4mg QW) vs. placebo for 12 weeks	<b>Primary Endpoint: number of patients with TEAEs up to 110 days</b> <u>Sep. 2022 + Dec. 2022 + EASL 2023:</u> - Pemvidutide (all doses) met the primary endpoint eliciting sign. and clinically relevant improvements in liver fat vs. pbo. - Pemvidutide (all doses) sign. reduced liver volume vs. pbo. - Pemvidutide reduced ALT in all patients and those with BL ALT ≥30U/L. - in pts with BL ALT ≥30U/L, reductions with pemvidutide were >17U/L for all doses and 27U/L in the 2.4mg cohort. - 75-100% of pemvidutide-treated pts achieved ≥80ms reduction in cT1 vs. pbo. - all pts on the highest pemvidutide (2.4mg) dose achieved this endpoint. - Pemvidutide elicited weight loss of up to -7.2% in non-diabetic and -5.3% in T2D pts. - Pemvidutide showed trends toward improving A1c or FPG in patients with T2D at 24 weeks (note small sample sizes). - Pemvidutide showed trends toward improving plasma lipids. - Pemvidutide was well-tolerated with the majority of AEs being GI related, and predominantly mild and transient in nature. - Three severe/serious AEs were reported, all deemed unrelated to study drug (chest pain following elective cardiac stent placement, salmonella infection, and hypertension >3 weeks after completion of treatment). - Meaningful reductions in SBP were observed, and minimal increases in HR consistent with the GLP-1 class were reported.

efocipegtrutide				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US June 2020) Phase I non-cirrhotic MASH (ROW April 2018)	Hanmi (Originator)	GLP-1/GRA/GIP triple agonist SC	MASH with obesity/T2D	• 2H 2025: Expected completion of Phase IIb trial
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>FDA Orphan Drug Designation for PSC and PBC</li> <li>FDA Fast Track Designation for MASH</li> <li>Potent weight loss in Phase I</li> </ul>		<ul style="list-style-type: none"> <li>Other GLP-1 based assets including semaglutide SC (Novo Nordisk), dual GLP-1/GIP agonist tirzepatide (Lilly), and dual GLP-1/GRAs pemvidutide (Altimimmune), survotudotide (BI), and efinopegdutide (Merck)</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>March 2021:</b> Hanmi conducting adaptive design Phase IIb trial in MASH F1-F3</li> <li><b>Aug. 2020:</b> Hanmi initiates US Phase II trial in MASH with fibrosis</li> <li><b>July 2020:</b> Efocipegtrutide receives Fast Track Designation from the US FDA</li> <li><b>Nov. 2018:</b> Hanmi initiates first-in-human US Phase I trial of efocipegtrutide in obese MASLD/MASH</li> </ul>		<p>GLP-1/GRA/GIP triple agonist efocipegtrutide (HM15211) is in US Phase II development for MASH and in Phase IIb development in MASH patients with F1-F3 in a yet undisclosed region. At ADA 2019, Hanmi presented first in human data of efocipegtrutide showing the triple agonist was safe and well-tolerated after a single injection in obese but otherwise healthy patients. The pharmacokinetic profile showed dose-dependent increases in exposure and a half life suggesting potential for weekly dosing. Data from a Phase Ib trial presented at ILC 2020, showed potent reductions in liver fat already at 8 and 12 weeks which was associated with up to 5% weight loss.</p>		

## efocipegtrutide - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II - US, S. Korea <a href="#">NCT04505436</a> Start: July 2020 1° Completion: May 2025 Completion: Nov. 2025	240 MASH patients aged 18-70 years (US) and 19-70 years (S. Korea), BMI $\geq 18\text{kg}/\text{m}^2$ , stable body weight (<5% change within 3 months), F1-F3 fibrosis, liver fat $\geq 8\%$ (MRI-PDFF)	efocipegtrutide (SC 2, 4, or 6mg QW) vs. placebo for 12 months	<b>Primary Endpoint:</b> proportion of patients achieving MASH resolution with no worsening in fibrosis from baseline at 12 months
Phase IIb - Location undisclosed Start: Dec. 2020 Completion: unknown	214 biopsy-confirmed MASH patients, NAS $\geq 4$ , F1-F3 (F1 <10% of patients)	efocipegtrutide (SC 2, 4, or 6mg QW) vs. placebo for 52 weeks	<b>Primary Endpoint:</b> MASH resolution without worsening in fibrosis from baseline at 52 weeks <b>Secondary Endpoints</b> include: $\geq 1$ stage improvement in fibrosis without worsening in MASH, change in liver fat by MRI-PDFF, and exploratory biomarkers of fibrosis
Phase I - US <a href="#">NCT03744182</a> Start: Nov. 2018 1° Completed: March 2020 <b>Completed: March 2020</b>	66 patients with obesity and MASLD/MASH aged 18-65 years, BMI $\geq 30\text{kg}/\text{m}^2$ , FPG $< 126\text{mg}/\text{dL}$ , A1c $< 6.5\%$ , CAP $\geq 300\text{dB}/\text{m}$ (FibroScan), and liver fat $\geq 10\%$ (MRI-PDFF).	efocipegtrutide multiple SC doses vs. placebo for 12 weeks	<b>Primary Endpoints:</b> AEs, incidence of clinical lab abnormalities, incidence and severity of clinical findings on physical exam, change in vital signs, and change in 12-lead ECG from baseline at 12 weeks. <u>ILC 2020:</u> <ul style="list-style-type: none"> <li>- Plasma exposure of efocipegtrutide reported as Cmax and AUC0-168h increased in a dose-dependent manner.</li> <li>- efocipegtrutide reached peak plasma concentration in 41 to 75 hours with a half life of 62 to 191 hours.</li> <li>- efocipegtrutide (<math>&gt;0.01\text{mg}/\text{kg}</math>) elicited sign. dose-dependent reductions in liver fat at 8 weeks vs. pbo; only the efocipegtrutide 0.8mg/kg dose reached sign. at 12 weeks showing <math>&gt;80\%</math> reduction in liver fat.</li> <li>- More efocipegtrutide (<math>&gt;0.01\text{mg}/\text{kg}</math>) treated patients achieved clinically relevant (<math>\geq 30</math> and <math>50\%</math>) reductions in liver fat vs. pbo at 8 weeks which was sustained at 12 weeks.</li> <li>- efocipegtrutide (<math>&gt;0.01\text{mg}/\text{kg}</math>) elicited sign. weight loss already at 8 weeks vs. pbo.</li> <li>- Most AEs were mild and most common AEs were dose-dependent GI AEs.</li> <li>- Two efocipegtrutide treated patients developed hyperglycemia, which resolved upon discontinuation of study drug.</li> <li>- No serious AEs were reported in any dose group.</li> </ul>

# Incretins

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# semaglutide SC

Status	Companies	MOA/ROA	Target Population
Phase II cirrhotic MASH (US Aug. 2019) Phase III non-cirrhotic MASH (US, EU Jan. 2021)	Novo Nordisk (Originator)	GLP-1 agonist SC (QW)	MASH with fibrosis MASH with obesity, prediabetes, or T2D
Strengths/Opportunities		Weaknesses/Threats	
<ul style="list-style-type: none"> <li>Large safety database, based on clinical trials in T2D and obesity</li> <li>Reduces CV events in T2D patients</li> <li>QW formulation approved for T2D and in US and EU and for obesity in US</li> <li>Breakthrough Therapy Designation from the US FDA</li> </ul>		<ul style="list-style-type: none"> <li>SC administration may deter some patients</li> <li>Incretin combinations including dual GLP-1/GIP agonist tirzepatide (Lilly), and GLP-1/GRA's survadutide (BI) and efinopegdutide (Merck)</li> </ul>	
Key Milestones		CVrg Synopsis	
<ul style="list-style-type: none"> <li><b>June 2022:</b> Semaglutide misses primary endpoint in MASH with compensated cirrhosis</li> <li><b>Aug. 2021:</b> Semaglutide SC/NN9499/cagrilintide, Novo Nordisk plans global Phase IIb trial in MASH F2-F4</li> <li><b>July 2021:</b> Semaglutide SC/cilofexor/firsocostat, Novo Nordisk and Gilead plan Phase IIb combination trial in MASH F4</li> <li><b>Feb. 2021:</b> Novo Nordisk initiates global Phase III trial ESSENCE in MASH F2-F3</li> <li><b>Nov. 2020:</b> Semaglutide/cilofexor/firsocostat, combi Tx safe - additive effects in non-invasive markers of efficacy</li> <li><b>June 2020:</b> MASH resolution with no worsening in fibrosis accompanied by improvement in non-invasive markers of fibrosis</li> <li><b>May 2020:</b> Topline data show more patients achieve MASH resolution without worsening of fibrosis in Phase II trial</li> <li><b>Feb. 2020:</b> Novo Nordisk changes primary endpoint and delays trial completion of Phase II trial in MASH patients with compensated cirrhosis</li> <li><b>Dec. 2019:</b> Combination trial ATLAS of selonsertib, firsocostat, and cilofexor (all Gilead) fails to meet primary endpoint</li> <li><b>June 2019:</b> Novo Nordisk and Gilead plan Phase II combination trial of semaglutide SC, firsocostat, and cilofexor in MASH with fibrosis</li> <li><b>May 2019:</b> Novo Nordisk initiates EU/US Phase II trial of semaglutide SC in MASH patients with F4</li> <li><b>Oct. 2016:</b> Novo initiates Phase II of semaglutide for MASH with fibrosis</li> <li><b>April 2016:</b> Top line results from SUSTAIN-6 with GLP-1 agonist semaglutide disclose significant reduction in cardiovascular risk</li> </ul>		<p>Novo Nordisk's long-acting GLP-1 agonist is approved for T2D in the US, EU, and Japan, approved for obesity in the US and EU. In May 2020, a global Phase IIb trial showed semaglutide (SC 0.1-0.4mg QD) elicited MASH resolution without worsening of fibrosis and dose-dependent improvements in markers of fibrosis. In 1Q 2021, Novo Nordisk initiated a Phase III trial of semaglutide (SC 2.4mg QW) in MASH F2-F3, to evaluate histological endpoints and liver-related clinical events at 72 and 240 weeks, respectively.</p> <p>Combination therapy of agents with complimentary MOAs has attracted attention in the treatment of MASH with fibrosis, and in April 2019, Novo Nordisk and Gilead announced a collaboration to investigate semaglutide in combination with Gilead's non-bile FXR agonist cilofexor and/or ACC inhibitor firsocostat in MASH F2-F3. Data from a 24-week Phase II trial presented at AASLD 2020 revealed no new safety concerns and showed additive effects of combination Tx on liver fat and liver enzymes. In March 2021, Novo Nordisk and Gilead announced an expansion to their collaboration to conduct a Phase IIb trial investigating safety and efficacy of semaglutide SC alone and in combination with a fixed-dose combination of firsocostat and non-bile FXR agonist cilofexor in MASH patients with compensated cirrhosis (F4), and in August 2021, Novo Nordisk initiated a global Phase IIb trial of semaglutide in combination with in-house FGF21 analog NN9500 and amylin analog cagrilintide in MASH F2-F4.</p> <p>Data from a Phase II trial in MASH patients with F4 presented at ILC 2022 showed semaglutide monotherapy failed to improve histology, and Novo will now only pursue semaglutide as combination therapy for this patient population.</p>	

## Next Milestone

- Late 2024: Expected data from Phase III trial ESSENCE

## Projected Launch

non-cirrhotic MASH: 2025 (US), 2025 (EU)  
Phase III initiated 1Q 2021. With Breakthrough Designation semaglutide could be approved in the US in 2025

## 2024 Sentinels

- Jan. 2024: Novo Nordisk updates endpoints of global Phase III trial ESSENCE

## Ozempic; Wegovy (semaglutide SC) - Clinical Trials (1 of 3)

Trial	Patients	Treatment	Endpoints
Phase IIb - Global <a href="#">NCT05016882</a> Start: Aug. 2021 1° Completion: May 2024 Completion: March 2025	672 MASH patients aged ≥18 years (≥19 years in S. Korea, ≥20 years in Japan, and ≥21 years in Singapore), F2-4 fibrosis, NAS ≥4 for patients with F2-F3 and ≥3 for patients with F4 (≥1 in each of steatosis, lobular inflammation, and ballooning)	NN9500 (SC 7.5, 15, or 30mg QW) ± semaglutide (SC 2.4mg QW) vs. cagrilintide (SC 2.4mg QW) + semaglutide (SC 2.4mg QW) vs. semaglutide (SC 2.4mg QW) vs. placebo for 19 months	<b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 52 weeks
<b>WAYFIND</b> Phase IIb - US, Canada, Japan, Puerto Rico <a href="#">NCT04971785</a> Start: Aug. 2021 1° Completion: Nov. 2024 Completion: Dec. 2024	457 MASH patients with compensated cirrhosis (F4) aged 18-80 years, eGFR ≥30mL/min/1.73m <sup>2</sup> , A1c ≤10%, BMI ≥23kg/m <sup>2</sup>	semaglutide (SC 2.4mg QW) ± cilofexor/firsocostat fixed-dose combination (oral 30/20mg QD) vs. cilofexor/firsocostat fixed-dose combination (oral 30/20mg QD) vs. placebo for 72 weeks semaglutide dose escalation every 4 weeks from 0.24mg	<b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 72 weeks
<b>ESSENCE</b> Phase III - Global <a href="#">NCT04822181</a> Start: April 2021 1° Completion: March 2029 Completion: April 2029	1200 MASH patients aged ≥18 years, F2-F3, NAS ≥4 (≥1 in each of steatosis, lobular inflammation, and ballooning)	semaglutide (SC 2.4mg QW) vs. placebo	<b>Primary Endpoints:</b> in patients with F2-F3 - resolution of MASH without worsening in fibrosis from baseline at 72 weeks - improvement in fibrosis without worsening in MASH from baseline at 72 weeks - cirrhosis-free survival from baseline at 240 weeks
<b>COMBAT_T2_NASH</b> Phase IV – Austria, Germany <a href="#">NCT04639414</a> Start: March 2021 1° Completion: Dec. 2023 Completion: Dec. 2023 Sponsor: Deutsche Diabetes Forschungsgesell-schaft/ BI/ German Center for Diabetes Research/ Federal Ministry of Health/ Ministry of Innovation, Science&Research in North Rhine-Westphalia/Novo Nordisk/ German Diabetes Center	192 MASH patients with F1-F3 and T2D aged 25-75 years, A1c ≤9.5%, BMI ≤45kg/m <sup>2</sup>	empagliflozin (oral 10mg QD) ± semaglutide (SC 1mg QW) vs. placebo for 48 weeks	<b>Primary Endpoint:</b> resolution of MASH without worsening in fibrosis from baseline at 48 weeks

## Ozempic; Wegovy (semaglutide SC) - Clinical Trials (2 of 3)

Trial	Patients	Treatment	Endpoints
Phase II - US, Germany, Spain, UK <a href="#">NCT03987451</a> Start: June 2019 1° Completed: April 2021 <b>Completed: June 2021</b>	65 MASH patients aged 18-75 years with F4 (cirrhosis) on biopsy, NAS ≥3 (score ≥1 for lobular inflammation and ballooning), BMI ≥27kg/m <sup>2</sup> or liver stiffness >14kPa by FibroScan	semaglutide (SC 2.4mg QW) vs. placebo	<p><b>Primary Endpoint:</b> ≥1 stage improvement of fibrosis with no worsening of MASH from baseline at 48 weeks  <u>ILC 2022:</u>      Semaglutide failed to meet primary endpoint of ≥1 stage impr. in fibrosis without worsening in MASH vs. pbo.      - The proportion of pts achieving MASH resolution was not sign. different for semaglutide vs. pbo.      - Semaglutide sign. reduced liver fat by MRI-PDFF at 24 weeks which was sustained at 48 weeks.      - Baseline MRE was slightly higher in the semaglutide arm vs. pbo, but despite a numerical reduction in MRE, no sign. effect of semaglutide was seen compared to pbo.      - Semaglutide sign. reduced PRO-C3 at 24 weeks which was sustained at 48 weeks.      - Semaglutide elicited early reductions in liver enzymes which were sustained at 48 weeks.      - Semaglutide sign. reduced BW (ETD -8.75kg P≤0.0001) and A1c (ETD -1.63% P≤0.0001) vs. pbo.      - Semaglutide sign. improved TG and VLDL-C vs. pbo, while no sign. changes in HDL-C, LDL-C, FFA, or total cholesterol were observed.      - Semaglutide appeared safe and was well-tolerated in MASH pts with compensated cirrhosis.      - Most common AEs were GI-related of mild to moderate severity.      - Hepatic and renal function remained stable.      - An exploratory post-hoc analysis evaluating histological endpoints by PathAI (machine learning) showed no sign. difference between semaglutide and pbo similarly to manual reading.      - PathAI tended to identify fewer pts achieving endpoint events vs. pathologist evaluation.</p>
Phase II - US <a href="#">NCT03987074</a> Start: July 2019 1° Completed: July 2020 <b>Completed: July 2020</b>	109 patients aged 18-75 years with MASH and F2-3 on historical biopsy OR MASLD with FibroTest, MRI-PDFF, and FibroScan, ALT ≤5xULN, eGFR ≥30mL/min/1.73m <sup>2</sup> , A1c ≤9.5%, BMI >23kg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>- semaglutide (0.24-2.4mg SC QW), semaglutide dose escalated every 4 weeks for all treatment arms vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 30mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 100mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) + cilofexor (oral 30mg QD) vs.</li> </ul>	<p><b>Primary Endpoint:</b> number of patients with TEAEs up to 24 weeks plus 30 days  <u>AASLD 2020 Oral LO2:</u>      All treatment regimens were safe and well-tolerated.      - Two SAEs occurred, one with semaglutide (grade 3 diarrhea) and one with sema + cilofexor (100mg) (grade 3 pancreatitis); both led to discontinuation of study drug.      - Most common AEs were GI related, consistent with GLP-1 agonism.      - Minimal (5-10%) pruritus was observed in cilofexor groups only; all grade 1 and none leading to discontinuation.      - 5-14% of pts discontinued any study drug due to AEs.      - of 8 pts with AEs leading to discontinuation of study drug, 6 were GI related, one due to skin burning sensation, and one due to hyperesthesia.      - Few grade 3 and 4 lab abnormalities were observed.       <ul style="list-style-type: none"> <li>- one event of hypertriglyceridemia (577mg/dL) was reported in a pt in the sema + fir arm (baseline TG 487mg/dL).</li> <li>- CPK elevations in two pts in the sema + cilofexor (100mg) arm; both deemed unrelated to study drug.</li> <li>- LDL-C increased in the sema + cilofexor (100mg) arm, but not in the sema + cilofexor (30mg) and sema + fir + cilofexor (30mg) arms.</li> <li>- Mild TG increases were observed in arms containing ACC inhibitor firsocostat.</li> <li>- Weight loss at 24 weeks was similar across treatment groups ranging -7.0 to -9.6%.</li> <li>- Absolute liver fat was reduced in all treatment groups with the greatest reductions in arms containing firsocostat.</li> <li>- similar findings to MRI-PDFF data were observed with CAP.</li> </ul> </p>

continued

## Ozempic; Wegovy (semaglutide SC) - Clinical Trials (3 of 3)

Trial	Patients	Treatment	Endpoints
Phase II - US <a href="#">NCT03987074</a> Start: July 2019 1° Completed: July 2020 Completed: July 2020	109 patients aged 18-75 years with MASH and F2-3 on historical biopsy OR MASLD with FibroTest, MRI-PDFF, and FibroScan, ALT ≤5xULN, eGFR ≥30mL/min/1.73m <sup>2</sup> , A1c ≤9.5%, BMI >23kg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>- semaglutide (0.24-2.4mg SC QW), semaglutide dose escalated every 4 weeks for all treatment arms vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 30mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + cilofexor (oral 100mg QD) vs.</li> <li>- semaglutide (0.24-2.4mg SC QW) + firsocostat (oral 20mg QD) + cilofexor (oral 30mg QD)</li> </ul>	<p><i>Continued</i></p> <ul style="list-style-type: none"> <li>- A large proportion of pts (≥80%) achieved ≥30% reduction in relative liver fat, and more pts in combination Tx groups achieved ≥30, 50, and 70% reduction in relative liver fat vs. semaglutide mono Tx.</li> <li>- Reductions in ALT were potentiated in all combination arms vs. semaglutide.</li> <li>- At 24 weeks, AST, GGT, CK18-M30, and ELF were sign. improved in all treatment arms from baseline, but no additive effect of combination Tx was observed.</li> <li>- Similar reductions in Liver stiffness by VCTE was observed across treatment arms, and no inter-group differences were observed with liver stiffness by MRE.</li> <li>- Liver stiffness was improved in all treatment arms, and to a greater extent with combination Tx.</li> <li>- More pts on combination therapy achieved ≥25% reduction in liver stiffness (53-60%) vs. semaglutide (36%).</li> <li>- FAST score was improved by all treatments and to a sign. greater extent with all combinations except sema + ciло (100mg) vs. semaglutide mono Tx.</li> <li>- Glycemic parameters were improved to a similar degree in all treatment arms.</li> </ul>
Phase II - Global <a href="#">NCT02970942</a> Start: Nov. 2016 1° Completed: Feb. 2020 Completed: March 2020	320 patients aged 18-75 years with biopsy-proven MASH, NAS ≥4 F2-F3	semaglutide (0.1, 0.2, or 0.4mg SC QD) vs. placebo for 72 weeks	<p><b>Primary Endpoint:</b> resolution of MASH without worsening of fibrosis at 72 weeks</p> <p><b>Secondary Endpoints:</b> ≥1 stage fibrosis improvement without worsening of MASH, change in NAS, change in fibrosis, change in activity component of steatosis-activity-fibrosis (SAF) score, change in FPG or A1c or ELF</p> <p><u>May 2020 press release + June R&amp;D investor presentation + AASLD 2020 Oral 10:</u></p> <ul style="list-style-type: none"> <li>- Sign. more patients in all semaglutide treated cohorts achieved MASH resolution without worsening of fibrosis vs. pbo.</li> <li>- Numerically, more patients achieved improvement in fibrosis without worsening of MASH, but this did not achieve sign. in any semaglutide dose groups.</li> <li>- Sign. fewer patients on semaglutide (0.4mg) experienced fibrosis progression vs. pbo</li> <li>- Semaglutide elicited a dose-dependent reduction in progression of fibrosis assessed by liver biopsy, biomarker panels, and elastography using FibroScan.</li> <li>- Improvements in ELF score were sign. greater for all semaglutide dose groups vs. pbo and liver stiffness was significantly reduced from baseline vs. pbo.</li> <li>- Liver enzymes were markedly improved by semaglutide.</li> <li>- In patients with T2D at baseline semaglutide elicited reductions in A1c to ~6% accompanied by double-digit weight loss.</li> <li>- Most common AEs were GI related, consistent with what is generally seen with GLP-1 agonism.</li> <li>- Four patients (three on semaglutide 0.4mg and one on pbo) discontinued treatment due to AEs; two patients in the semaglutide 0.4mg dose group discontinued treatment due to GI AEs.</li> </ul>

# Insulins

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## ORMD-0801

## Next Milestone

Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US, EU Nov. 2020; Israel April 2018)	Oramed Pharmaceuticals Inc. (Originator)	prandial insulin oral	MASH with T2D	
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<ul style="list-style-type: none"> <li>Oral</li> <li>The Office of the Chief Scientist of Israel's Ministry of Industry, Trade and Labor has awarded Oramed a\$US540 000 grant to support advancement OMD-0801 and oral GLP-1 ORMD 0901. The grant provides the funding Oramed needs to assist in covering the cost of the upcoming FDA-approved Phase II trials.</li> </ul>	<ul style="list-style-type: none"> <li>Risk of oral cancer</li> </ul>			
Key Milestones	CVrg Synopsis			
<ul style="list-style-type: none"> <li><b>Nov. 2020:</b> Oramed initiates Belgian Phase II trial in MASLD patients with T2D</li> <li><b>Nov. 2020:</b> Oramed initiates US/Israeli Phase II trial in MASLD patients with T2D</li> <li><b>Nov. 2017:</b> Oramed to initiate exploratory trial of oral insulin ORMD-0801 in MASH patients</li> </ul>	<p>ORMD-0801 is an oral insulin formulation in Phase III development for T2D and in Phase II development for MASH. Oral insulin is an interesting concept, since it more closely mimics physiological insulin than SC dosing, though, many experts believe having high levels of insulin circulating through the body increases health risks.</p> <p>ORMD-0801 has demonstrated significant reductions in A1c in T2D patients accompanied by an excellent safety profile with no serious drug-related adverse events and no increased frequency of hypoglycemic episodes or weight gain vs. placebo. Topline data on ORMD-0801 from a small (N=8) pilot study in T2D patients with MASH showed improvements in liver fat and GGT, and data from a Phase II trial in MASLD patients with T2D showed consistent clinically favorable data for liver fat by MRI-PDFF, steatosis and fibrosis by FibroScan, lipids, and A1c. A potential role for oral insulin in MASH needs further validation in a larger scale trial.</p>			

## ORMD-0801 - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II - Belgium <a href="#">NCT04616014</a> Start: March 2021 1° Completed: July 2022 <b>Completed: Sep. 2022</b>	7 MASLD patients with T2D aged 18-70 years, BMI $\geq 25\text{kg/m}^2$ , FPG $\geq 126\text{mg/dL}$ or 2h PPG following an OGTT $\geq 200\text{mg/dL}$ or A1c $> 6.5\%$ or treated with metformin $\pm \leq 2$ of SU, DPP+4i, GLP+1, and TZDs, liver fat $> 8\%$ (MRI-PDFF), CAP $\geq 238\text{dB/m}$ , abnormal liver enzymes $\leq 5\times\text{ULN}$ , F2-3 defined by FibroScan liver stiffness 6-12kPa	ORMD-0801 (oral 16mg QDAM) for 12 weeks	<b>Primary Endpoint:</b> safety <u>ClinicalTrials.gov:</u> <ul style="list-style-type: none"> <li>- Liver fat increased by 0.3% at 12 weeks.</li> <li>- LSM by FibroScan was reduced by <math>-0.7\text{kPa}</math> (BL <math>7.7\text{kPa}</math>).</li> <li>- FibroScan CAP increased by <math>10.7\text{dB/m}</math> (BL <math>318\text{dB/m}</math>).</li> <li>- No deaths or SAEs were reported.</li> </ul>
Phase II - US, Israel <a href="#">NCT04618744</a> Start: Nov. 2020 1° Completed: June 2022 <b>Completed: June 2022</b>	33 MASLD patients with T2D aged 18-70 years, BMI $\geq 25\text{kg/m}^2$ , FPG $\geq 126\text{mg/dL}$ or 2h PPG following an OGTT $\geq 200\text{mg/dL}$ or A1c $> 6.5\%$ or treated with metformin $\pm \leq 2$ of SU, DPP+4i, GLP+1, and TZDs, liver fat $> 8\%$ (MRI-PDFF), CAP $\geq 238\text{dB/m}$ , abnormal liver enzymes $\leq 5\times\text{ULN}$ , F2-3 defined by FibroScan liver stiffness 6-12kPa	ORMD-0801 (oral 8mg BID) for 12 weeks	<b>Primary Endpoint:</b> safety <u>Sep. 2022:</u> <ul style="list-style-type: none"> <li>- ORMD-0801 was safe and well-tolerated showing no difference in AEs vs. placebo.</li> <li>- ORMD-0801 showed consistent clinically favorable data for liver fat by MRI-PDFF, steatosis and fibrosis by FibroScan, lipids, and A1c.</li> </ul>
Phase II - Israel <a href="#">NCT02653300</a> Start: Sep. 2018 1° Completed: March 2020 <b>Completed: April 2020</b>	10 T2D patients with moderate hepatic steatosis (6-32% hepatocytes with steatosis by ultrasound)	ORMD-0801 (oral undisclosed dose) for 12 weeks	<b>Primary Endpoint:</b> change in MRI-PDFF from baseline at 12 weeks Previous primary endpoints of change in liver stiffness (FibroScan) and fibrosis score are now secondary endpoints <u>ADA 2020, 115-LB:</u> <ul style="list-style-type: none"> <li>- ORMD-0801 sign. reduced absolute liver fat from baseline in all included patients with a mean of <math>-6.9\%</math> (<math>P=0.047</math>); this corresponded to a relative reduction of <math>-29.8\%</math></li> <li>- ORMD-0801 sign. reduced GGT by <math>-14.3\text{ U/L}</math> (<math>P=0.008</math>) and fasting insulin levels by <math>-96.5\text{pmol/L}</math> (<math>P=0.035</math>)</li> <li>- No serious or severe AEs were observed throughout the study</li> </ul>

# Lipid Modulators

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Ervogastat				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US June 2020)	Pfizer (Originator)	DGAT2 inhibitor oral (BID)	MASH	
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinel
<ul style="list-style-type: none"> <li>Mitigates ACCi induced hypertriglyceridemia in rodents</li> <li>Fast Track Designation in combination with clesacostat</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Aug. 2020:</b> Pfizer initiates US Phase II dose-finding trial in MASLD</li> <li><b>Nov. 2019:</b> PF-05221341 + PF-06865571: no increased toxicity or meaningful PK interactions with co-administration</li> </ul>		<p>Ervogastat is a small molecule inhibitor of systemic DGAT2. At AASLD 2019, Pfizer presented data from a US Phase I trial showing improvements in liver fat, plasma lipids, and liver enzymes with ervogastat in MASLD patients. DGAT2 inhibition has shown to mitigate ACCi induced increases in plasma TG and Pfizer is investigating those two MOAs in a combination dubbed PF-07055341. Phase II data presented at ILC 2020 showed potent reductions in liver fat with clesacostat and DGAT2 inhibitor ervogastat while no additive effect was seen of combination. Ervogastat fully mitigated the ACCi induced increase in TG. A Phase IIb trial, MIRNA, investigating the effect of ervogastat monotherapy or combination treatment on histological endpoints in ~250 MASH patients with F2-F3 fibrosis was initiated in June 2020. The trial completed in April 2024 – no data have yet been released.</p>		

## ervogastat - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>MIRNA</b> Phase II - Global <a href="#">NCT04321031</a> Start: June 2020 1° Completion: Jan. 2024 <b>Completed:</b> April 2024	258 MASH patients aged 18-75 years, F2-F3 fibrosis, BMI $\geq 22.5\text{kg/m}^2$	<ul style="list-style-type: none"> <li>- ervogastat (oral 25, 75, 150, or 300mg BID or 150 or 300mg QD vs.</li> <li>- ervogastat + clesacostat (oral 150mg/5mg or 300mg/10mg BID) vs.</li> <li>- placebo for 48 weeks</li> </ul>	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- resolution of MASH without worsening of fibrosis from baseline at 48 weeks AND/OR</li> <li>- <math>\geq 1</math> stage improvement in fibrosis without worsening in MASH from baseline at 48 weeks</li> </ul>
Phase II - US <a href="#">NCT03776175</a> Start: Jan. 2019 1° Completed: Sep. 2019 <b>Completed: Oct. 2019</b>	99 MASLD patients with overweight/obesity aged 18-70 years, BMI $\geq 25\text{kg/m}^2$ , body weight $>50\text{kg}$ liver fat $\geq 8\%$ by MRI-PDFF, T2D on $\leq 1$ OAD OR metabolic syndrome with $\geq 2$ of FPG $\geq 10\text{mg/dL}$ , $\geq 1$ stage hypertension, HDL $<40\text{mg/dL}$ (males) $<50\text{mg/dL}$ (females), TG $\geq 150\text{mg/dL}$ , or waist circumference $>102\text{cm}$ (males) $>89\text{cm}$ (females)	clesacostat (oral 15mg BID) or ervogastat (oral 300mg BID) or clesacostat + ervogastat (oral 15mg and 300mg BID, respectively) vs. placebo for 6 weeks	<p><b>Primary Endpoint:</b> relative change in liver fat (by MRI-PDFF) from baseline at 6 weeks</p> <p><b>ILC 2020:</b></p> <ul style="list-style-type: none"> <li>- Improvements in liver fat were sign. greater with all active treatments vs. pbo; ACCi monoTx and ACCi+DGAT2i combiTx showed numerically greater reduction vs. DGAT2i monoTx.</li> <li>- More ACCi and ACCi+DGAT2i treated patients achieved <math>\geq 30</math> and <math>\geq 50\%</math> relative reduction in liver fat vs. DGAT2i.</li> <li>- TEAE occurrence was low and similar across treatment groups.</li> <li>- Most common TEAEs were diarrhea, UTI, and rash; all TEAEs were mild to moderate except for one severe TEAE of TG increase which was considered treatment related (on ACCi, resolved and patient discontinued Tx).</li> <li>- ALT and AST transiently increased with all active treatments, and after day 14, levels trended down ending below and near baseline for ALT and AST, respectively.</li> <li>- ACCi monoTx and ACCi+DGAT2i combiTX elicited an increase in GGT, while DGAT2i monoTx significantly reduced GGT.</li> <li>- ACCi monoTx sign. increased ALP, while DGAT2i monoTx significantly reduced ALP vs. pbo, both trending back to baseline in follow-up; ALP for ACCi+DGAT2i combiTX was similar to pbo.</li> <li>- In the ACCi monoTx arm, triglycerides were sign. increase vs. pbo starting at day 14, which was mitigated by combination treatment with DGAT2i.</li> <li>- HDL-C was significantly reduced in all active treatment arms vs. pbo.</li> <li>- Patients receiving ACCi and DGAT2i combination treatment experienced a significant decrease in total cholesterol at day 42 vs. pbo (-9.6% [90% CI: -16.3, -2.4]), as well as sign. greater reductions in PCSK9 vs. pbo.</li> <li>- Changes in ApoB100 were not significantly different from placebo in any active treatment group.</li> <li>- ACCi treated patients experienced sign. increases in ApoC3 vs. pbo (<math>P &lt; 0.001</math>), while ApoC3 levels in the combination group were no different than pbo indicating DGAT2i mitigated the ACCi induced increase.</li> </ul>

## ION224

## Next Milestone

Status	Companies	MOA/ROA	Target Population
Phase IIb non-cirrhotic MASH (US Jan. 2021)	Ionis (Originator)	DGAT2 inhibitor SC	MASH with T2D and/or overweight/obesity
Strengths/Opportunities		Weaknesses/Threats	
<ul style="list-style-type: none"> <li>Data on predecessor IONIS-DGAT2Rx data showed improved liver fat</li> <li>Significant improvements in liver histology</li> </ul>		<ul style="list-style-type: none"> <li>Other DGAT inhibitors including Pfizer's ervogastat currently in Phase II development</li> </ul>	
Key Milestones		CVrg Synopsis	
<ul style="list-style-type: none"> <li><b>March 2024:</b> ION224 potently reduces liver fat and improves MASH and fibrosis</li> <li><b>June 2021:</b> Ionis initiates US Phase IIb trial in MASH</li> <li><b>May 2020:</b> ION224, DGAT2 inhibitor in Phase I development for MASH</li> </ul>		<p>ION224 is a second-generation ligand conjugated antisense (LICA) DGAT2 inhibitor with a similar sequence to previous Phase II asset IONIS-DGAT2Rx, but this LICA version targets the liver with higher specificity increasing potency allowing for less frequent and smaller doses, and potentially fewer side effects. DGAT2 inhibition is intended to reduce hepatic synthesis of triglycerides, and clinical data on IONIS-DGAT2Rx showed potent reductions in liver fat with no changes in plasma lipids, glucose, or body weight in a Phase II trial in MASLD patients with T2D (ILC 2019). A Phase IIb trial of ION224 in MASH patients was initiated in June 2021, and data released in March 2024 showed significant improvements in both MASH and fibrosis. No future development plans have yet been disclosed.</p>	

## 2024 Sentinels

- March 2024:** ION224 (Ionis) potently reduces liver fat and improves MASH and fibrosis

## ION224 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - US  <a href="#">NCT04932512</a>          Start: June 2021          1° Completion: Jan. 2023  <b>Completed:</b> March 2024</p>	<p>160 MASH patients aged 18-75 years, BMI <math>\geq 25\text{kg}/\text{m}^2</math>, liver fat <math>\geq 10\%</math>, &lt;5% weight loss in previous 3 months, ALT and AST <math>\leq 200\text{U/L}</math>, bilirubin <math>\leq 1.3\text{mg/dL}</math></p>	<p>- Part 1: 93 patients received ION224 (SC 60, 90, or 120mg Q4W) vs. placebo for 49 weeks-          Part 2: 67 patients received ION224 (SC 90 or 120mg Q4W) vs. placebo for 49 weeks</p>	<p><b>Primary Endpoint:</b> <math>\geq 2</math>-point reduction in NAS (<math>\geq 1</math>-point improvement in ballooning or lobular inflammation) without worsening in fibrosis  <b>March 2024:</b>          - ION224 (both doses) met the primary endpoint with sign. more pts achieving <math>\geq 2</math>-pt improvement in NAS vs. pbo.          - A subgroup analysis showed sign. histological improvements in both F2 and F3 pts.          - Sign. more ION224-treated pts achieved MASH resolution without worsening in fibrosis vs. pbo.          - 44% of ION224 (120mg) treated pts achieved <math>\geq 50\%</math> reduction in liver fat by MRI-PDFF vs. 3% for pbo.          - 32% of ION224 (120mg) treated pts achieved <math>\geq 1</math> stage improvement in fibrosis without worsening in MASH vs. 12.5% for pbo.          - ION224 was generally safe and well-tolerated with no worsening of hepatic or renal function, and no GI AEs were reported.          - The rate of termination was lower for ION224 vs. placebo, and no deaths or treatment-related SAEs were reported.</p>

icosabutate				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US July 2019)	BASF (Owner), NorthSea Therapeutics (Netherlands)	structurally enhanced omega-3 fatty acid oral (QD)	MASH and dyslipidemia	<ul style="list-style-type: none"> <li>NorthSea plans to pursue Phase III dev. in MASH with T2D</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Improvement of liver enzymes in dyslipidemic patients at risk for MASH</li> <li>Improved TG, non-HDL-C, and insulin sensitivity</li> <li>Improved fibrosis NITs in MASH patients</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Nov. 2023:</b> ICONA: icosabutate fails to meet primary endpoint – shows efficacy in MASH with T2D</li> <li><b>Jan. 2021:</b> Icosabutate, topline interim data from Phase IIb ICONA show improvement in liver enzymes and plasma lipids</li> <li><b>Aug. 2019:</b> NorthSea initiates US Phase II trial of icosabutate in MASH F1-3</li> </ul>		<p>Omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are approved for the management of hypertriglyceridemia, however, the nature of unmodified fatty acids has previously shown to be challenging due to marked dose-related increases in β-oxidation. Icosabutate is a structurally engineered fatty acid (SEFA) that in a range of patients with elevated liver enzymes showed rapid improvements in liver enzymes, TG, non-HDL-C, and insulin sensitivity. In July 2019, NorthSea initiated Phase IIb trial ICONA to investigate efficacy of two doses of icosabutate in MASH patients with fibrosis. Interim data from a cohort of 90 patients at 16 weeks released in January 2021, showed significant reductions in liver enzymes, plasma TG, and non-invasive markers of fibrosis, and further data presented at ILC 2021 showed early improvements in non-invasive fibrosis marker ELF. Histology data from ICONA presented at AASLD 2023 showed icosabutate failed to meet the primary endpoint of MASH resolution without worsening in fibrosis in the overall study population but showed significant improvements in MASH patients with baseline T2D. NorthSea plans to “<i>pursue a registrational development path</i>” for icosabutate for the treatment of MASH patients with T2D.</p>		

## icosabutate - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>ICONA</b> Phase II - US <a href="#">NCT04052516</a> Start: July 2019 1° Completed: Feb. 2022 <b>Completed: Dec. 2022</b>	280 MASH patients aged 18-75 years, NAS ≥4, F1-3 fibrosis (F1 <30% of patients), liver fat ≥10% (MRI-PDFF)	icosabutate (oral 300 or 600mg QD) vs. placebo for 52 weeks	<p><b>Primary Endpoint:</b> MASH resolution (ballooning score=0, lobular inflammation score=0 or 1) without worsening of fibrosis from baseline at 52 week</p> <p><b>AASLD 2023:</b></p> <ul style="list-style-type: none"> <li>- At 52 weeks, icosabutate (both doses) failed to meet the primary endpoint of MASH resolution without worsening in fibrosis vs. pbo.</li> <li>- Sign. more icosabutate (600mg) treated pts achieved MASH resolution with ≥2-pt reduction in NAS and no worsening in fibrosis vs. pbo.</li> <li>- While a numerically greater proportion of icosabutate-treated pts achieved improvement in fibrosis without worsening in NAS vs. pbo, neither achieved statistical sign..</li> <li>- Among pts with BL T2D, icosabutate efficacy on histology endpoints was greater compared to the full study cohort with sign. more icosabutate (600mg) treated pts achieving MASH resolution without worsening in fibrosis and MASH resolution with ≥2-pt reduction in NAS and no worsening in fibrosis.</li> <li>- Among pts with BL T2D, sign. more icosabutate-treated pts (both doses) achieved improvement in fibrosis without worsening in NAS vs. pbo.</li> <li>- Sign. more icosabutate-treated pts (600mg) in the overall and T2D population achieved ≥1 stage improvement in qFibrosis.</li> <li>- Icosabutate (both doses) rapidly (4 weeks) reduced liver enzymes which was sustained for the remainder of the study.</li> <li>- Icosabutate (600mg) sign. reduced fibrosis markers ELF and PRO-C3 vs. pbo, which was even more pronounced in pts with baseline T2D.</li> <li>- T2D pts with baseline PRO-C3 levels ≥15.5ng/mL (cut-off level for detection of ≥F3) saw even greater reductions.</li> <li>- Among T2D pts with A1c ≥6.5%, icosabutate (both doses) sign. reduced A1c vs. pbo.</li> <li>- Icosabutate (both doses) sign. reduced hsCRP vs. pbo.</li> <li>- Icosabutate showed 30% reduction in LDL-C among pts with baseline LDL-C &gt;100mg/dL, while no effects on liver fat or body weight with icosabutate were reported.</li> <li>- Icosabutate was well-tolerated with most frequently reported AEs being mild to moderate GI-related events.</li> <li>- No DILI or clinically significant changes in vital signs, physical exams, or ECGs were reported.</li> <li>- No differences between the overall population and pts with baseline T2D were identified.</li> </ul> <p><b>Press release Jan. 2021 + ILC 2021:</b></p> <ul style="list-style-type: none"> <li>- Icosabutate (600mg) sign. reduced liver enzymes ALT by -25U/L and GGT -29U/L (pbo-adjusted) vs. pbo (both P&lt;0.0001).</li> <li>- Icosabutate sign. reduced plasma triglycerides -35% from baseline (P&lt;0.02).</li> <li>- Icosabutate sign. reduced non-invasive markers of fibrosis including PRO-C3.</li> <li>- Baseline hsCRP levels varied widely among treatment groups and was generally higher in the two icosabutate arms, however, icosabutate (600mg) sign. reduced hsCRP vs. pbo.</li> <li>- Icosabutate dose-dependently improved ELF as well as individual components of ELF vs. pbo.</li> <li>- Icosabutate (600mg) sign. reduced A1c (-0.2% estimated from graph) vs. pbo.</li> <li>- Median HOMA-IR at baseline varied among groups and was generally higher in the two icosabutate arms; numerical improvements did not reach sign. vs. pbo.</li> <li>- Icosabutate (both doses) significantly improved AST, ALP, and total bilirubin (600mg only) vs. placebo.</li> </ul>

AZD2693				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (EU, Asia, S. America March 2023)	AZ (Originator)	PNPLA3 inhibitor SC	MASH with genetic risk factors	• Nov. 2025: Expected completion of Phase IIb trial FORTUNA
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Genetic target implicated in MASLD</li> </ul>		<ul style="list-style-type: none"> <li>Early-phase programs targeting PNPLA3 including ARO-PNPLA3 (J&amp;J/Arrowhead), LY3849891 (Lilly), and ALN PNP (Alnylam/Regeneron)</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>April 2023:</b> AZ initiates Phase IIb trial in MASH F2-F3 carriers of PNPLA3 rs738409 148M</li> </ul>		<p>AZD2693 is an antisense oligonucleotide (ASO) targeting patatin-like phospholipase domain-containing protein 3 (PLPNA3), which is involved in intracellular lipid metabolism. Expression of the rs738409 148 allele is associated with liver fat accumulation, and depletion of PNPLA3 in preclinical models has shown to resolve excess fat accumulation, suggesting PNPLA3 targeting as a potential treatment strategy.</p> <p>In March 2023, AZ initiated Phase IIb study, FORTUNA, in 180 MASH F2-F3 carriers of rs738409 (PNPLA3 148M).</p>		

## AZD2693 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>FORTUNA</b> Phase II - Global <a href="#">NCT05809934</a> Start: March 2023 1° Completion: Nov. 2025 Completion: Nov. 2025	180 MASH patients aged 18-75 years, carriers of rs738409 (PNPLA3 148M), F2-F3, NAS ≥4	AZD2693 (SC one of two undisclosed doses QM) vs. placebo	<b>Primary Endpoint:</b> MASH resolution without worsening in fibrosis from baseline at 52 weeks
Phase I - US, Mexico <a href="#">NCT04483947</a> Start: Nov. 2020 1° Completed: Dec. 2023 <b>Completed:</b> Dec. 2023	74 MASH patients aged 18-75 years, F0-F3, homozygous for rs738409 (PNPLA3 148M), liver fat ≥7%, BMI 25-45kg/m <sup>2</sup> , liver fat ≥7% and one of the following: - liver biopsy (<3 years) F0-F3 or - MRE 2.55-3.63kPa or VCTE 7.1-11.9kPa or - consent for liver biopsy or MRE/VCTE at screening if previous date not available One cohort will enroll participants who are heterozygous for PNPLA3 148M	AZD2693 (one of three undisclosed doses SC QM) vs. placebo for 8 weeks; the first and third drug administration will follow a 10h fast	<b>Primary Endpoint:</b> AEs from baseline up to 32 weeks

# GSK4532990

GSK4532990				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US Jan. 2023) Phase IIb cirrhotic MASH (US March 2024)	Arrowhead (Originator), GSK (Licensee)	HSD17B13 siRNA SC	MASH with genetic risk factors	<ul style="list-style-type: none"> <li>Sep. 2025: Expected primary completion of Phase IIb trial HORIZON</li> </ul>
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<ul style="list-style-type: none"> <li>Genetic target implicated in MASLD</li> </ul>	<ul style="list-style-type: none"> <li>rapirosiran sodium (Alnylam/Regeneron)</li> </ul>			<ul style="list-style-type: none"> <li><b>March 2024:</b> GSK4532990, GSK updates protocol of US Phase IIb trial HORIZON to include F4 patients</li> </ul>
Key Milestones	CVrg Synopsis			
<ul style="list-style-type: none"> <li><b>March 2024:</b> GSK updates protocol of US Phase IIb trial HORIZON to include F4 patients</li> <li><b>Oct. 2022:</b> GSK plans Phase IIb trial HORIZON in MASH F3</li> <li><b>Nov. 2021:</b> GSK and Arrowhead enter exclusive license agreement for ARO-HSD in all territories except Greater China</li> <li><b>Nov. 2021:</b> ARO-HSD, dose-dependent inhibition of hepatic HSD17B13 associated with ALT reduction in MASH</li> </ul>	<p>GSK4532990 is an siRNA therapeutic targeting hydroxysteroid dehydrogenase HSD17B13, which is involved in metabolism of hormones, fatty acids, and bile acids. Genetic human data show loss of function of HSD17B13 provides protection from chronic liver disease, and Phase I data of GSK4532990 (previously ARO-HSD) presented at ILC and AASLD 2021 showed strong dose-dependent PD effects markedly reducing HSD17B13 mRNA and protein levels, which were accompanied by reductions in ALT and AST; however, effects on liver fat and liver stiffness were highly variable between patients.</p> <p>GSK4532990 was the first RNA technology targeting HSD17B13 to clinical development for the treatment of MASH and is now in late-stage development in Phase IIb trial HORIZON that will evaluate efficacy of GSK4532990 on liver histology in ~250 MASH F3 patients; in March 2024 the study population of HORIZON was expanded to include F4 patients.</p>			

## GSK4532990 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>SKYLINE</b> Phase II - US, EU <a href="#">NCT06104319</a> Start: Jan. 2024 1° Completion: June 2025 Completion: June 2025	48 MASH patients aged 18-75 years	GSK4532990 (SC one of four undisclosed single doses)	<b>Primary Endpoint:</b> %change in liver HSD17B13 protein and mRNA expression levels from baseline at 16 weeks
<b>HORIZON</b> Phase II - US <a href="#">NCT05583344</a> Start: Jan. 2023 1° Completion: Sep. 2025 Completion: Dec. 2025	246 MASLD patients aged 18-75 years, BMI $\geq 25\text{kg}/\text{m}^2$ (BMI $\geq 23\text{kg}/\text{m}^2$ for Asians), NAS $\geq 4$ ( $\geq 1$ point in each of steatosis, inflammation, and ballooning, F3-F4)	GSK4532990 (SC low or high dose likely QM) vs. placebo	<b>Primary Endpoints:</b> - $\geq 1$ stage improvement in fibrosis without worsening in MASH from baseline at 52 weeks (F3 patients) - MASH resolution without worsening in fibrosis from baseline at 52 weeks (F3 patients)
<b>AROHSD1001</b> Phase I - NZ <a href="#">NCT04202354</a> Start: March 2020 1° Completed: Sep. 2021 <b>Completed: Nov. 2021</b>	50 healthy subjects and patients with MASH or suspected MASH aged 18-65 years	ARO-HSD single and multiple ascending SC doses vs. placebo	<b>Primary Endpoint:</b> Safety up to 113 days post-dose in SAD and up to 196 days post-dose in MAD <u>ILC 2021 + AASLD 2021:</u> - ARO-HSD was safe and well-tolerated and all AEs were mild; no grade 3 or 4 lab abnormalities were reported. - No drug related serious or severe AEs were reported, and no pts discontinued treatment. - Two cases of mild injection site bruising and two cases of erythema were reported with ARO-HSD. - ARO-HSD dose-dependently reduced HSD17B13 mRNA in all pts by up to $>90\%$ in the 200mg dose group. - HSD17B13 protein levels at day 71 were reduced by all ARO-HSD dose-levels with multiple measurements $<$ lower limit of detection for the assay. - ARO-HSD ( $\geq 100\text{mg}$ ) decreased ALT and AST. - ARO-HSD decreased liver fat in 9 of 18 pts (ranging 4-41%) and liver stiffness in 6 of 18 pts (ranging 4-37%). - PD of ARO-HSD were not affected by HSD17B13 (rs72613567, T>TA) or PNPLA3 (rs738409, C>G) mutations.

rapirosiran sodium (ALN-HSD)				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US, Jp Oct. 2022)	Alnylam (Originator), Regeneron (Licensee)	HSD17B13 RNAi SC	MASH with genetic risk factors	<ul style="list-style-type: none"> <li>Sep. 2027: Expected completion of Phase IIb trial NASHGEN-2</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Genetic target implicated in MASLD</li> </ul>		<ul style="list-style-type: none"> <li>GSK4532990 (previously ARO-HSD, GSK/Arrowhead)</li> </ul>		<ul style="list-style-type: none"> <li><b>March 2024:</b> Rapirosiran sodium (ALN-HSD), Regeneron terminates UK Phase I trial due to business reasons</li> <li><b>Feb. 2024:</b> ALN-HSD, Regeneron reduces N and number of arms, delays completion of Phase IIb NASHGEN-2 by 9 months</li> </ul>
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Sep. 2022:</b> Phase I data of rapirosiran sodium show knockdown of HSD17B13 associated with reduction in liver enzymes and NAS</li> <li><b>Aug. 2022:</b> Regeneron plans Phase IIb trial in MASH F2-F3 evaluating efficacy on qFibrosis</li> <li><b>Sep. 2020:</b> Alnylam initiates UK Phase I SAD/MAD trial</li> </ul>		<p>Rapirosiran sodium (ALN-HSD) is an RNAi therapeutic targeting hydroxysteroid dehydrogenase HSD17B13, which is involved in metabolism of hormones, fatty acids, and bile acids. Genetic human data show loss of function of HSD17B13 provides protection from chronic liver disease. Alnylam is developing rapirosiran sodium in collaboration with Regeneron utilizing Alnylam's Enhanced Stabilization Chemistry Plus (ESC+) GalNAc-conjugate technology, which enables subcutaneous dosing with increased selectivity and a wide therapeutic index.</p> <p>Rapirosiran sodium was the second RNA technology targeting HSD17B13 to enter clinical development for MASH following GSK/Arrowhead's GSK-4532990.</p> <p>Following release of data from a Phase I trial showing potent knockdown of HSD17B13, Alnylam/Regeneron initiated a Phase IIb study in MASH F2-F3 patients with genetic risk factors.</p>		

## ALN-HSD - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>NASHGEN-2</b> Phase II - US, Japan, S. Korea, Puerto Rico <a href="#">NCT05519475</a> Start: Feb. 2023 1 <sup>o</sup> Completion: Sep. 2027 Completion: Sep. 2027	120 MASH patients aged 18-75 years, F2-F3, NAS ≥4, undisclosed genetic risk factors	rapirosiran sodium (SC on undisclosed dose) vs. placebo	<b>Primary Endpoint:</b> change in qFibrosis from baseline at 52 weeks Secondary endpoints include: ≥1 stage improvement in fibrosis without worsening in MASH and resolution of MASH without worsening in fibrosis
Phase I - UK <a href="#">NCT04565717</a> Start: Oct. 2020 1 <sup>o</sup> Completion: Jan. 2023 <b>Completed:</b> Dec. 2023	114 subjects aged 18-65 years Part A: healthy with BMI 18-30kg/m <sup>2</sup> Part B+C: BMI 18-40kg/m <sup>2</sup> , NAS ≥3	Part A: rapirosiran sodium (single SC dose) vs. placebo Part B: rapirosiran sodium (multiple undisclosed SC doses) vs. placebo Part C: rapirosiran sodium (multiple undisclosed SC doses)	<b>Primary Endpoints:</b> Parts A+B: AEs up to 3.5 months (Part A) and 12.5 months (Part B) Part C: change in HSD17B13 mRNA from baseline at 6 months <b>Part A:</b> - Among rapirosiran sodium-treated (all doses) pts, 38.6% reported TEAEs vs. 21.4% for pbo. - The only AE reported in >10% of patients was injection site reactions (11.4%) of which all were transient and mild in severity. - One SAE (tonsillitis) was reported and deemed unrelated to study drug. - No severe TEAEs, deaths, or TEAEs of clinical interest (including elevated ALT or AST) were reported. - Plasma concentrations of rapirosiran sodium declined rapidly by 24h post-dose and were undetectable at 48h in most subjects with t <sub>1/2</sub> of 4.2-6.7h. - rapirosiran sodium showed a slightly more than dose-proportional increases in exposures across doses. - rapirosiran sodium showed 17–37% excretion in urine. <b>Part B:</b> - No patients had homozygous protective alleles for any of the three variants of HSD17B13. - the proportion of pts heterozygous or homozygous for PNPLA3 I148M risk allele was balanced between rapirosiran sodium and pbo arms. - rapirosiran sodium was safe and well-tolerated; the majority of TEAEs were mild or moderate in severity. - No deaths or serious TEAEs were reported. - Two severe TEAEs were deemed unrelated to study drug (appendicitis and tooth infection). - No study interruptions or discontinuations related to study drug were reported. - No cases of Hy's law and no DILI were reported. - rapirosiran sodium (pooled) showed a trend towards lower ALT levels over time vs. pbo. - rapirosiran sodium dose-dependently reduced liver HSD17B13 mRNA vs. pbo. - rapirosiran sodium (pooled) showed numerical improvements in total NAS, ballooning, and inflammation at 6 or 12 months vs. pbo. - Numerically more rapirosiran sodium-treated (pooled) pts achieved improvement in fibrosis and fewer worsened vs. pbo.

denifanstat				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US May 2021) Phase II non-cirrhotic MASH (ROW April 2018)	Sagimet Biosciences (Originator), Ascleitis (China)	FASN inhibitor oral (QD)	MASH with fibrosis	<ul style="list-style-type: none"> <li>2H 2024: Phase III development in MASH F2-F3 expected</li> </ul>
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<ul style="list-style-type: none"> <li>TVB2640 reduced DNL, liver fat, and liver enzymes in healthy subjects and MASH patients</li> <li>Also in development for the treatment of recurrent glioblastoma</li> <li>Fast Track Designation for MASH</li> </ul>				<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> Denifanstat (Sagimet) meets primary endpoint showing impressive histology improvements in Phase IIb trial FASCINATE-2</li> </ul>
Key Milestones	CVrg Synopsis			
<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> Denifanstat meets primary endpoint showing impressive histology improvements in Phase IIb trial FASCINATE-2</li> <li><b>May 2021:</b> Sagimet initiates global Phase IIb trial FASCINATE-2 in MASH F2-F3</li> <li><b>March 2021:</b> Topline data from Chinese cohort show reductions in liver fat and ALT</li> <li><b>June 2020:</b> Topline Phase II data from FASCINATE-1 show reduced liver fat</li> <li><b>May 2019:</b> 3V Biosciences initiates US Phase II trial, FASCINATE-1, of TVB40 in MASH F1-3</li> <li><b>Feb. 2019:</b> Ascleitis enters agreement with 3-V Biosciences to develop FASN inhibitor ASC40 in Greater China, to initiate US, planning Phase II trial in MASH</li> </ul>	<p>Fatty acid synthase (FASN) inhibitor denifanstat is in development for treatment of solid tumors and metabolic disorders by Sagimet (as ASC40 by Ascleitis in China, Macau, Hong Kong, and Taiwan). Data from a small Phase I/II trial in healthy subjects, showed reductions in de novo lipogenesis, ALT, and AST. In April 2019, denifanstat entered Phase II development and data presented at ILC and AASLD 2020 showed denifanstat (50mg) elicited reductions in liver fat, accompanied by improvement of markers of inflammation and fibrosis. An additional cohort of 25-30 Chinese patients treated with denifanstat (50mg) was added to the trial in June 2020, and top-line data showed similar efficacy in this cohort compared to the initial cohorts.</p> <p>In May 2021, Sagimet initiated Phase IIb trial FASCINATE-2 to evaluate efficacy of denifanstat on histological endpoints in MASH patients with F2-F3. FASCINATE-2 met histological endpoints of both MASH resolution and fibrosis improvement compared to placebo in MASH patients with F2-F3; fibrosis improvements were confirmed by AI-based digital pathology showing significant improvements in qFibrosis. Sagimet will now hold an end-of-Phase II meeting with the FDA and anticipates initiating Phase III development with denifanstat in MASH F2-F3 patients in 2H 2024.</p>			

## TVB2640 - Clinical Trials (1 of 2)

Trial	Patients	Treatment	Endpoints
<b>FASCINATE-2</b> Phase II - US, Canada, Poland, Puerto Rico <a href="#">NCT04906421</a> Start: Aug. 2021 1° Completed: Oct. 2023 <b>Completed: Oct. 2023</b>	162 MASH patients aged ≥18 years, BMI ≥25kg/m <sup>2</sup> (for Asians BMI ≥23kg/m <sup>2</sup> ), liver stiffness ≥8.5kPa by FibroScan, CAP ≥280dB/m, F2-3 fibrosis, NAS ≥4 (≥1 in each component of NAS), A1c <9.5%	denifanstat (oral 50 QD) vs. placebo for 52 weeks	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- improvement in NAS without worsening in fibrosis from baseline at 52 weeks OR</li> <li>- resolution of MASH without worsening in fibrosis from baseline at 52 weeks</li> <li>- safety and tolerability up to 52 weeks</li> </ul> <p><u>EASL 2023 + Jan. 2024:</u></p> <ul style="list-style-type: none"> <li>- <b>At 26 weeks</b>, denifanstat reduced absolute and relative liver fat vs. pbo, and sign. more denifanstat-treated pts achieved ≥30% reduction in liver fat (responders) vs. pbo.               <ul style="list-style-type: none"> <li>- around half of responders achieved ≥50% reduction in liver fat vs. pbo.</li> </ul> </li> <li>- Denifanstat sign. improved markers of fibrosis ELF and PRO-C3, and markers of hepatocyte injury CK16 (m30) and (M65) vs. pbo.</li> <li>- Marker of target engagement tripalmitin was significantly reduced with denifanstat vs. pbo.</li> <li>- Saturated di- and triglycerides are upregulated in MASH. Denifanstat reversed MASH-related dyslipidemia, decreasing levels of saturated diacylglycerol (DAG) and increasing polyunsaturated DAG and TG vs. pbo.</li> <li>- Denifanstat reduced lipotoxic ceramides C16 and C22 vs. pbo.</li> </ul> <p><u>At 52 weeks in patients with BL and EOT biopsies:</u></p> <ul style="list-style-type: none"> <li>- Denifanstat met both primary endpoints showing sign. more pts achieving MASH resolution without worsening in fibrosis with a ≥2-pt reduction in NAS and ≥2-pt reduction in NAS without worsening in fibrosis vs. pbo.</li> <li>- Sign. more denifanstat-treated pts achieved ≥1 stage improvement in fibrosis without worsening in MASH and MASH resolution without worsening in fibrosis vs. pbo.</li> <li>- AI-based evaluation of liver biopsies showed a sign. greater reduction in qFibrosis with denifanstat vs. pbo.</li> <li>- Among pts on stable GLP-1 therapy at BL, 42% of denifanstat-treated pts (N=12) achieved ≥1 stage improvement in fibrosis without worsening in MASH and 42% achieved MASH resolution without worsening in fibrosis vs. no pbo-treated pts.</li> <li>- Denifanstat sign. reduced liver fat at 26 and 52 weeks, and sign. more denifanstat-treated pts were considered MRI-PDFF responders vs. pbo.</li> <li>- Denifanstat sign. reduced non-invasive fibrosis marker FAST at 26 and 52 weeks, while improvements in ELF did not achieve sign. at either time point vs. pbo.</li> <li>- Denifanstat sign. improved liver enzymes and LDL-C in pts with elevated baseline LDL-C vs. pbo, while TG levels remained largely unchanged.</li> <li>- Denifanstat was generally safe and well-tolerated with the majority of AEs being mild to moderate (Grade 1 and 2) in severity; no Grade ≥3 AEs were reported.</li> <li>- Most commonly reported AEs were skin and subcutaneous tissue disorders including hair thinning which reversed completely upon down-titration or discontinuation of study drug.</li> <li>- No treatment-related SAEs and deaths were reported.</li> </ul>

## TVB2640 - Clinical Trials (2 of 2)

Trial	Patients	Treatment	Endpoints
<b>FASCINATE-1</b> Phase II - US, China <a href="#">NCT03938246</a> Start: March 2019 1° Completed: Oct. 2021 <b>Completed: Oct. 2021</b>	142 MASH patients aged ≥18 years, BMI ≤40kg/m <sup>2</sup> , F1-3 fibrosis, NAS ≥4 (score of ≥1 in steatosis, ballooning, and lobular inflammation), liver fat ≥8% OR if biopsy not available: overweight or obese or diabetic or ALT ≥30U/L or fatty liver on ultrasound, ≥one additional feature of metabolic syndrome and MRE ≥2.5kPa, and liver fat ≥8% by MRI-PDFF	denifanstat (oral 25 or 50mg QD) vs. placebo for 12 weeks; at one trial site patients receiving placebo in the blinded part of the study will be recruited to an open-label cross-over cohort receiving denifanstat (oral QD) for 12 weeks	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- change in liver fat from baseline at 12 weeks (MRI-PDFF)</li> <li>- safety</li> </ul> <p><u>June 2020 press release + ILC 2020 + AASLD 2020 + ILC 2021 + AASLD 2021:</u></p> <ul style="list-style-type: none"> <li>- denifanstat (50mg) met the primary endpoint sign. reducing liver fat from baseline vs. pbo.</li> <li>- Sign. more denifanstat (50mg) treated patients achieved ≥30% reduction in liver fat vs. pbo.</li> <li>- denifanstat (50mg) sign. reduced ALT by -20.4% vs. pbo, and denifanstat (both doses) significantly reduced ALP vs. pbo ; no sign. effects were observed on AST or GGT.</li> <li>- In pts with elevated baseline ALT, more denifanstat (50mg) treated pts achieved ≥17U/L ALT reduction and normalization of ALT.</li> <li>- denifanstat (50mg) sign. reduced LDL-C and HDL-C vs. pbo; no effects on total cholesterol or ApoB were observed.</li> <li>- Adiponectin and FGF21 were sign. increased with denifanstat (50mg) vs. pbo.</li> <li>- While no effect was seen on fibrosis marker PIINP, denifanstat (50mg) sign. reduced TIMP1 vs. pbo.</li> <li>- denifanstat significantly decreased tripalmitin levels, a marker of de novo lipogenesis suppression, vs. pbo.</li> <li>- In a responder analysis evaluating possible correlation of biomarker changes with liver fat response, sign. associations with ALT, FGF21, TIMP1, and tripalmitin were identified.</li> <li>- denifanstat was well-tolerated, benign AE profile, predominantly grade 1 events, no on-treatment SAEs.</li> </ul> <p><u>March 2021 press release:</u></p> <p><i>Chinese cohort:</i></p> <ul style="list-style-type: none"> <li>- Chinese patients were younger, had lower body weight, and higher ALT vs. US patients, while liver fat was similar between cohorts; &gt;90% of Chinese patients were enrolled based on biopsy.</li> <li>- In Chinese pts, denifanstat sign. reduced liver fat from baseline vs. pbo (-28.2 s. -11.1%).</li> <li>- 50% of ASC40 treated pts achieved ≥30% reduction in liver fat.</li> <li>- ASC40 sign. reduced ALT by -29.8% (P=0.0499), corresponding to a -33U/L reduction at 12 weeks.</li> <li>- 63% of ASC40 treated pts achieved ALT reduction ≥17U/L.</li> <li>- ASC40 was well-tolerated with no reported SAEs.</li> <li>- All TEAEs were grade 1 or 2, and no significant changes in serum TG were observed.</li> </ul>

norursodeoxycholic acid				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (EU May 2019)	Dr. Falk Pharma (Originator), EA Pharma (Licensee, Jp)	homolog of ursodeoxycholic acid oral (QD)	MASLD	• 2022: Expected completion of EU Phase IIb trial
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Derived from ursodeoxycholic acid, which is standard of care for primary sclerosing cholangitis (PSC)</li> <li>Reduces atherosclerosis, fatty liver, and inflammation in Western diet-fed apoE-/ mice (Trauner, 2014) <a href="http://media.falkfoundation.de/index.php?id=110&amp;L=1">http://media.falkfoundation.de/index.php?id=110&amp;L=1</a></li> <li>Also in phase II for PSC, for which it has Orphan Drug Designation in the EU</li> <li>Developed by established company with focus on GI and liver diseases</li> </ul>		<ul style="list-style-type: none"> <li>AEs seen in Phase II for PSC include pruritus</li> </ul>		2024 Sentinels
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>May 2019:</b> Dr. Falk initiates European Phase IIb trial of norursodeoxycholic acid in MASH patients with fibrosis</li> <li><b>Nov. 2017:</b> norUDCA reduces ALT and shows trend to improvements in steatosis and liver stiffness in POC study</li> <li><b>May 2016:</b> Norudca improves liver injury and glucose sensitivity in mouse models of obesity and steatosis</li> </ul>		<p>Norursodeoxycholic acid (NorUDCA) is currently in development for treatment of PSC for which it has Orphan Drug Designation in the EU. A European Phase II showed NorUDCA improves liver cell injury via reducing MASH features such as inflammation and ER stress. Beneficial effects on WAT were observed, resulting in an overall improved metabolic situation. NorUDCA may open a new avenue of pharmacological treatment for fatty liver disease and clinical studies are warranted. In May 2019, Dr. Falk initiated a Phase IIb trial of NorUDCA in non-diabetic MASH patients with fibrosis.</p>		

## norursodeoxycholic acid - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase IIb - Czech Republic, Greece, Hungary, Poland, Spain EudraCT2018-003443-31 Start: June 2019 Completion: TBD	363 non-diabetic MASH patients aged ≥18 years with liver fibrosis, ALT >0.8ULN, BMI <45kg/m <sup>2</sup>	norursodeoxycholic acid (oral 1,000 or 1,500mg) vs. placebo for 72 weeks	<b>Primary Endpoint:</b> MASH resolution without worsening of fibrosis from baseline at 72 weeks
Phase II - EU EudraCT2013-004605-38 Start: Dec. 2014 1° Completed: <b>Completed: Sep. 2016</b>	195 MASLD patients (mean baseline age 48 years; BMI 30.2kg/m <sup>2</sup> ; ALT 79U/L; MASLD duration 2.5 years; NFS 2; T2D 9.1%)	norursodeoxycholic acid (oral 500 or 1,500mg) vs. placebo for 12 weeks	<p><b>Primary Endpoint:</b> change in ALT at 12 weeks  <u>AASLD 2017:</u></p> <ul style="list-style-type: none"> <li>- ALT was sign. reduced by norUDCA (1,500mg) vs. placebo and vs. norUDCA (500mg).</li> <li>- Of patients with elevated baseline ALT (&gt;0.8 ULN), more norUDCA treated patients (~15%) had ALT &lt;0.8 ULN at 12 weeks vs. placebo.</li> <li>- In subgroup analyses, relative change in ALT from baseline to end of treatment was stratified by gender, age, presence of T2D, or NAFLD fibrosis score. No differences were indicated as sign. (due to low N), but numerically, norUDCA (1,500mg) elicited a greater reduction of ALT for all comparisons vs. norUDCA (500mg) or placebo.</li> <li>- In the placebo group, female patients had larger numerical increases in ALT vs. men and older patients had larger increases vs. younger patients (non-sign.).</li> <li>- Placebo treated non-diabetics appeared to have an increase in ALT, while diabetics had decreased ALT (note N=63 vs. N=4 in the two groups, respectively).</li> <li>- In the placebo group patients with no fibrosis had an increase in ALT, whereas ALT was modestly reduced in patients with fibrosis.</li> <li>- ALT lowering effects of norUDCA (1,500mg) were consistent within each subgroup, while effects of norUDCA (500mg) were consistent but modest.</li> <li>- TG were not affected by treatment.</li> <li>- LDL increased in a dose-dependent manner with norUDCA treatment, while HDL was unchanged.</li> <li>- More patients in the norUDCA arms showed regression vs. progression of fibrosis stage (21 vs. 15% and 25 vs. 14% for 500mg and 1,500mg doses, respectively).</li> <li>- Hepatic fat fraction was assessed (by MRI-CSI/MRS) in a small subset of patients (5-8 patients in each study arm); a trend toward a 20% decrease was seen in the norUDCA (1,500mg) group while no change was seen in the norUDCA (500mg) group or with placebo.</li> <li>- NorUDCA was generally safe and well-tolerated.</li> <li>- The share of patients experiencing TEAEs and adverse drug reactions was similar between groups, TEAEs were generally mild, with headache, nasopharyngitis, and diarrhea being the most common TEAEs.</li> </ul>

aramchol				Next Milestone			
Status	Companies	MOA/ROA	Target Population				
Phase III non-cirrhotic MASH (Global Sep. 2019)	Galmed (Originator), Samil (S. Korea)	SCD1 modulator (oral)	MASH with fibrosis MASH with obesity, prediabetes, or T2D	• 2H 2023: Initiation of placebo-controlled part of Phase III trial ARMOR was expected			
Strengths/Opportunities		Weaknesses/Threats					
<ul style="list-style-type: none"> <li>Early improvements in fibrosis in open-label arm of Phase III ARMOR</li> <li>Fast Track Designation for MASH</li> </ul>		<ul style="list-style-type: none"> <li>Trials to date have relied on measurements other than the gold standard liver biopsy</li> </ul>					
Key Milestones		CVrg Synopsis					
<ul style="list-style-type: none"> <li><b>Aug. 2020:</b> Galmed plans bioequivalence studies of aramchol meglumine</li> <li><b>May 2020:</b> Galmed to discuss PK data on aramchol meglumine (salt version) with the FDA</li> <li><b>Sep. 2019:</b> Galmed initiates Global Phase III/IV registrational trial ARMOR of aramchol in pre-diabetic/T2D MASH F2-F3</li> <li><b>June 2018:</b> Galmed completes global Phase IIb ARREST of aramchol in MASH patients</li> <li><b>June 2018:</b> Galmed releases topline results from global Phase IIb ARREST of aramchol, meets primary endpoint of reduced liver fat</li> <li><b>Feb. 2018:</b> Aramchol fails to meet primary endpoint in Phase IIa ARRIVE in MASLD with HIV-associated lipodystrophy</li> <li><b>July 2016:</b> Galmed licenses aramchol to Samil for commercialization in S. Korea</li> <li><b>Jan. 2015:</b> Dose-ranging Phase II/III ARREST of aramchol in patients with MASH initiated</li> <li><b>Jan. 2012:</b> Israeli Phase IIa of aramchol in MASLD/MASH initiated</li> </ul>		<p>Aramchol was accidentally discovered to reduce liver fat infiltration in animal models with HFD during research to solubilize bile stones. A Phase II study showed aramchol to be safe and effective in reducing liver fat content and improve metabolic parameters associated with MASLD. In January 2015, Galmed initiated global dose-ranging Phase II/III trial, ARREST, in which 247 MASH patients received aramchol vs. placebo for 52 weeks. Topline data released in June 2018 showed the primary endpoint of improvement in liver TG was met, and MASH was resolved in more aramchol treated patients vs. placebo. A global Phase III/IV trial ARMOR investigating BID oral doses of 300mg aramchol for 52 weeks in MASH F2-F3 with overweight/obesity and prediabetes/T2D was initiated in 3Q 2019. Due to the COVID-19 pandemic randomization of patients to the registrational part of ARMOR was temporarily suspended in December 2020, and enrolled patients were transitioned to an open-label cohort investigating histology endpoints at various time points. Early findings from 20 patients in this cohort (AASLD 2021), showed 60% of patients achieved histological fibrosis improvement accompanied by improvements in non-invasive markers, with the antifibrotic effect occurring as early as 24 weeks.</p> <p>In May 2022, Galmed discontinued the open-label arm of ARMOR since it was deemed the open-label part of the study met its objective showing anti-fibrotic effects as early as 24 weeks, and initiation of the double-blind placebo-controlled part of ARMOR was been postponed to 2H 2023, subject to “<i>data from the open-label part of the trial, sufficient funding, and clarification of the regulatory approval process for NASH drugs</i>”. Additionally, the Company discussed plans to expand development of aramchol into new undisclosed anti-fibrotic indications with high unmet need and potentially faster development for regulatory approval. The shift in strategy involves a cost reduction effort that will enable focus on new indications as well as preparation for the registrational part of ARMOR; Galmed is hoping to leverage clinical data from the ARMOR study to rapidly progress aramchol into Phase II and III development for new indications.</p> <p>In their 4Q 2019 company call, Galmed announced to have agreed with the US FDA on pediatric plans for aramchol; planning a clinical trial for end of 2022 - no further details on pediatric development have been released since 4Q 2019.</p>					
2024 Sentinels							
<ul style="list-style-type: none"> <li><b>March 2024:</b> Aramchol (Galmed), EU patent for combination Tx with resmetirom (Madrigal) in MASH fibrosis granted</li> </ul>							

## aramchol - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>ARMOR</b> Phase III - Global <a href="#">NCT04104321</a> Start: Sep. 2019 1° Completion: Dec. 2024 Completion: June 2027 <b>Suspended</b>	2000 MASH patients aged 18-75 years, NAS ≥4, F2-3, BMI 25-40kg/m <sup>2</sup> , AST >20U/L, T2D/prediabetes (for T2D glycemia must be controlled) Open-label part: ~150 MASH patients with F1-F3, ± overweight, ± T2D/prediabetes	aramchol (oral 300mg BID) vs. placebo for up to 5 years, all patients will be offered the opportunity to transition to an open-label part Open-label part: aramchol (oral 300mg BID) with liver biopsy at 24, 48, or 72 weeks	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- MASH resolution without worsening of fibrosis from baseline at 52 weeks OR</li> <li>- ≥1 stage improvement in fibrosis without worsening of MASH from baseline at 52 weeks</li> <li>- Composite endpoint of all-cause mortality, liver transplant, histological progression to cirrhosis, MELD score &gt;15, and hospitalization due to hepatic decompensation event(s) up to 5 years</li> </ul> <p><u>Nov. 2021 + AASLD 2021:</u> Data for the first 20 patients from an open-label cohort in ARMOR showed 60% of pts treated with aramchol exhibited fibrosis improvement, with the antifibrotic effect occurring as early as 24 weeks.</p> <p>- Aramchol elicited rapid and significant reductions in ALT and AST (at 8 weeks) in both cohorts which was sustained for 48 weeks.</p> <p>- Markers of fibrosis FIB-4 and PRO-C3 were significantly reduced from baseline in both cohorts.</p> <p><u>Jan. 2023 open-label (N=51):</u></p> <ul style="list-style-type: none"> <li>- 39% of pts with ≥48-week biopsies achieved ≥1 stage improvement in fibrosis by histology evaluation.             <ul style="list-style-type: none"> <li>- 61% of pts achieved sign. improvement in ranked fibrosis score by AI digital pathology evaluation.</li> </ul> </li> <li>- When evaluated by AI pathology FibroNest, all pts with ≥48-week biopsies achieved fibrosis improvement by absolute reduction in FCS &gt;0.3.             <ul style="list-style-type: none"> <li>- 65% achieved fibrosis improvement by relative reduction &gt;25%.</li> </ul> </li> <li>- 26.5% of pts achieved MASH resolution without worsening in fibrosis.</li> <li>- At 72 weeks, pts (N=154) achieved significant reductions in FibroScan (-2.5kPa, P&lt;0.0001), liver enzymes ALT (-22U/L, P&lt;0.0001) and AST (-18U/L, P&lt;0.0001), and FIB-4 (-0.30, P&lt;0.0001).</li> <li>- At 24 weeks, pts (N=43) showed significant improvements in fibrosis markers PRO-C3 (P&lt;0.0001), and ELF.</li> <li>- Aramchol showed a good safety profile with SAE incidence of 10.4% and early discontinuation rates due to AE at 4.5% of pts.</li> </ul>
<b>ARREST</b> Phase II - Global <a href="#">NCT02279524</a> Start: April 2015 1° Completed: May 2018 <b>Completed: May 2018</b>	247 MASH patients, aged 18-75 years, BMI 25-40 kg/m <sup>2</sup> , with T2D or prediabetes, histologically proven MASH (liver fat ≥ 5.5%, NAS≥4)	aramchol (1 tablet 400mg aramchol and 1 tablet matching placebo; or 1 tablet 400mg aramchol and 1 tablet 200mg aramchol) vs. placebo (2 tablets) QD for 52 weeks	<p><b>Primary Endpoint:</b> change in average liver triglyceride concentration measured by NMRS between aramchol treated arms and placebo arm from baseline at 52 weeks</p> <p><u>Topline results released in June 2018 + AASLD 2018:</u></p> <ul style="list-style-type: none"> <li>- The primary endpoint was met with a sign. greater reduction in liver TG in patients treated with aramchol 400mg vs. pbo, while the change with the 600mg dose did not achieve sign. (P=0.07).</li> <li>- In a post hoc analysis, more patients treated with aramchol 600mg (47.0%) achieved ≥5% reduction in liver fat (defined as responders) vs. pbo (24.4%).</li> <li>- More pts treated with aramchol 600mg achieved resolution of MASH without worsening of fibrosis vs. pbo.</li> <li>- Both doses of aramchol sign. reduced ALT and AST vs. pbo.</li> <li>- More aramchol treated patients achieved ≥2 points improvement in NAS and SAF activity score vs. pbo.</li> <li>- Aramchol was safe and well tolerated.</li> <li>- Fewer patients treated with aramchol (600mg) progressed to cirrhosis (1.3%) vs. pbo (7.5%).</li> <li>- Less than 10% of patients experience SAEs regardless of treatment.</li> <li>- No changes in body weight or lipid parameters were observed with aramchol treatment.</li> </ul>

# ASC41

ASC41				Next Milestone	
Status	Companies	MOA/ROA	Target Population	2024 Sentinels	
Phase IIb non-cirrhotic MASH (China July 2021)	Asclexis (Originator)	THRβ agonist oral	MASH with dyslipidemia		
<b>Strengths/Opportunities</b>		<b>Weaknesses/Threats</b>			
<ul style="list-style-type: none"> <li>ASC41 significantly reduced LDL-C, triglycerides, and total cholesterol in patients with overweight/obesity</li> <li>Development in combination with in-house non-bile FXR agonist ASC42</li> </ul>		<ul style="list-style-type: none"> <li>Late-stage THRβ agonist in development for MASH including resmetirom (Madrigal), VK2809 (Viking), and TERN-501 (Terns)</li> </ul>			
<b>Key Milestones</b>		<b>CVrg Synopsis</b>			
<ul style="list-style-type: none"> <li><b>March 2023:</b> Gannex withdraws Chinese Phase IIb trial in MASH with T2D</li> <li><b>Nov. 2021:</b> Asclexis initiates global Phase I development of fixed dose combination of THRβ agonist ASC41 and non-bile FXR agonist ASC42</li> <li><b>Nov. 2021:</b> Gannex plans Phase IIa/b trial in MASH with T2D</li> </ul>		<p>ASC41 is a THRβ agonist in development for the treatment of MASH. Early Phase I data showed a benign safety profile and early benefits on plasma lipids. In July 2022, Gannex initiated Phase IIb development in China in non-diabetic MASH patients; the trial was withdrawn in February 2023, and it is unclear if this might be related to Viking suing Asclexis for violating trade secret acts related to Viking's lead MASH-asset THRβ agonist VK2809.</p> <p>In December 2021, Gannex initiated global Phase I development investigating ASC41 (5mg) in fixed dose combination with in-house FXR agonist ASC42 (15mg) dubbed ASC43F; the trial will evaluate safety, tolerability, and pharmacokinetics of ASC43F in healthy subjects.</p>			

## ASC41 - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase IIb - China <a href="#">NCT05462353</a> Start: July 2022 1° Completion: May 2024 Completion: June 2024	180 MASH patients aged 18-80 years, liver fat ≥7.5% by MRI-PDFF, A1c ≤9.5% and eGFR ≥50mL/min/1.73m <sup>2</sup> , without presence or history of cirrhosis	ASC41 (oral 2 or 4mg QD) vs. placebo for 52 weeks	<p><b>Primary Endpoint:</b> ≥2 point improvement in NAS (from reduction in inflammation and ballooning) without worsening in fibrosis from baseline at 52 weeks</p> <p><u>Dec. 2023:</u></p> <ul style="list-style-type: none"> <li>- ASC41 (both doses) elicited sign. reductions in liver fat vs. pbo.</li> <li>- Most (&gt;90%) of ASC41-treated pts achieved ≥30% reduction in liver fat vs. 21.4% for pbo.</li> <li>- Mean baseline ALT and AST levels ranged 65.9-84.8U/L and 44.2-53.8U/L, respectively.           <ul style="list-style-type: none"> <li>- ASC41 elicited mean pbo-adjusted reductions in ALT and AST of up to -34.2 and -21.4U/L, respectively.</li> <li>- the proportion of ASC41-treated pts achieving &gt;17U/L reduction in ALT was up to 51.9%.</li> </ul> </li> <li>- ASC41 (both doses) showed sign. and clinically meaningful reductions in LDL-C, total cholesterol, and TG vs. pbo.</li> <li>- ASC41 sign. reduced Lp(a) but did not impact HDL-C vs. pbo (data not shown).</li> <li>- ASC41 was generally safe and well-tolerated.           <ul style="list-style-type: none"> <li>- one ASC41-treated pts discontinued study drug due to a Grade 1 drug-related AE.</li> <li>- More ASC41 (2mg) pts reported GI AEs vs. ASC41 (4mg) and pbo; namely diarrhea.</li> <li>- No pts reported nausea, vomiting, upper abdominal pain, constipation, dyspepsia, or frequent bowel movements.</li> <li>- Levels of thyroid axis hormones, including TSH, fT3, and fT4 were relatively unchanged from baseline for ASC41 vs. pbo.</li> </ul> </li> </ul>
Phase IIb - China <a href="#">NCT05118360</a> Start: Dec. 2023 1° Completion: Nov. 2024 <b>Withdrawn:</b> Feb. 2023	0 MASH patients with T2D aged 18-80 years, liver fat ≥8%, NAS ≥4 (at least one point in each of ballooning and inflammation), A1c ≤9.5% (if on vitamin E stable dose <400U/d, TZD, or GLP-1 agonist stable dose for 6 months prior to qualifying biopsy)	ASC41 (oral 2 or 4mg QD) vs. placebo for 52 weeks	<p><b>Primary Endpoint:</b> ≥2 point improvement in NAS (from reduction in inflammation and ballooning) without worsening in fibrosis from baseline at 52 weeks</p>
Phase I - China <a href="#">NCT04686994</a> Start: Dec. 2020 1° Completed: Jan. 2021 <b>Completed:</b> Feb. 2021	20 patients aged 18-59 years with overweight/obesity, BMI 23-40kg/m <sup>2</sup> , LDL-C >110mg/dL	ASC41 (oral 10mg QD) vs. placebo for 28 days	<p><b>Primary Endpoint:</b> safety up to 28 days</p> <p><u>Feb. 2021:</u></p> <ul style="list-style-type: none"> <li>- ASC41 sign. reduced LDL-C, triglycerides, and total cholesterol vs. placebo at 14 days, which was sustained at 28 days.</li> <li>- No sign. change in HDL-C was observed.</li> <li>- ASC41 displayed a relatively benign safety profile with the majority of AEs being grade 1 or 2.           <ul style="list-style-type: none"> <li>- Three grade 3 AES (two in ASC41 and one in pbo group) were reported.</li> <li>- No SAEs were reported.</li> </ul> </li> </ul>
Phase I - China <a href="#">NCT04527250</a> Start: Aug. 2020 1° Completed: Dec. 2020 <b>Completed:</b> Dec. 2020	65 subjects aged 18-45 years, BMI 19-30kg/m <sup>2</sup> , (body weight ≥45 and 50kg for females and males, respectively)	SAD: ASC41 (oral 1, 2, 5, 10, or 20mg single dose) vs. placebo MAD: ASC41 (oral 1, 2, or 5mg QD) vs. placebo for 14 days	<p><b>Primary Endpoint:</b> safety and tolerability up to 32 days</p> <p><u>Jan. 2021:</u></p> <ul style="list-style-type: none"> <li>- Single doses of ASC41 were safe and well-tolerated up to 20mg.</li> <li>- ASC41 showed a dose-proportional PK profile from 1 to 20mg.</li> <li>- Multiple doses of ASC41 sign. reduced LDL-C and TG vs. pbo.</li> <li>- Following 14 days of ASC41 dosing no ≥grade-3 AEs, SAEs or premature discontinuations were reported.</li> <li>- Similarly to single doses, following 14 days of dosing ASC41 showed a dose-proportional PK profile from 1 to 5mg.</li> </ul>

## VK2809

## Next Milestone

- 1H 2024: Expected histology data from Phase IIb VOYAGE

## 2024 Sentinels

Status	Companies	MOA/ROA	Target Population
Phase IIb non-cirrhotic MASH (US Nov. 2019)	Ligand (Originator), Viking (Global)	THR $\beta$ agonist oral (QD)	MASLD with hypercholesterolemia
Strengths/Opportunities	Weaknesses/Threats		
<ul style="list-style-type: none"> <li>• Selective THR<math>\beta</math> agonist aims to boost liver specific receptor activation, thereby modulating lipid metabolism, without affecting respiration outside the liver</li> <li>• Reduced hepatic fat and non-invasive markers of fibrosis</li> <li>• Potential to be used for broad population of patients with hypercholesterolemia and MASLD</li> </ul>	<ul style="list-style-type: none"> <li>• Development by small biotech, which has not progressed any agents beyond Phase II</li> <li>• Late-stage THR<math>\beta</math> agonist in development for MASH including resmetrirom (Madrigal), TERN-501 (Terns), and ASC41 (Ascletis)</li> </ul>		
Key Milestones	CVrg Synopsis		
<ul style="list-style-type: none"> <li>• <b>May 2023:</b> VK2809 meets primary endpoint in Phase IIb VOYAGE showing impressive reductions in liver fat</li> <li>• <b>Nov. 2019:</b> Viking initiates US Phase IIb trial VOYAGE in MASH F2-F3</li> <li>• <b>Sep. 2018:</b> Viking's THR-<math>\beta</math> agonist VK2809 meets primary endpoint reducing LDL-C in US Phase II trial in MASLD</li> <li>• <b>Oct. 2016:</b> Viking begins dosing in Phase II of VK2809</li> <li>• <b>Aug. 2016:</b> Viking to initiate Phase II of THR<math>\beta</math> agonist VK2809 for hypercholesterolemia and MASLD</li> <li>• <b>May 2014:</b> Viking obtains exclusive global license to five therapeutic programs from Ligand including VK2809</li> <li>• <b>June 2008:</b> Metabasis (now Ligand) completes Phase Ib of VK2809 in healthy volunteers with modestly elevated LDL-C</li> </ul>	<p>While most agents in development for MASLD target MASH with fibrosis or compensated cirrhosis, VK2809 could potentially be used in the much wider population of patients with MASLD/MASH and hypercholesterolemia. In January 2018, Viking delayed completion of the Phase II trial by a year, and in the Q4 2017 company call CEO Brian Lian commented, that identifying patients with elevated LDL, triglycerides, and MASLD, but no T2D and minimal CVD had been challenging.</p> <p>In September 2018, Viking released topline results from the Phase II trial showing significant reductions of LDL-C and a potent reduction in liver fat. More than 80% of VK2809 treated patients achieved <math>\geq 30\%</math> relative reduction of liver fat. Further results were presented at AASLD 2018; and data from the 5mg dose group presented at ILC 2019 showed potency even at the low dose. In November 2019, Viking initiated a Phase IIb trial, VOYAGE, of VK2809 in MASH patients with F2-F3 fibrosis evaluating multiple doses for up to 12 months. Topline data from VOYAGE released in May 2023 showed impressive improvements with VK2809 in liver fat consistent with prior data from a Phase II study in MASLD patients, and significant improvements in plasma lipids and early non-invasive markers of fibrosis.</p>		

## VK2809 - Clinical Trials (1 of 2)

Trial	Patients	Treatment	Endpoints
<b>VOYAGE</b> Phase IIb - US, Belgium, France, Mexico, Puerto Rico <a href="#">NCT04173065</a> Start: Nov. 2019 1 <sup>o</sup> Completion: May 2023 Completion: June 2024	337 MASH patients aged 18-75 years, F1-F3, NAS ≥4 (score ≥1 in ballooning, lobular inflammation, and steatosis), patients with F1 fibrosis must have ≥1 additional risk factor (T2D, BMI ≥30kg/m <sup>2</sup> , ALT >1.5xULN), liver fat ≥8%	VK2809 (oral 1.0 or 2.5 QD, or 5, or 10mg Q2D) vs. placebo for 52 weeks followed by a 4-week off-drug period	<p><b>Primary Endpoint:</b> change in liver fat from baseline at 12 weeks</p> <p><b>Secondary Endpoint:</b> proportion of patients achieving resolution of MASH without worsening of fibrosis from baseline at 52 weeks</p> <p><b>May 2023:</b></p> <ul style="list-style-type: none"> <li>- VOYAGE met the primary endpoint showing sign. greater reductions in liver fat of up to ~52% (mean) at 12 weeks in VK2809-treated pts (&gt;1mg) vs. pbo.</li> <li>- Sign. more VK2809-treated (all doses) pts achieved ≥30% reduction in liver fat vs. pbo.</li> <li>- VK2809 showed comparable efficacy on liver fat in pts with and without T2D at baseline</li> <li>- VK2809 showed sign. reductions in liver fat in pts with F2 and F3 at baseline vs. pbo.</li> <li>- VK2809 elicited sign. pbo-adj reductions in LDL-C (11-20%) as well as sign. reductions in TG, ApoB, Lp(a), and ApoC-III.</li> <li>- VK2809 showed encouraging safety and tolerability where most reported treatment-related AEs were mild or moderate.</li> <li>- Discontinuation rates due to AEs were low and balanced across arms.</li> <li>- One treatment-related SAE of worsened symptoms in a patient with history of psychiatric disorders was reported in a VK2809 treated pt.</li> <li>- No numerical or clinically meaningful changes in ALT or AST were observed.</li> <li>- Thyroid hormones including TSH, fT4, and fT3 were relatively unchanged among VK2809- and pbo-treated pts.</li> <li>- Changes in vital signs including BP, HR, and body weight were similar across arms.</li> <li>- VK2809 elicited modest but significant changes in ELF, NIS4, and TIMP1 from baseline.</li> </ul>

## VK2809 - Clinical Trials (2 of 2)

Trial	Patients	Treatment	Endpoints
<p>Phase II - US  <a href="#">NCT02927184</a>          Start: Sep. 2016          1° Completed: March 2019  <b>Completed: March 2019</b></p>	<p>59 patients aged 18-75 years with hypercholesterolemia (LDL &gt;130mg/dL) and MASLD (<math>\geq 10\%</math> liver fat by MRS) and one of the following: triglycerides <math>\geq 150\text{mg/dL}</math> (or on hypertriglyceridemia medication), BP &gt;130/85 (or on HTN medication), or waist circumference &gt;40inches men &gt;35inches women, BMI 18.5-40.0kg/m<math>^2</math></p>	<p>VK2809 (oral 5 or 10mg QD, or 10mg Q2D) vs. placebo for 12 weeks</p>	<p><b>Primary Endpoints:</b> change in LDL-C from baseline at 12 weeks  <u>Viking press release Sep. 2018 + AASLD 2018 + ILC 2019:</u></p> <ul style="list-style-type: none"> <li>- Primary endpoint of significant reduction in LDL-C with VK-2809 was met; <math>\geq 20\%</math> pbo adjusted reduction, however the 5mg dose cohort did not reach statistical sign.</li> <li>- VK2809 significantly improved additional lipids including apolipoprotein B and lipoprotein(a).</li> <li>- VK2809 reduced median relative liver fat by -53.8 (5mg), -56.5% (10mg QOD), and -59.7% (QD) vs. -9.4% for pbo.</li> <li>- Mean absolute liver fat was significantly reduced by with all three VK2809 cohorts (-8.7%, -8.9%, and -10.6%, respectively) vs. pbo (-1.1%).</li> <li>- 75-100% of all VK2809 treated patients achieved <math>\geq 30\%</math> relative reduction of liver fat vs. 16.7% for pbo.</li> <li>- 70% of all VK2809 treated patients achieved <math>\geq 50\%</math> relative reduction of liver fat.</li> <li>- ALT levels were reduced from baseline in VK2809 vs. pbo, regardless of baseline ALT.</li> <li>- Improvements in ALT with VK2809 was greater in patients with elevated baseline ALT (N=30 of which 21 in VK2809 cohorts).</li> <li>- No effect of VK2809 was seen on bilirubin, ALP, or international normalized ration (INR), and no changes to the thyroid hormone axis was seen with VK2809 vs. pbo.</li> <li>- VK2809 was safe and well-tolerated with no SAEs.</li> <li>- More patients on VK2809 (76%) completed the trial vs. patients on pbo (65%); discontinuations due AEs were similar between VK2809- and pbo-treated patients (both 12%).</li> <li>- Incidence of CV-related AEs were lower in VK-treated patients (10%) vs. pbo (18%) (not sign.).</li> <li>- HR, BP, and BW were not affected by treatment</li> </ul> <p><u>ILC 2020:</u></p> <ul style="list-style-type: none"> <li>- Sign. improvements in liver fat were maintained 4 weeks post EOT for most VK2809 dose groups.</li> <li>- When combining all VK2809 groups, ~70% of patients maintained a relative liver fat reduction <math>\geq 30\%</math> vs. 22% for pbo.</li> <li>- VK2809 displayed consistent reduction in liver fat across a spectrum of baseline liver fat at 12 weeks, which was maintained at 16 weeks.</li> <li>- Improvements in liver fat at week 12 were independent of risk factors including: BMI <math>\geq 30\text{kg/m}^2</math>, baseline BP <math>\geq 140\text{mmHg}</math>, baseline glucose <math>&gt;100\text{mg/dL}</math>, and Hispanic ethnicity.</li> </ul>

## ALG-055009

ALG-055009				Next Milestone			
Status	Companies	MOA/ROA	Target Population				
Phase II non-cirrhotic MASH (US March 2024)	Aligos (Originator)	THRβ agonist oral	MASLD/MASH, dyslipidemia	• 4Q 2024: Expected topline data from Phase II trial HERALD			
Strengths/Opportunities		Weaknesses/Threats					
<ul style="list-style-type: none"> <li>Appears more selective for THRβ in vitro vs. resmetirom (Madrigal) and VK2809 (Viking)</li> </ul>		<ul style="list-style-type: none"> <li>Late-stage THRβ agonist in development for MASH including resmetirom (Madrigal), VK2809 (Viking), and ASC41 (Ascleitis)</li> </ul>					
Key Milestones		CVrg Synopsis					
<ul style="list-style-type: none"> <li><b>March 2024:</b> Aligos initiates US Phase II trial HERALD in MASH F1-F3</li> <li><b>Dec. 2023:</b> ALG-055009 safe and well-tolerated in French Phase I trial</li> </ul>		<p>ALG-055009 is a THRβ agonist in development for the treatment of MASH. Early Phase I data showed a benign safety profile, potent target engagement, and longer half-life suggesting less variable PK.</p> <p>In March 2024, Aligos initiated US Phase II trial HERALD of ALG-055009; topline data expected in 4Q 2024.</p>					
2024 Sentinels							
<ul style="list-style-type: none"> <li><b>March 2024:</b> ALG-055009, Aligos initiates US Phase II trial HERALD in MASH F1-F3</li> </ul>							

## ALG-055009 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>HERALD</b> Phase II - US <a href="#">NCT06342947</a> Start: March 20224 1° Completed: Nov. 2024 Completion: Dec. 2024	100 patients with presumed MASH F1-F3 aged 18-75 years, BMI $\geq 25\text{kg/m}^2$ , NAS $\geq 4$ OR $\geq 2$ metabolic syndrome criteria and FibroScan 7-20kPa, CAP $>300\text{dB}/\text{m}$ , liver fat $\geq 10\%$	ALG-055009 (oral 0.3, 0.5, 0.7, or 0.9mg QD) vs. placebo for 12 weeks	<b>Primary Endpoint:</b> change in liver fat from baseline at 12 weeks

## TERN-501 discontinued

TERN-501 discontinued				Next Milestone			
Status	Companies	MOA/ROA	Target Population				
Discont. non-cirrhotic MASH (US Jan. 2024)	Terns (Originator)	THR $\beta$ agonist oral	MASLD/MASH, dyslipidemia	• Development discontinued due to strategic pipeline considerations			
Strengths/Opportunities		Weaknesses/Threats					
<ul style="list-style-type: none"> <li>TERN-501 significantly reduced LDL-C, triglycerides, ApoB, and total cholesterol in healthy subjects</li> <li>In development in combination with in-house non-bile FXR agonist TERN-101</li> <li>Fast Track Designation from the US FDA</li> </ul>		<ul style="list-style-type: none"> <li>Other late-stage THR<math>\beta</math> agonists including resmetirom (Madrigal), VK2809 (Viking), and ASC41 (Ascletis)</li> </ul>					
Key Milestones		CVrg Synopsis					
<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> Terns discontinues development for MASH to focus on obesity and cancer</li> <li><b>Aug. 2023:</b> TERN-501/TERN-101 meet primary endpoint in Phase II trial DUET</li> <li><b>May 2022:</b> Terns plans a Phase II trial of combination therapy in MASH with fibrosis</li> <li><b>Jan. 2021:</b> Terns plans US FIH Phase I trial</li> </ul>		<p>TERN-501 is a THR<math>\beta</math> agonist in development for the treatment of MASH. Early Phase I data showed a benign safety profile, potent target engagement, and early benefits on plasma lipids.</p> <p>Phase II trial DUET evaluating TERN-501 alone and in combination with in-house non-bile FXR agonist TERN-101 was initiated in July 2022, and data released in August 2023 showed significant improvements in liver fat and cT1 with TERN-501 already at 12 weeks. Combination therapy with in-house FXR agonist TERN-101 showed only minor improvements in efficacy without any need for dose-adjustment or unexpected safety findings.</p> <p>In a J.P. Morgan presentation January 2024, Terns provided an update on its pipeline and strategic priorities for 2024, and despite reporting positive data from Phase II trial DUET the Company will be prioritizing capital allocation towards oncology and obesity programs, while limiting near-term development spend on TERN-501 in MASH.</p>					
2024 Sentinels							
<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> Terns discontinues development for MASH to focus on obesity and cancer</li> </ul>							

## TERN-501 - Clinical Trials *discontinued*

Trial	Patients	Treatment	Endpoints
<b>DUET</b> Phase II - US <a href="#">NCT05415722</a> Start: July 2022 1° Completed: July 2023 <b>Completed: July 2023</b>	140 MASH patients with fibrosis aged 18-75 years, BMI $\geq 25\text{kg}/\text{m}^2$ , liver fat $\geq 10\%$ by MRI-PDFF, cT1 $\geq 800\text{ms}$	TERN-501 (oral 1, 3, 6, or 10mg QD) vs. TERN-101 (oral 10mg QD) vs. TERN-501 + TERN-101 (oral 3mg/10mg or 6mg/10mg QD) vs. placebo for 12 weeks plus follow-up at 16 weeks	<p><b>Primary Endpoint:</b> %change in liver fat from baseline at 12 weeks (TERN-501 monoTx)</p> <p>Secondary endpoints include: change in liver fat of combination Tx and change in cT1 for TERN-501 alone and in combination with TERN-101</p> <p><u>Aug. 2023:</u></p> <ul style="list-style-type: none"> <li>- TERN-501 monoTx (3 and 6mg) sign. reduced liver fat vs. pbo.</li> <li>- Sign. more TERN-501-treated pts achieved <math>\geq 30\%</math> reduction in liver fat vs. pbo.</li> <li>- TERN-501 (6mg) sign. reduced cT1 vs. pbo.</li> <li>- TERN-501 showed a trend toward improvement in LDL-C, HDL-C, and TG, and sign. improved ApoB.</li> <li>- TERN-501 dose-dependently increased SHBG.</li> <li>- Changes in thyroid axis hormones and liver enzymes with TERN-501 were similar to pbo.</li> <li>- TERN-501/TERN-101 combination Tx elicited modest improvements in liver fat reduction and responder rate vs. TERN-501 monoTx.</li> <li>- Combination Tx did not increase LDL-C, and no treatment emergent safety signals were reported.</li> <li>- TERN-501 was safe and well-tolerated with AEs generally being mild; no drug-related SAEs were reported.</li> <li>- Drug-related AEs of interest were similar across all arms with similar rates of GI events, including nausea, diarrhea and vomiting; no drug-related CV AEs were reported.</li> <li>- Changes in thyroid axis hormones and liver enzymes with TERN-501 were similar to pbo.</li> </ul>

# Metabolism Modulators

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# aldafermin

aldafermin				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb cirrhotic MASH (US, ROW Dec. 2019) discontinued non-cirrhotic MASH (US, ROW May 2021)	NGM Biopharmaceuticals (Originator)	recombinant variant of FGF19 SC (QD)	MASH with cirrhosis	<ul style="list-style-type: none"> <li>Unclear if further development will be pursued</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Lowers liver fat and improves histological features of MASH</li> <li>Already in Phase II for primary biliary cirrhosis (for which it has Orphan Drug Designation in both the US and EU, and Fast Track Designation in the US), so NGM was able to proceed directly from preclinical to Phase II in MASH</li> </ul>		<ul style="list-style-type: none"> <li>Increase in LDL-C</li> <li>In development by a smaller company which has not yet brought any agents to market</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>March 2024:</b> NGM enters merger agreement with Atlas to go private</li> <li><b>May 2023:</b> Aldafermin meets primary endpoint improving ELF in Phase IIb trial ALPINE 4 in MASH F4</li> <li><b>May 2021:</b> Aldafermin misses primary endpoint in Phase IIb trial ALPINE 2/3 in MASH F2-F3</li> <li><b>Aug. 2020:</b> Aldafermin shows durable histological benefit on MASH and fibrosis at 24 weeks - LDL-C controlled with statin</li> <li><b>Dec. 2019:</b> NGM initiates Phase II trial ALPINE 4 of aldafermin in MASH with compensated cirrhosis</li> <li><b>April 2019:</b> NGM initiates US Phase IIb trial ALPINE 2/3 of aldafermin in MASH F2-3</li> <li><b>April 2018:</b> Aldafermin demonstrated benefits across histological and noninvasive endpoints for MASH</li> <li><b>April 2017:</b> Aldafermin normalized liver fat in &gt;one third of MASH pts in Phase II study, but LDL-C rise a concern</li> <li><b>May 2015:</b> NGM initiates Phase II of aldafermin in MASH patients</li> <li><b>Jan. 2013:</b> Aldafermin in Australian Phase I development</li> </ul>		<p>FGF19 analog aldafermin is NGM's leading asset. Results from a Phase II trial of aldafermin presented at ILC 2017, showed significant and rapid reductions in liver fat content, liver enzymes, and other biomarkers suggestive of improvements in MASH. However, a rise in LDL-C was observed and all future trials of aldafermin will incorporate routine statin use for LDL elevations; interim data presented at AASLD 2017 showed that LDL levels are successfully controlled with co-administration of statins. At ILC 2018 and AASLD 2018, 12-week biopsy data from 1 and 3mg doses showed benefits across histological and noninvasive endpoints for MASH; additionally, aldafermin was shown to have a sustained effect at six weeks after last dosing. Data from a final histology cohort (4) presented at ILC and AASLD 2020 showed consistent histological improvements with aldafermin. In April 2019, NGM initiated a Phase IIb trial, ALPINE 2/3, of aldafermin in MASH F2-F3. Topline data from ALPINE 2/3 released in May 2021, disappointingly showed aldafermin missed the primary endpoint of <math>\geq 1</math> stage improvement in fibrosis without worsening in MASH, and while secondary endpoints were significantly improved, NGM decided not pursue further development of aldafermin in this patient population.</p> <p>A second Phase IIb trial ALPINE 4 in MASH F4 was initiated in December 2019, and topline data released May 2023 showed the primary endpoint was met with significantly greater improvement in fibrosis marker ELF vs. placebo. While the trial was not powered for histology endpoints, numerically more aldafermin-treated patients achieved improvements in fibrosis, MASH resolution, and both histology endpoints compared to placebo.</p> <p>In March 2024, NGM entered a merger agreement with Atlas Neon Parent to go private. No further development plans for aldafermin in MASH have been disclosed.</p>		
2024 Sentinels			<ul style="list-style-type: none"> <li><b>March 2024:</b> NGM enters merger agreement with Atlas to go private</li> </ul>	

## aldafermin - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>ALPINE 4</b> Phase IIb - Global <a href="#">NCT04210245</a> Start: March 2020 1° Completed: Jan. 2023 <b>Completed: Feb. 2023</b>	160 MASH patients with compensated cirrhosis (F4) aged 18-75 years	aldafermin (SC 0.3, 1.0, or 3.0mg QD) vs. placebo for 48 weeks	<p><b>Primary Endpoints:</b> change in ELF score from baseline at 48 weeks (was ≥1 stage improvement in fibrosis without worsening of MASH and AEs from baseline at 48 weeks)</p> <p><u>May 2023:</u></p> <ul style="list-style-type: none"> <li>- Aldafermin (3mg) met the primary endpoint showing sign. greater reduction in ELF vs. pbo at 48 weeks.</li> <li>- the change with aldafermin 1mg did not reach statistical sign. vs. pbo.</li> <li>- While the study was not powered for histological endpoints, aldafermin (1 and 3mg) showed numerically more pts achieving ≥1 stage improvement in fibrosis vs. pbo.               <ul style="list-style-type: none"> <li>- the aldafermin 0.3mg dose group was discontinued following enrollment of 7 pts.</li> <li>- Aldafermin (1 and 3mg) showed sign. improvements in liver fat, ALT, AST, and PRO-C3 vs. pbo.</li> <li>- Generally, more aldafermin-treated pts achieved histology endpoints vs. pbo</li> <li>- Aldafermin was generally well-tolerated with a safety profile consistent with previous trials of aldafermin; most frequently reported AEs were GI-related.</li> <li>- No SAEs were deemed treatment related.</li> <li>- LDL-C appeared well managed with concomitant rosuvastatin use; 48-week LDL-C levels were below baseline levels in all groups.</li> </ul> </li> </ul>
<b>ALPINE 2/3</b> Phase IIb - US, Puerto Rico <a href="#">NCT03912532</a> Start: May 2019 1° Completed: March 2021 <b>Completed: March 2021</b>	171 MASH patients aged 18-75 years, histological MASH with F2-F3 fibrosis, liver fat ≥8% (MRI-PDFF)	aldafermin (SC 0.3, 1, or 3mg QD) vs. placebo for 24 weeks	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- proportion of patients achieving histological treatment effect by MASH CRN from baseline at 24 weeks</li> <li>- safety and tolerability from baseline at 24 weeks</li> </ul> <p><u>May 2021 press release:</u></p> <ul style="list-style-type: none"> <li>- No sign. effect of aldafermin (all doses) was seen on the proportion of pts achieving ≥1 stage improvement in fibrosis without worsening in MASH vs. pbo (primary endpoint; P=0.55).</li> <li>- Sign. more aldafermin (3mg) treated pts achieved MASH resolution without worsening in fibrosis vs. pbo (P=0.027).</li> <li>- Aldafermin (1 and 3mg) sign. improved secondary endpoints liver fat (MRI-PDFF), ALT, AST, and PRO-C3 vs. pbo.</li> <li>- Aldafermin was generally well-tolerated with an overall safety profile similar to pbo.</li> <li>- No SAEs were deemed related to treatment.</li> <li>- One fatal AE occurred in the aldafermin (1mg) arm 30 days after last dosing; deemed unrelated to treatment.</li> <li>- Aldafermin increased LDL-C, which was fully mitigated by concomitant statin use.</li> </ul>

# efruxifermin

efruxifermin				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase III non-cirrhotic MASH (US Nov. 2023) Phase IIb cirrhotic MASH (US July 2021)	Akero (Owner)	FGF21 analog SC (QW)	MASH with fibrosis/cirrhosis	<ul style="list-style-type: none"> <li>1H 2024: Expected initiation of Phase III trial SYNCHRONY Outcomes in MASH F4</li> </ul>
Strengths/Opportunities			Weaknesses/Threats	
<ul style="list-style-type: none"> <li>Improved insulin sensitivity and lipoproteins in T2D patients</li> <li>Robust histology improvements in MASH F2-F3 patients</li> <li>Breakthrough Therapy Designation from the US FDA</li> <li>PRIME designation in the EU</li> </ul>			<ul style="list-style-type: none"> <li>Other FGF21 analogs in late-stage development for MASH including pegozafermin (89bio), NN9500 (Novo Nordisk), and BOS580 (Boston Pharma)</li> </ul>	
Key Milestones			CVrg Synopsis	2024 Sentinels
<ul style="list-style-type: none"> <li><b>March 2024:</b> 96-week data from Phase IIb trial HARMONY show sustained histology improvements in MASH F2-F3</li> <li><b>Jan. 2024:</b> Akero releases details of US Phase III trial SYNCHRONY Histology</li> <li><b>Dec. 2023:</b> Akero initiates US Phase III trial SYNCHRONY Real-World</li> <li><b>Oct. 2023:</b> Efruxifermin fails to meet primary histology endpoint in Phase IIb trial SYMMETRY in MASH F4 patients</li> <li><b>Sep. 2022:</b> Topline data from Phase IIb trial HARMONY of efruxifermin show impressive histological improvements</li> <li><b>Oct. 2021:</b> Efruxifermin receives Fast Track Designation from the US FDA</li> <li><b>Sep. 2021:</b> Akero initiates US Phase IIb trial SYMMETRY in MASH F4</li> <li><b>March 2021:</b> Akero releases impressive histology data from F4 expansion cohort of Phase II trial BALANCED</li> <li><b>Feb. 2021:</b> Akero initiates US/Puerto Rican Phase IIb HARMONY in MASH F2-F3</li> <li><b>Oct. 2020:</b> Efruxifermin receives PRIME designation in the EU</li> <li><b>June 2020:</b> Impressive histological effect in responders in Phase II trial BALANCED</li> <li><b>March 2020:</b> All dose groups met primary endpoint significantly reducing liver fat in Phase II trial BALANCED</li> <li><b>Jan. 2020:</b> AKR-001, Akero expands US Phase II trial BALANCED to include MASH cohort with compensated cirrhosis</li> <li><b>May 2019:</b> Akero doses first patient in Phase IIa study of AKR-001 in MASH patients</li> </ul>			<p>Efruxifermin is a long-acting FGF21 exclusively licensed to Akero from Amgen; efruxifermin targets FGFR1c (adipose tissue), 2c, and 3c (both liver) but not FGFR4. Phase I data showed improvements in insulin sensitivity and lipoprotein markers in T2D patients with once weekly dosing.</p> <p>Akero initiated Phase IIb trial HARMONY in February 2021, and topline data released in September 2022 showed impressive histological improvements on both fibrosis and MASH in patients with F2-F3, already at 24 weeks which were sustained at 96 weeks.</p> <p>In Phase IIb trial SYMMETRY of efruxifermin in MASH F4 failed to meet the primary endpoint of improvement in fibrosis without worsening in MASH but showed significant improvements in non-invasive markers of fibrosis. The trial will continue in a long-term safety follow-up for 96 weeks of treatment including a 96-week biopsy.</p> <p>Data from a cohort in SYMMETRY (Cohort D) of non-cirrhotic MASH patients on a stable dose of GLP-1 showed greater improvements in liver fat, markers of liver injury and fibrosis, glycemic control, and dyslipidemia with addition of efruxifermin than GLP-1 therapy alone Phase III program, SYNCHRONY initiated in 4Q 2023.</p>	<ul style="list-style-type: none"> <li><b>March 2024:</b> Efruxifermin (Akero), 96-week data from Phase IIb trial HARMONY show sustained histology improvements in MASH F2-F3</li> <li><b>Jan. 2024:</b> Efruxifermin, Akero releases details of US Phase III trial SYNCHRONY Histology</li> </ul>

## efruxifermin - Clinical Trials (1 of 3)

Trial	Patients	Treatment	Endpoints
<b>SYNCHRONY Real-World</b> Phase III - US <a href="#">NCT06161571</a> Start: Nov. 2023 1° Completion: April 2026 Completion: Oct. 2026	600 non-invasively diagnosed MAFLD/MASH patients aged 18-80 years, Hx of ≥2 of obesity, dyslipidemia, hypertension, elevated FPG, or Hx of T2D  For open-label rollover: prior participation in placebo arm of Phase II study of efruxifermin	- efruxifermin (SC 50mg QW) vs. placebo  - open-label efruxifermin (SC 50mg QW)	<b>Primary Endpoint:</b> safety and tolerability up to 52 weeks
<b>SYNCHRONY Histology</b> Phase III – US, Puerto Rico <a href="#">NCT06215716</a> Start: Dec. 2023 1° Completion: Dec. 2026 Completion: March 2027	1,000 MASH F2-F3 patients aged 18-80 years, Hx or presence of 2 of 4 components of metabolic syndrome (obesity, dyslipidemia, hypertension, elevated FPG) or T2D, FibroScan >7.5kPa, ELF ≥7.7, NAS ≥4 (score of ≥1 in steatosis ballooning, and lobular inflammation)	efruxifermin (SC 28 or 50mg) vs. placebo for 96 weeks	<b>Primary Endpoints:</b> MASH resolution AND ≥1 stage improvement in fibrosis from baseline at 52 weeks

## efruxifermin - Clinical Trials (2 of 3)

Trial	Patients	Treatment	Endpoints
<b>SYMMETRY</b> Phase II - US <a href="#">NCT05039450</a> Start: July 2021 1° Completion: Oct. 2023 Completion: April 2024	200 MASH patients with F4 (compensated cirrhosis) aged 18-75 years, history or presence of T2D or two of the following: obesity, dyslipidemia, hypertension, elevated FPG  Cohort D: MASH patients with F1-F3 and history or presence of T2D or two of the following: obesity, dyslipidemia, hypertension, elevated FPG	efruxifermin (SC 28 or 50mg QW) vs. placebo for 96 weeks  Cohort D: efruxifermin (SC 50mg QW) vs. placebo in addition to existing GLP-1 therapy	<b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH at 36 weeks <u>Oct. 2023 + AASLD 2023:</u> <ul style="list-style-type: none"> <li>- Efruxifermin missed the primary endpoint of 1 stage improvement in fibrosis without worsening in MASH.</li> <li>- 4% of pts in each efruxifermin arm achieved a three or two stage improvement in fibrosis without worsening in MASH vs. 0% for pbo.</li> <li>- Sign. more efruxifermin-treated pts achieved MASH resolution vs. pbo.</li> <li>- The proportion of pts achieving both improvement in fibrosis and MASH resolution was not sign. different between efruxifermin and pbo.</li> <li>- Efruxifermin (both doses) showed sign. improvements in non-invasive markers of fibrosis and rapid and sign. reductions in liver enzymes vs. pbo.</li> <li>- Sign. improvements in platelet count was observed for both efruxifermin doses (data not shown)</li> <li>- Additionally, efruxifermin sign. improved markers of insulin sensitivity and plasma lipids.</li> <li>- One placebo-treated pt died from pneumonia.</li> <li>- Slightly more efruxifermin (28mg) treated pts reported SAEs vs. pbo and efruxifermin (50mg).</li> <li>- no SAEs were deemed related to study drug.</li> <li>- More efruxifermin-treated pts discontinued study drug due to TEAEs vs. pbo, predominantly due to diarrhea which appeared dose-related.</li> <li>- Most frequently reported (≥15% of pts) TEAEs included diarrhea, nausea, increased appetite, and injection site erythema which all appeared dose-related.</li> <li>- No clinically meaningful changes in heart rate or diastolic blood pressure were reported. <ul style="list-style-type: none"> <li>- at 36 weeks, systolic blood pressure increased 4-7mmHg with efruxifermin (both doses).</li> </ul> </li> <li>- Small reductions in bone mineral density were observed for efruxifermin (both doses) in the lumbar spine region (≤1%) and the femoral neck region (2-3%).</li> </ul> <u>June 2023 Cohort D:</u> <ul style="list-style-type: none"> <li>- Efruxifermin on top of GLP-1 therapy was generally well-tolerated with a tolerability profile similar to that seen in Phase II trials BALANCED and HARMONY.</li> <li>- Most common AEs were Grade 1 or 2 GI events (diarrhea, nausea, and increased appetite); one efruxifermin-treated pt discontinued due to nausea, and one withdrew consent.</li> <li>- No drug-related SAEs were reported.</li> <li>- At 12 weeks, efruxifermin sign. reduced liver fat vs. pbo; sign. more efruxifermin-treated pt achieved ≥50 and ≥70% reduction in liver fat vs. pbo.</li> <li>- Efruxifermin-treated pts achieved sign. improvement in liver enzymes and non-invasive markers of fibrosis including PRO-C3, ELF, liver stiffness by FibroScan and FAST score.</li> <li>- Efruxifermin elicited significant improvements in glycemic control and plasma lipids.</li> <li>- Among pts with A1c ≥6.5% at baseline (efruxifermin N=13, and placebo N=4), more efruxifermin-treated pts achieved normalization of A1c (&lt;6.5%) vs. pbo.</li> </ul>

## efruxifermin - Clinical Trials (3 of 3)

Trial	Patients	Treatment	Endpoints
<b>HARMONY</b> Phase II - US, Puerto Rico <a href="#">NCT04767529</a> Start: Feb. 2021 1° Completion: July 2022 Completion: May 2024	128 MASH patients with F2-F3 aged 18-75 years, NAS ≥4 (≥1 in each of steatosis, ballooning, lobular inflammation), liver fat ≥8%, liver stiffness by FibroScan >8.5kPa, history or presence of two of the following: obesity, dyslipidemia, hypertension, elevated FPG, if T2D on stable dose of anti-diabetic therapy	efruxifermin (SC 28 or 50mg QW) vs. placebo for 96 weeks	<p><b>Primary Endpoint:</b> ≥1 stage improvement in fibrosis without worsening in MASH at 24 weeks  <b>Key secondary endpoints:</b> MASH resolution, fibrosis markers, lipoproteins, A1c, weight loss  <u>Sep. 2022 + EASL 2023 + March 2024:</u></p> <ul style="list-style-type: none"> <li>- At 96 weeks, sign. more EFX-treated pts (50mg) achieved ≥1 stage improvement in fibrosis without worsening in MASH vs. pbo; the proportion of responders at 96 weeks was markedly higher than at 24 weeks.</li> <li>- Sign. more EFX-treated pts achieved ≥2 stages improvement in fibrosis without worsening in MASH vs. pbo.</li> <li>- Sign. more EFX-treated pts achieved MASH resolution without worsening in fibrosis, and sign. more EFX-treated pts achieved both histology endpoints of ≥1 stage impr. in fibrosis AND MASH resolution vs. pbo.</li> <li>- Among pts with ≥1 stage improvement in fibrosis without worsening in MASH at 24 weeks, 92 and 83% of EFX-treated pts (50 and 28mg, respectively) remained responders at 96 weeks vs. 40% for pbo.</li> <li>- among 24-week non-responders, 63 and 14% of EFX-treated pts (50 and 28mg) achieved ≥1 stage improvement in fibrosis without worsening in MASH at 96 weeks vs. 21% for pbo.</li> <li>- Among pts with BL F3, sign. more EFX-treated pts (50mg) achieved ≥1 stage improvement in fibrosis without worsening in MASH at 96 weeks vs. pbo (40 and 68% vs. 14%).</li> <li>- among BL F3 pts meeting this endpoint the majority of EFX-treated pts (both doses) achieved ≥2 stages improvement in fibrosis vs. none for pbo.</li> <li>- EFX (both doses) elicited sign. reductions in fibrosis markers PRO-C3, ELF, and FibroScan vs. pbo. <ul style="list-style-type: none"> <li>- improvements in FibroScan with EFX were markedly higher at 96 weeks from 24 weeks.</li> </ul> </li> <li>- Liver enzymes sign. and rapidly reduced with EFX vs. pbo which was sustained throughout the trial.</li> <li>- Improvements in dyslipidemia and insulin sensitivity with EFX at 24 weeks were sustained at 96 weeks.</li> <li>- Body weight was sign. reduced from BL with EFX (50mg) at 24 weeks which was sustained at 96 weeks.</li> <li>- EFX was generally well-tolerated with a profile comparable to previous studies.</li> <li>- No deaths were reported.</li> <li>- Two drug-related SAEs were reported; one SAE of pancreatitis (EFX 28mg – not confirmed on imaging, pt discharged within 24h) and one SAE of esophagitis (EFX 50mg - pt w Hx of gastroesophageal reflux disease).</li> <li>- Nine EFX-treated pts discontinued Tx due to AEs (N=4 for 28mg, N=5 for 50mg - two of which were reported to be unrelated to study drug) vs. none for pbo. <ul style="list-style-type: none"> <li>- between weeks 24 and 96, a total of three EFX-treated pts discontinued due to AEs.</li> </ul> </li> <li>- Most frequent AEs were transient grade 1 or 2 GI events (diarrhea, nausea, increased appetite).</li> <li>- At 98 weeks EFX saw a significant 3-4% decrease in lumbar spine BMD vs. a ~1% increase for pbo a &lt;3% decrease was seen in femoral neck regions EFX (50mg only). <ul style="list-style-type: none"> <li>- one vertebral fracture (L1) was reported in the placebo group vs. no vertebral fractures with EFX.</li> </ul> </li> </ul>

# pegozafermin

Status	Companies	MOA/ROA	Target Population	Next Milestone
Phase III non-cirrhotic MASH (US March 2024)	TEVA (Originator), 89bio (Owner, Global)	FGF21 analog SC	MASH with fibrosis, hypertriglyceridemia	• 2Q 2024: Initiation of Phase III trial ENLIGHTEN-Cirrhosis
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Dose-dependent improvements in liver fat, serum lipids, and liver enzymes</li> <li>Potential for bi-weekly dosing</li> <li>In Phase III development for severe hypertriglyceridemia (SHTG)</li> <li>Breakthrough Therapy Designation for MASH</li> <li>PRIME Designation for MASH with fibrosis and compensated cirrhosis</li> </ul>		<ul style="list-style-type: none"> <li>Other FGF21 analogs in late-stage development for MASH including efruxifermin (Akero), NN9500 (Novo Nordisk), and BOS580 (Boston Pharma)</li> </ul>		<ul style="list-style-type: none"> <li><b>March 2024:</b> Pegozafermin (89bio) receives PRIME designation in the EU</li> <li><b>March 2024:</b> Pegozafermin, 89bio initiates Phase III trial ENLIGHTEN-Fibrosis in MASH F2-F3</li> </ul>
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>March 2024:</b> 89bio initiates Phase III trial ENLIGHTEN-Fibrosis in MASH F2-F3</li> <li><b>March 2023:</b> Pegozafermin met both histology primary endpoints in Phase IIb trial ENLIVEN in MASH F2-F3</li> <li><b>April 2021:</b> 89bio plans Phase IIb ENLIVEN in 2Q 2021</li> <li><b>Nov. 2020:</b> BIO89-100, dose-dependent reductions in liver fat of clinically relevant magnitude in high % of patients</li> </ul>		<p>Pegozafermin, is a site-specific glycoPEGylated analog of FGF21 in Phase III development for MASH and severe hypertriglyceridemia (SHTG) by Teva spinout 89bio. Data from a Phase I/II trial showed significant dose-dependent improvements in liver fat, serum lipids, and liver enzymes in MASH patients, and in an expansion cohort, pegozafermin showed corresponding impressive improvements in histological measures of MASH and fibrosis. Topline data from Phase IIb trial ENLIVEN in MASH F2-F3 released in March 2023 showed impressive improvements in both histology-based primary endpoints accompanied by improvements in non-invasive markers of fibrosis. A Phase III trial of pegozafermin in SHTG initiated in June 2023, and in March 2024, 89bio initiated Phase III trial ENLIGHTEN-Fibrosis in MASH F2-F3; ENLIGHTEN-Cirrhosis in MASH F4 is expected in 2Q 2024.</p>		

## pegozafermin - Clinical Trials

Trial	Patients	Treatment	Endpoints
ENLIGHTEN-Fibrosis Phase III – Location undisclosed <a href="#">NCT06318169</a> Start: March 2024 1° Completion: Dec. 2026 Completion: Feb. 2029	1,050 non-cirrhotic MASH patients with F2-F3 aged 18-75 years, NAS ≥4 (≥1 in each of steatosis, ballooning, and lobular inflammation), BMI 25 to <50kg/m <sup>2</sup> (≥23 for Asians)	pegozafermin (SC 30mg QW or 44mg Q2W) vs. placebo	<b>Primary Endpoints:</b> ≥1 stage improvement in fibrosis with no worsening in MASH and MASH resolution without worsening in fibrosis from baseline at 52 weeks
<b>ENLIVEN</b> Phase IIb – US <a href="#">NCT04929483</a> Start: June 2021 1° Completion: Feb. 2023 Completion: Sep. 2024	216 MASH patients aged 21-75 years, F2-F3, NAS ≥4, liver fat ≥8%, FibroScan ≥8.5kPa	pegozafermin (SC 15 or 30mg QW) vs. pegozafermin (SC 44mg Q2W) vs. placebo for 24 weeks followed by a blinded 24-week extension	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- MASH resolution without worsening in fibrosis from baseline at 24 weeks</li> <li>- ≥1 stage improvement in fibrosis without worsening in MASH from baseline at 24 weeks</li> </ul> <p><u>March 2023 + EASL 2023 + Nov. 2023:</u></p> <ul style="list-style-type: none"> <li>- Pegozafermin (30mg QW+44mg Q2W) met both primary endpoints with sign. more pts achieving ≥1 stage improvement in fibrosis without worsening in MASH and MASH resolution without worsening in fibrosis vs. pbo at 24 weeks. <ul style="list-style-type: none"> <li>- consistent and sign. benefit of pegozafermin on fibrosis improvement in prespecified subgroups.</li> <li>- Sign. more pegozafermin-treated pts (30mg QW+44mg Q2W) achieved ≥2-point improvement in NAS vs. pbo.</li> <li>- The two higher pegozafermin doses elicited sign. greater reductions in liver fat, ALT, liver stiffness, and PRO-C3 vs. pbo. <ul style="list-style-type: none"> <li>- sign. more pegozafermin-treated pts (30mg QW+44mg Q2W) achieved ≥50% reduction in liver fat vs. pbo.</li> <li>- sign. more pegozafermin-treated pts (30mg QW+44mg Q2W) with BL ALT ≥30U/L achieved normalizat. of ALT vs. pbo.</li> </ul> </li> <li>- Sign. more pegozafermin-treated pts (30mg QW+44mg Q2W) considered responders achieving ≥80ms cT1 red. vs. pbo.</li> <li>- 12 (of 14) pts enrolled in ENLIVEN with MASH F4 (not part of the primary analysis) had a 24-week biopsy. <ul style="list-style-type: none"> <li>- five of 11 pegozafermin-treated pts achieved ≥1 stage improvement in fibrosis without worsening in MASH vs. 0 of 1 pts on pbo; additional four pegozafermin-treated pts achieved ≥1 stage improvement in fibrosis.</li> <li>- Sign. more pegozafermin-treated pts (30mg QW) achieved reduction in A1c vs. pbo.</li> <li>- Sign. more pegozafermin-treated pts (30mg QW) achieved reduction in TG and increase in HDL-C vs. pbo.</li> <li>- In pts on background GLP-1 therapy, pegozafermin (pooled 30mg QW + 44mg Q2W) showed greater numerical improvements in ELF, liver stiffness, ALT, liver fat, and A1c vs. pbo; tolerability was acceptable with nausea being the most commonly reported AE - no treatment-related discontinuations</li> </ul> </li> <li>- Pegozafermin showed a favorable safety and tolerability profile consistent with previous studies. <ul style="list-style-type: none"> <li>- most frequently reported AEs were Grade 1 or 2 GI related AEs (diarrhea, nausea, and increased appetite).</li> </ul> </li> <li>- Discontinuation rates were low across all treatment arms; three pts discontinued treatment due to diarrhea (one on pegozafermin 15mg QW, two on 30mg QW), one due to nausea (pegozafermin 30mg QW), one due to injection site erythema (pegozafermin 30mg QW), and one due to pancreatitis (pegozafermin 44mg Q2W). <ul style="list-style-type: none"> <li>- three discontin. deemed unrelated to study drug were reported (angina - pbo; colon cancer and COVID-19 - 30mg QW).</li> </ul> </li> <li>- One serious AE (uncomplicated pancreatitis) reported for pegozafermin 44mg Q2W following a single dose, which resolved in a "short time period".</li> </ul> <p><i>At 48 weeks:</i></p> <ul style="list-style-type: none"> <li>- benefits of pegozafermin were consistent with 24-week findings regardless of concomitant GLP-1 use.</li> </ul> </li> </ul>

## BOS580

BOS580				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US May 2021)	Boston Pharmaceuticals (Global), Novartis (Originator)	FGF21 SC	MASH	<ul style="list-style-type: none"> <li>Early 2024: Expected histology data from Part B of Phase II trial <a href="#">NCT04880031</a></li> </ul>
Strengths/Opportunities	Weaknesses/Threats			2024 Sentinels
<p><b>Key Milestones</b></p> <ul style="list-style-type: none"> <li><b>June 2023:</b> BOS-580 shows impressive reductions in liver fat, liver enzymes, and PRO-C3</li> <li><b>May 2021:</b> Boston Pharmaceuticals initiates Phase II trial in MASH with obesity</li> <li><b>Sep. 2020:</b> Boston Pharmaceutical licenses FGF21 analog from Novartis</li> </ul>			<p><b>CVrg Synopsis</b></p> <p>In September 2020, Boston Pharmaceutical licensed FGF21 analog BOS-580 from Novartis for the treatment of MASH, and in May 2021 Boston Pharmaceutical initiated a US Phase II trial in MASH patients with obesity. First clinical data were presented at EASL 2023, showing potent reductions in liver fat accompanied by improvements in liver enzymes, fibrosis marker PRO-C3, and metabolic health. In May 2023, Boston Pharmaceuticals added a cohort of 80 MASH patients with F2-F3 fibrosis to this trial (Part B) to evaluate efficacy on liver histology at 24 weeks; data are expected early 2024</p>	

## BOS580 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - US  <a href="#">NCT04880031</a>            Start: Sep. 2021            1° Completion: Dec. 2024            Completion: Dec. 2024</p>	<p>180 MASH patients aged 18-75 years with obesity, BMI <math>\geq 27\text{kg/m}^2</math>, liver fat <math>\geq 8\%</math>, AST <math>&gt; 25\text{U/L}</math>, A1c <math>&lt; 9.5\%</math>            Part A: VCTE 7.0-9.9kPa            Part B: VCTE 7.0-20.0kPa, histology confirmed MASH F2-F3</p>	<p>Part A: BOS-580 (SC one of five undisclosed doses) vs. placebo for 12 weeks            Part B: BOS-580 (SC one undisclosed dose level) vs. placebo for 24 weeks</p>	<p><b>Primary Endpoint:</b> safety up to 197 days  <u>EASL 2023:</u>            - Most frequently reported AEs were GI-related and appeared dose-related.            - Treatment discontinuations due to TEAEs were low and similar in BOS-580 and pbo treated pts (4.6 and 5.4%, respectively).            - Two SAEs were reported; one in BOS-580 (150mg Q2W) and one in a pbo-treated pt.            - No clinically sign. changes in vital signs, no worsening in LDL-C, no hypoglycemia, and no worsening of pre-existing biliary disease were reported.            - BOS-580 elicited sign. dose-dependent reduced liver fat and liver enzymes vs. placebo.            - <math>\geq 90\%</math> of BOS-580-treated (<math>\geq 75\text{mg Q2W}</math>) pts achieved <math>\geq 30\%</math> reduction in liver fat and <math>\geq 70\%</math> of pts achieved <math>\geq 50\%</math> reduction in liver fat vs. 6.7 and 3.3% for pbo, respectively.            - BOS-580 sign. reduced fibrosis marker PRO-C3 by up to 30%.            - Most (80-100%) of BOS-580-treated pts achieved <math>\geq 30\%</math> reduction in liver fat AND <math>&gt; 15\%</math> reduction in PRO-C3 vs. 22% for pbo.            - BOS-580 (<math>\geq 75\text{mg Q2W}</math>) reduced triglycerides vs. pbo, which reached significance at the higher dose levels.            - BOS-580 sign. increased HDL-C (data not shown).            - BOS-580 (<math>\geq 150\text{mg Q4W}</math>) elicited dose-dependent reductions in A1c vs. no change in lower dose groups or pbo; additionally, BOS-580 (<math>\geq 150\text{mg Q4W}</math>) achieved numerically greater reductions in C-peptide and insulin vs. pbo.            - BOS-580 (all doses) sign. increased adiponectin by up to 77% (pbo-adjusted) (data not shown).</p>

# HPG1860

HPG1860				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US Dec. 2021)	Hepagene (Originator)	non-bile FXR agonist oral (QD)	MASH	• Expected combination trial with in-house THR $\beta$ agonist HPG7233
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Combination Tx with in-house THR<math>\beta</math> agonist HPG7233</li> </ul>		<ul style="list-style-type: none"> <li>Other non-bile FXR agonists in development for MASH</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Jan. 2023:</b> HPG1860, topline data from Phase II trial RISE show improvements in liver fat</li> <li><b>Dec. 2021:</b> Hepagene initiates US Phase II trial RISE in MASH</li> </ul>		<p>Hepagene is developing non-bile FXR agonist HPG1860 for the treatment of MASH, PBC, and PSC. In January 2023, Hepagene released topline data from Phase II trial RISE showing improvements in liver fat and liver enzymes and dose-dependent pruritus consistent with the FXR class. Hepagene plans a trial evaluating HPG1860 in combination with in-house THR<math>\beta</math> agonist HPG7233 for the treatment of MASH.</p>		

## HPG1860 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>RISE</b> Phase II - US <a href="#">NCT05338034</a> Start: Nov. 2021 1 <sup>o</sup> Completion: Feb. 2023 Completion: March 2023	89 MASH patients	HPG1860 (oral 3, 5, or 8mg QD) vs. placebo for 12 weeks	<p><b>Primary Endpoint:</b> safety and tolerability  <u>Jan. 2023 + EASL 2023:</u></p> <ul style="list-style-type: none"> <li>- HPG1860 was generally safe and well-tolerated, and most AEs were mild and moderate in severity.</li> <li>- Treatment related pruritus was the most commonly reported TEAE, reported in 9.1, 9.5, and 27.3% of HPG1860-treated pts (3, 5, and 8mg, respectively).</li> <li>- HPG1860 (3 and 8mg) elicited significantly greater reductions in relative liver fat vs. placebo (see table).</li> <li>- significantly more HPG1860-treated (3 and 8mg) patients achieved ≥30% reduction in liver fat vs. placebo.</li> <li>- C4 and bile acids were reduced with HPG1860, and lower efficacy with HPG1860 (5mg) could be due to lower baseline liver fat vs. other groups.</li> <li>- In pts with elevated ALT at baseline, HPG1860 showed a trend toward dose-dependent reductions in ALT at 12 weeks.</li> <li>- Three HPG1860-treated pts (one 3mg, two 8mg) reported LDL-C elevations, which recovered to baseline without dose-modification.</li> </ul>

linafexor				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US Feb. 2023)	Cascade (Originator)	non-bile FXR agonist oral (QD)	MASH	
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Fast Track Designation from the US FDA</li> </ul>		<ul style="list-style-type: none"> <li>Other non-bile FXR agonists in development for MASH</li> </ul>		2024 Sentinels
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Oct. 2021:</b> Cascade plans Phase II trial in MASH</li> </ul>		<p>Cascade is developing non-bile FXR agonist linafexor for the treatment of MASH, PSC, PBC, and IBD. In February 2023, Cascade initiated a Phase II trial of linafexor in MASH patients.</p>		

## linafexor - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II - US <a href="#">NCT05591079</a> Start: Feb. 2023 1° Completed: Nov. 2023 <b>Completed: Nov. 2023</b>	100 MASH patients aged 18-75 years, BMI >25kg/m <sup>2</sup> , (>23 for Asian-Americans)	linafexor (oral 1.4 or 2.0mg QD) vs. placebo for 12 weeks	<b>Primary Endpoints:</b> change in liver fat and safety and tolerability from baseline at 12 weeks

# azemiglitazone

azemiglitazone				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US May 2016)	Metabolic Solutions (Originator), Cirius Therapeutics (US)	mTOT modulator oral (QD)	MASH with fibrosis	<ul style="list-style-type: none"> <li>June 2022: Initiation of Phase III MMONARCH was expected</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Fat reduction in liver observed in T2D trials</li> <li>Safe and tolerable in previous Phase IIa <a href="#">NCT01280695</a> in T2D</li> <li>Long-term toxicology and carcinogenicity studies have been completed in T2D</li> <li>Improved liver enzymes and metabolic function in Phase IIb EMMINENCE</li> </ul>		<ul style="list-style-type: none"> <li>In preclinical mouse studies, reduces steatosis and inflammation in treatment model but not in prevention model (ADA 2016 Oral 138-OR)</li> <li>Not being developed by a well-funded or experienced company</li> </ul>		
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Jan. 2021:</b> Cirius delays Phase III trial MMONARCH for a second time by 6 months</li> <li><b>July 2020:</b> Cirius delays Phase III trial MMONARCH by 19 months and amends protocol</li> <li><b>Nov. 2019:</b> EMMINENCE: MSDC-0602K, despite missing 1° endpoint improvements in glycemic control and LFTs</li> <li><b>May 2019:</b> Cirius plans Phase III trial of MSDC-0602K in diabetic MASH fibrosis</li> <li><b>April 2019:</b> MSDC-0602K: reduces liver enzymes and improves glycemic control in MASH ± T2D</li> <li><b>Oct. 2018:</b> Cirius releases interim data from Phase IIb EMMINENCE of MSDC-0602K showing improved liver enzymes and metabolic function</li> <li><b>June 2016:</b> MSDC forms Octeta to advance clinical development of MSDC-0602K for MASH</li> <li><b>May 2016:</b> Octeta initiates Phase II of MSDC-0602 (mTOT modulator) in MASH</li> </ul>		<p>Azemiglitazone (was MSDC-0602) is a thiazolidinedione (TZD) analog that modulates mitochondrial target of TZD (mTOT). Azemiglitazone was in Phase II development for T2D, which was suspended to focus on development in MASH and polycystic kidney disease. US Phase II, EMMINENCE, was initiated in July 2016, and interim 6-month data showed improvements in liver enzymes, metabolic function including FPG and A1c, and trends of improvements in non-invasive measures of fibrosis. 12-month histology data presented at AASLD 2019, showed azemiglitazone failed to meet primary endpoint of 2-point improvement in NAS without worsening of fibrosis, but showed significant improvements in liver enzymes.</p> <p>In May 2019, Cirius announced a Phase III trial, MMONARCH-1, of azemiglitazone to enroll 3,600 MASH patients with fibrosis, T2D, and a history of CV disease. In July 2020, the trial protocol was updated to include 1,800 MASLD patients with pre-diabetes/T2D, in January 2021 the trial was postponed for a second time to 3Q 2021, and in July 2021 the trial was postponed another 10 months to June 2022. As of March 2024, no further updates on MMONARCH-1 were provided.</p>		

## azemiglitazone - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>MMONARCH-1</b> Phase III - Location Undisclosed <a href="#">NCT03970031</a> Start: June 2022 1° Completion: Sep. 2024 Completion: Sep. 2024	1800 MASLD patients with pre-diabetes/T2D aged 18-80 years, A1c >6%, AST >27U/L, history of macrovascular CV disease, not on insulin or TZDs	azemiglitazone (oral QD) vs. placebo	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- change in A1c from baseline at 26 weeks 6 months in first 800 patients with poorly controlled T2D (baseline A1c &gt;7%)</li> <li>- change in a composite endpoint of weighted average of standardized AST, CK-18, and A1c from baseline at 26 weeks</li> </ul>
<b>EMMINENCE</b> Phase II - US <a href="#">NCT02784444</a> Start: Sep. 2016 1° Completed: June 2019 <b>Completed: June 2019</b>	392 patients aged >18 years, with biopsy proven MASH (NAS≥4) with fibrosis (stage 1-3) and no cirrhosis; patients will be stratified by T2D, use of vitamin E ≥400IU, and fibrosis score	MSDC-0602 (oral 62.5, 125, or 250mg QD) vs. placebo for 1 year	<p><b>Primary Endpoint:</b> histological improvement in NAS (decrease of at least 2 points with no concurrent worsening of fibrosis stage) at 12 months</p> <p><u>Interim 6-month data, Cirius press release October 2018 + ILC 2019 + ADA 2019:</u></p> <ul style="list-style-type: none"> <li>328 patients (mean baseline age 57 years; ALT 56U/L; AST 44U/L; GGT 65U/L; ALP 85U/L; NAS 5.3; 59% females; 52% T2D; 59% F2-F3; 8.5% on Vitamin E) who completed 6 month visit included in interim analysis:</li> <li>- More pts with high baseline ALT and AST treated with MSDC-0602K achieved normalized liver enzymes vs. pbo.</li> <li>- MSDC-0602K (125mg and 250mg) sign. reduced ALT, while AST reductions only achieved sign. with 125mg.</li> <li>- MSDC-0602K improved markers of fibrosis across a spectrum of non-invasive tests (APRI, ELF, CK-18, FIB-4, and FibroTest); generally to the greatest extent with the 125mg dose.</li> <li>- Fasting glucose, A1c, insulin levels, and HOMA-IR were all sign. improved with MSDC-0602K.</li> <li>- In T2D pts (N=170), MSDC-0602K sign. improved A1c by -0.37-0.55% despite a low baseline A1c of 6.83%.</li> <li>- Overall rate of TEAEs were similar across all four treatment groups; rate of musculoskeletal and connective tissue disorders (mostly arthralgia and back pain) related TEAEs were higher with MSDC-0602K 250mg vs. pbo.</li> <li>- 14 SAEs were reported for the interim cohort, all determined to be unrelated to treatment.</li> <li>- A modest dose-dependent increase in body weight was seen in MSDC-0602K treated patients.</li> <li>- Rate of peripheral edema was not affected by treatment.</li> </ul> <p><u>AASLD 2019 (12 months):</u></p> <ul style="list-style-type: none"> <li>- No sign. effects of MSDC-0602K were seen on primary endpoint 2-pt NAS improvement without worsening of fibrosis; however, a post-hoc analysis using the study qualification read of biopsy as baseline the 250mg dose reached statistical sign.</li> <li>- The proportion of patients achieving fibrosis improvement with no worsening of MASH, and MASH resolution without worsening of fibrosis was no different between MSDC-0602K and pbo.</li> <li>- MSDC-0602K (125mg and 250mg) rapidly induced a significant reduction in ALT and AST from baseline.</li> <li>- All dose levels of MSDC-0602K sign. improved GGT and ALP vs. pbo.</li> <li>- A1c was improved by MSDC-0602K (all doses), and fasting glucose, insulin, and HOMA-IR were sign. improved with MSDC-0602K (125 and 250mg).</li> <li>- In pts with baseline A1c &gt;7%, MSDC-0602K (125 and 250mg) the magnitude of A1c improvement was &gt;1%.</li> </ul>

HU6				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US Aug. 2020)	Rivus (Originator)	mitochondrial uncoupler oral	MASLD, obesity-related HFpEF	• Nov. 2024: Expected completion of Phase II trial in MASH and T2D
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Increased resting expenditure, dose-dependent weight loss, and reduction in liver fat</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Nov. 2021:</b> HU6 SAD/MAD safe and well-tolerated - increased resting energy expenditure and weight loss</li> <li><b>May 2021:</b> Rivus initiates US Phase II trial in MASLD with obesity</li> </ul>		<p>Rivus is developing a new class of oral, once daily, small molecule therapeutics, CMAs, that activate mitochondrial uncoupling, and are designed to improve cellular metabolism and treat the underlying cause of cardiometabolic diseases. Data from a Phase I SAD/MAD trial showed HU6 was safe and well-tolerated, and increased resting energy expenditure, elicited dose-dependent weight loss, and improved in undisclosed metabolic parameters. In a Phase II trial in MASLD patients, HU6 elicited improvements in liver fat and weight loss up to 6lbs. An exploratory Phase II trial in patients with obesity and HFpEF was initiated in October 2022 and a Phase II study in MASH with T2D was initiated in August 2023.</p>		
2024 Sentinels				

## HU6 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>M-ACCEL</b> Phase II - US <a href="#">NCT05979779</a> Start: Sep. 2023 1° Completion: Sep. 2024 Completion: Nov. 2024	280 T2D patients with MASLD and obesity aged ≥18 years, BMI ≥30kg/m <sup>2</sup> , CAP >306dB/m, liver fat ≥8%, A1c 6.5-10.5%, treated with exercise alone or on stable metformin, DPP-4i, and or SGLT-2i	HU6 (oral 150, 300, or 450mg QD) vs. placebo for 26 weeks	<b>Primary Endpoint:</b> change in liver fat from baseline at 26 weeks
Phase II - US <a href="#">NCT04874233</a> Start: April 2021 1° Completed: Nov. 2021 <b>Completed: Dec. 2021</b>	80 MASLD patients aged 28-65 years, BMI 28-45kg/m <sup>2</sup> , FibroScan CAP >300dB/m, liver fat ≥8%, if on obesity-related and/or T2D medication (metformin, DPP4i, SU only) stable dose ≥2 months, stable body weight ≥3 months (±5%)	HU6 (oral 170, 340, or 510mg) vs. placebo for 61 days	<b>Primary Endpoint:</b> Cmax up to 61 days <b>February 2022:</b> <ul style="list-style-type: none"> <li>- HU6 met the primary endpoint eliciting sign. dose-dependent reductions in relative liver fat vs. pbo.</li> <li>- Up to ~70% of pts achieved &gt;30% reduction in liver fat at the two highest HU6 dose-levels (300 and 450mg) vs. 5% of pbo treated pts.</li> <li>- HU6 (all doses) elicited sign. dose-dependent reductions in body weight at 8 weeks, almost exclusively due to loss of body fat with an average weight loss of 6lbs with HU6 (450mg, P&lt;0.001 vs. pbo).           <ul style="list-style-type: none"> <li>- pts with elevated baseline A1c experienced greater weight and fat loss with an average weight loss of 10lbs with HU6 (450mg, P&lt;0.0001 vs. pbo).</li> <li>- fat loss by MRI was observed in hepatic, visceral, and subcutaneous compartments.</li> </ul> </li> <li>- HU6 elicited sign. dose-dependent reductions in glycated albumin and hsCRP.</li> <li>- HU6 improved measure of steatosis CAP, while markers of fibrosis were unaffected.</li> <li>- HU6 was well-tolerated at all dose levels; no SAEs or deaths were reported.</li> <li>- Most commonly reported TEAEs were intermittent diarrhea and transient flushing, of which the majority were mild.</li> <li>- one pt discontinued HU6 (150mg) due to diarrhea.</li> </ul>

# Other

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DA-1241				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US Sep. 2023)	Dong A (Originator), NeuroBo (Licensee)	GPR119 agonist oral	MASLD, T2D	<ul style="list-style-type: none"> <li>4Q 2024: Expected interim data from Phase II trial in MASH and T2D</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Novel MOA that has shown promise to improve glycemic control and body weight</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>May. 2023:</b> NeuroBo announces details of planned Phase II study in prediabetes/T2D with presumed MASH</li> <li><b>Sep. 2022:</b> NeuroBo licenses GPR119 agonist DA-1241 and dual GLP-1/GRA from Dong A for development in MASH, obesity, and T2D</li> </ul>		<p>DA-1241 is a small molecule selective G-protein coupled receptor 119 (GPR119) agonist. GPR119 expressed on pancreatic β-cells and intestinal L-cells stimulate insulin and incretin secretion and may enhance glucagon secretion during hypoglycemia, and data from a single-center Phase I study presented at EASD 2021 showed DA-1241 was safe and well-tolerated in T2D patients uncontrolled on metformin with trends to improve glycemic control and weight loss.</p> <p>In September 2022, NeuroBo licensed DA-1241 and dual GLP-1/GRA DA-1726 from Dong A and a Phase II trial in patients with prediabetes/T2D and presumed MASH was initiated in September 2023.</p>		
2024 Sentinels				
<ul style="list-style-type: none"> <li><b>Jan. 2024:</b> DA-1241 (DongA), preclinical data supports ongoing development in combination with DPP4i sitagliptin</li> </ul>				

## DA-1241 - Clinical Trials

Trial	Patients	Treatment	Endpoints
Phase II – US <a href="#">NCT06054815</a> Start: Sep. 2023 1° Completion: Aug. 2024 Completion: Dec. 2024	87 prediabetic/T2D patients with presumed MASH, stratified by baseline T2D status	Part 1: 49 patients will receive DA-1242 (oral 50 or 10mg) vs. placebo (randomized 1:2:1) for 16 weeks  Part 2: 37 patients will receive DA-1241 (100mg) plus sitagliptin (100mg) vs. placebo	<b>Primary Endpoint:</b> change in ALT from baseline at 16 weeks

## Egrifta (tesamorelin)

Egrifta (tesamorelin)				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US July 2015)	Theratechnologies (Originator)	growth hormone releasing factor analog SC (QD)	MASLD with lipodystrophy (due to HIV)	<ul style="list-style-type: none"> <li>Seeking partner to initiate Phase II/III trial in MASH</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>Single vial formulation for treatment of lipodystrophy launched in the US</li> <li>Reduces liver fat/resolves MASLD</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>July 2022:</b> TheraTechnologies amends protocol of Phase III to a seamless Phase IIb/III trial; program still on pause</li> <li><b>Jan. 2021:</b> Thera reveals details on planned Phase III trial in MASH F2-F3</li> <li><b>June 2019:</b> Thera plans a Phase III trial of tesamorelin in HIV patients with MASH</li> </ul>		<p>Thus far, Thera has focused its efforts in MASH on patients with HIV infection due to a high prevalence and more severe disease profile in this population, and in June 2019, the company announced plans of a 12-month Phase III trial of a new F8 formulation of tesamorelin for the treatment of patients living with HIV and MASH (NAS <math>\geq 4</math> and F2-3 fibrosis) with histology endpoints. The trial was expected to initiate in 3Q 2021, but in February 2022, the company announced to be submitting an amended trial protocol with the FDA for Phase IIb/III design, embedding an interim analysis of the first 350 patients at 18 months of treatment by a data monitoring committee to assess the efficacy of tesamorelin on a smaller subset of patients. In their 2Q 2022 Company Call, TheraTechnologies provided a further update on the awaited Phase III program for tesamorelin in MASH, confirming an amended protocol including a Phase IIb/III seamless study design has been submitted to and approved by the US FDA. The MASH program remains on pause pending a resolution on the F8 formulation, which was hampered by supply issues of bacteriostatic water for injection (BWFI). The F8 formulation of tesamorelin is stable at room temperature up to seven days after reconstitution and volume of administration is 12.5 times smaller than F1 and two times smaller than F4 allowing for a single multidose vial containing seven days of treatment.</p> <p>As of June 2022, Theratechnologies "...continues to seek an ideal partner with both credibility and the capability to assist us in the MASH program going forward. Alternatively, we are seeking financing alternatives to execute the trial on our own...".</p>		

## Egrifta (tesamorelin) - Clinical Trials

Trial	Patients	Treatment	Endpoints
<p>Phase II - US  <a href="#">NCT03375788</a>            Start: Jan. 2019            1° Completion: June 2024            Completion: Dec. 2024            Sponsor: Massachusetts General Hospital</p>	<p>76 non-diabetic patients aged 18-65 years, BMI <math>\geq 30\text{kg}/\text{m}^2</math> (if MASH, BMI <math>\geq 25\text{kg}/\text{m}^2</math>), grade 1 steatosis or liver fat <math>\geq 5\%</math></p>	<p>tesamorelin (SC 2mg QD) vs. placebo for 12 months followed by 6 months open-label for all patients</p>	<p><b>Primary Endpoint:</b> change in liver fat from baseline at 12 months</p>
<p>Not Applicable - US  <a href="#">NCT02196831</a>            Start: July 2015            1° Completed: Jan. 2019  <b>Completed: July 2019</b>            Sponsor: Massachusetts General Hospital/NIAID</p>	<p>61 MASLD patients with HIV aged 18-70 years on stable antiretroviral treatment for <math>\geq 6</math> months, liver fat <math>\geq 5\%</math> (MRS)</p>	<p>tesamorelin (2mg SC QD) vs. placebo followed by open-label treatment for 6 months</p>	<p><b>Primary Endpoint:</b> change in liver fat from baseline at 12 months</p>

## HTD1801

## Next Milestone

- Dec. 2024: Expected completion of Phase IIb CENTRICITY

Status	Companies	MOA/ROA	Target Population
Phase IIb non-cirrhotic MASH (US Nov. 2022)	HighTide Therapeutics (Originator)	berberine/ursodeoxycholic acid oral (BID)	MASLD with dyslipidemia and/or T2D

## Strengths/Opportunities

## Weaknesses/Threats

## 2024 Sentinels

- HTD1801 is also in development for the treatment of Primary Sclerosing Cholangitis (PSC) and hypercholesterolemia.
- US Fast Track status for MASH and PSC

## Key Milestones

- Nov. 2022:** HighTide initiates Phase IIb trial in MASH F2-F3 with T2D/prediabetes
- May 2020:** HTD1801, improves liver fat in Phase II proof-of-concept trial
- Nov. 2018:** HighTide receives US FDA Fast Track Designation for HTD1801 for the treatment of MASH
- Sep. 2018:** HighTide plans Phase II proof-of-concept study of HTD1801 in MASH patients with T2D

## CVrg Synopsis

HTD1801 is a novel compound consisting of naturally occurring berberine and bile acid ursodeoxycholic acid. In October 2018, HighTide initiated a proof-of-concept study designed to investigate efficacy and safety of HTD1801 in adult MASH patients with T2D. In May 2020, topline data showed significant reductions in liver fat as well as improvements in A1c and liver enzymes in HTD1801 treated patients. A post-hoc analysis presented at AASLD 2021 showed improvement in non-invasive measures of fibrosis.

HTD1801 was awarded a Chinese grant of \$1.25 million as the “National Science and Technology Major Project” for new drug R&D in November 2017. This award grants HTD1801 priority regulatory review status for China. In November 2018, HTD1801 received US Fast Track Designation for the treatment of MASH. This enables regular contact between HighTide and the FDA, thus expediting development and review. HTD1801 already has Orphan Drug Designation and Fast Track Designation for the treatment of PSC. In November 2022, HighTide initiated US Phase IIb trial CENTRICITY in MASH with F2-F3.

## HTD1801 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>CENTRICITY</b> Phase IIb - US <a href="#">NCT05623189</a> Start: Dec. 2022 1° Completion: Dec. 2024 Completion: Dec. 2024	210 MASH patients aged 18-75 years, F2-F3, T2D or prediabetes, BMI >25kg/m <sup>2</sup> (>23kg/m <sup>2</sup> for Asians)	HTD1801 (oral 1,250mg BID) vs. placebo	<b>Primary Endpoint:</b> ≥2-pt improvement in NAS (≥1-pt in lobular inflammation or ballooning) without worsening in fibrosis from baseline at 60 weeks
Phase II - China no NCT# Start: April 2022 Completion: TBD	99 patients with T2D and MASLD	HTD1801 (oral)	<b>Primary Endpoint:</b> change in A1c from baseline at 12 weeks Secondary Endpoints include: changes in markers of MASLD, liver function, and metabolic parameters
Phase II - US <a href="#">NCT03656744</a> Start: Nov. 2018 1° Completed: Feb. 2020 <b>Completed: March 2020</b>	101 MASH patients aged 18-75 years with T2D, BMI >25kg/m <sup>2</sup>	HTD1801 (oral 500 or 1,000mg BID) vs. placebo	<b>Primary Endpoint:</b> change in liver fat by MRI-PDFF from baseline at 18 weeks <u>May 2020 press release + AASLD 2020 + AASLD 2021:</u> <ul style="list-style-type: none"> <li>- HTD1801 met the primary endpoint sign. reducing liver fat vs. pbo.</li> <li>- Additionally, HTD1801 dose-dependently improved A1c, ALT, and GTT, but not FPG levels and HOMA-IR vs. pbo.</li> <li>- No sign. effect of HTD1801 was seen on fibrosis markers ELF and PRO-C3 vs. pbo.</li> <li>- HTD1801 (1,000mg) elicited a ~3-fold greater reduction in APRI and FIB-4, with twice as many pts showing improvements in APRI and FIB-4 to levels associated with less severe fibrosis.</li> <li>- A trend towards improvement of LDL-C and TG as well as weight loss were seen in HTD1801 treated patients.</li> <li>- HTD1801 was generally well-tolerated with no unexpected adverse events.</li> </ul>

miricorilant				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase IIb non-cirrhotic MASH (US Oct. 2023)	Corcept (Originator)	glucocorticoid receptor antagonist oral (BIW)	MASH	• Dec. 2025: Expected completion of Phase IIb MONARCH
Strengths/Opportunities		Weaknesses/Threats		
<ul style="list-style-type: none"> <li>In development for the treatment of weight gain induced by antipsychotic medications</li> </ul>				
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Oct. 2023:</b> Corcept initiates Phase IIb trial MONARCH in MASH</li> </ul>		<p>Miricorilant is a glucocorticoid receptor antagonist that has shown promise to prevent and reverse MASLD and fibrosis. In December 2020, a Phase II trial investigating miricorilant in MASH patients was initiated, however, in April 2021 the trial record was updated to reflect the trial is “<i>suspended by sponsor, pending investigation of abnormal laboratory values in patients with MASH</i>”. Interim findings showed elevated ALT and AST levels in four of the first five dosed patients, which was the reason for suspension of the study; increased liver enzyme levels resolved when miricorilant was withdrawn. These four patients also experienced much greater reductions in liver fat than expected despite follow-up measures being performed 2-10 weeks after the last dose of miricorilant. In October 2023, Corcept initiated Phase IIb trial MONARCH to evaluate efficacy of miricorilant (oral 100mg QMF) in 150 MASH patients.</p>		

## miricorilant - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>MONARCH</b> Phase IIb - US <a href="#">NCT06108219</a> Start: Oct. 2023 1° Completion: Dec. 2025 Completion: Dec. 2025	150 MASH F2-F3 patients aged 18-75 years, NAS ≥4 ( $\geq 1$ point in each of steatosis, inflammation, ballooning), OR presumed MASH with FibroScan $\geq 8$ kPa and CAP $\geq 300$ dB/m, liver fat $\geq 8\%$ , $\geq 1$ of T2D or FPG $\geq 100$ mg/dL or Tx for elevated FPG, SBP/DBP $\geq 130/85$ mmHg or Tx for hypertension, TG $\geq 150$ mg/dL or Tx for elevated TG, HDL-C $<40$ / $<50$ mg/dL for males/females or Tx for low HDL-C, BMI $\geq 25$ kg/m $^2$ ( $\geq 23$ in Asians), WC $\geq 102/88$ cm in males/females	miricorilant (oral 100mg BIW) vs. placebo for 48 weeks	<b>Primary Endpoint:</b> reduction in liver fat from baseline at 24 weeks Secondary endpoints include: MASH resolution and fibrosis improvement
Phase II - US <a href="#">NCT03823703</a> Start: Nov. 2020 1° Completion: April 2021 <b>Terminated:</b> April 2021	12 patients aged 18-75 years with probable MASH with fibrosis (based on blood tests and imaging)	miricorilant (oral 600 or 900mg) vs. placebo for 12 weeks	<b>Primary Endpoint:</b> relative change in liver fat from baseline at 12 weeks (MRI-PDFF) <b>May 2021:</b> - Miricorilant treated patients with elevated liver enzymes exhibited large reductions in liver fat ranging -38.5 to -73.8%. - follow-up MRI-PDFF assessment was performed 16-64 days after last dose of miricorilant. - Increased liver enzyme levels resolved when miricorilant was withdrawn.

# PPAR Modulators

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# lanifibranor

Status	Companies	MOA/ROA	Target Population
Phase III non-cirrhotic MASH (Global July 2021)	Inventiva (Originator), Sino (Licensee, Greater China), Hepalys (Japan, S. Korea)	PPAR pan agonist oral (QD)	MASH (with T2D, with dyslipidemia)
Strengths/Opportunities		Weaknesses/Threats	
<ul style="list-style-type: none"> <li>Clinical trials in T2D showed lanifibranor improves insulin resistance and dyslipidemia, and increases adiponectin</li> <li>Trials to date have shown no signs of edema or weight gain, a common side effect of PPAR gamma agonists</li> <li>Inventiva has major collaborations with AbbVie and BI in other areas, demonstrating confidence in company's approach</li> <li>Fast Track Designation from US FDA and Breakthrough Therapy designation from Chinese NMPA</li> </ul>		<ul style="list-style-type: none"> <li>Pan-PPAR action may mean an increase in side effects</li> <li>Other PPAR modulators, including dual PPAR<math>\alpha/\delta</math> agonist dual PPAR<math>\gamma</math> agonist saroglitazar (Approved in India by Zydus Cadila, Phase II in US)</li> </ul>	
Key Milestones		CVrg Synopsis	
<ul style="list-style-type: none"> <li><b>Jan. 2023:</b> Inventiva updates design of Phase III trial NATiV3 - to initiate a new Phase III trial in MASH F4</li> <li><b>Sep. 2021:</b> Lanifibranor receives US FDA Fast Track Designation for MASH with compensated cirrhosis</li> <li><b>Jan. 2021:</b> Inventiva presents design for Phase III trial NATiV3 in MASH F2-F3</li> <li><b>Nov. 2020:</b> Inventiva plans Phase III trial in H1 2021 - awaiting feedback from the EMA</li> <li><b>Oct. 2020:</b> Lanifibranor receives US FDA Breakthrough Therapy Designation for MASH</li> <li><b>June 2020:</b> Lanifibranor meets primary endpoint of Phase IIb trial NATIVE showing impressive histological improvements</li> <li><b>Sep. 2019:</b> Inventiva completes enrollment for Phase IIb trial NATIVE of lanifibranor in MASH and receives Fast Track Designation</li> <li><b>May 2019:</b> Partial clinical FDA hold on lanifibranor lifted following review of carcinogenicity data</li> <li><b>Dec. 2016:</b> Inventiva initiates Phase IIb trial, NATIVE, of pan PPAR agonist lanifibranor in MASH</li> <li><b>April 2016:</b> Lanifibranor has positive effects on precursors to MASH</li> </ul>		<p>Lanifibranor is Inventiva's leading agent which is in Phase III development for MASH. Since some single and dual PPAR agonists have been associated with toxicity and adverse effects on heart, kidney, skeletal muscle, bladder, body weight, water retention, and bone mineral density. Consequently, the US FDA requires two-year carcinogenicity and one-year <i>in vivo</i> toxicity studies of PPAR class compounds to be performed prior to agents entering clinical trials of a duration &gt;6 months. In May 2019, the US FDA lifted the partial clinical hold on lanifibranor following review of two-year carcinogenicity studies.</p> <p>In June 2020, topline data from NATIVE showed lanifibranor met the primary endpoint and improved histological features of MASH and fibrosis in significantly more patients vs. placebo and generally found to be safe and well tolerated. At AASLD 2020, further data from NATIVE showed lanifibranor to be effective across baseline fibrosis stages and regardless of diabetes status, and a post-hoc analysis presented at AASLD 2021 showed reversal of prediabetes to normoglycemia and improvement of insulin resistance suggesting a therapeutic benefit of lanifibranor on glucose metabolism in prediabetic patients with MASH.</p> <p>Pivotal Phase III trial NATiV3 was initiated in July 2021, and will evaluate efficacy on histology endpoints. In January 2023, Inventiva updated its clinical development program, adding an outcomes-driven Phase III trial in MASH F4 to support full approval.</p>	

## Next Milestone

- 1Q 2024: Expected data from Phase II trial LEGEND
- 2H 2025: Expected topline data from interim cohort of Phase III trial NATiV3

## Projected Launch

non-cirrhotic MASH: 2026 (US, EU)  
Inventiva could file 1H 2026

## 2024 Sentinels

- March 2024:** Lanifibranor, Inventiva resumes screening/randomization in Phase III trial NATiV3
- March 2024:** Lanifibranor (Inventiva)  $\pm$  empagliflozin shows benefit on glycemic control and MASH in Phase II trial LEGEND
- Feb. 2024:** Lanifibranor, Inventiva pauses screening/randomization in NATiV3 due to liver-related AE in one patient
- Feb. 2024:** Lanifibranor/empagliflozin, Inventiva completes enrollment and delays completion of Phase II trial LEGEND in MASH + T2D by 12m

## lanifibranor - Clinical Trials (1 of 2)

Trial	Patients	Treatment	Endpoints
Phase III - Global no NCT# Start: 2023/2024 Completion: TBD likely 2026	800 MASH patients with compensated cirrhosis	lanifibranor (oral QD) vs. placebo	<p><b>Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>- time to first clinical event (all-cause mortality, hepatic decompensation events including hepatic encephalopathy, variceal bleeding/progression to varices that require prophylactic treatment, new onset varices, MELD ≥15, liver transplant)</li> </ul>
<b>NATiV3</b> Phase III - Global <a href="#">NCT04849728</a> Start: Aug. 2021 1° Completion: Sep. 2025 Completion: Sep. 2026	950 MASH patients aged ≥18 years, SAF: steatosis ≥1, activity ≥3, fibrosis F2-F3, MELD score ≤12, stratified by baseline T2D status, if on anti-diabetic treatment (GLP-1 agonist or SGLT-2) or statin for ≥3 months, if on vitamin E for ≥6 months, stable body weight (±5%) for stratified by baseline T2D status 6 months	lanifibranor (oral 800 or 1,200mg QD) vs. placebo for 72 weeks (Part A) followed by a double-blind active treatment extension period (Part B); patients will remain in their respective treatment arms	<p><b>Primary Endpoints:</b></p> <p>Part A:</p> <ul style="list-style-type: none"> <li>- MASH resolution and improvement in fibrosis from baseline at 72 weeks</li> <li>- safety analyses 48 weeks after completion of Part A (120 weeks)</li> </ul> <p>Part B:</p> <ul style="list-style-type: none"> <li>- AEs, adjudicated liver events, DILI, and MACE events from baseline at 120 weeks</li> <li>(was time to first clinical event (progression to cirrhosis, all-cause mortality, liver transplant, MELD ≥15, new onset ascites requiring treatment, overnight hospitalization due to hepatic decompensation events))</li> </ul>
<b>LEGEND</b> Phase II - US, EU <a href="#">NCT05232071</a> Start: June 2022 1° Completion: March 2024 Completion: Dec. 2024	42 patients with non-cirrhotic MASH and T2D aged ≥18 years, A1c 7-10% treated with diet alone and/or DDP4 inhibitor, BMI ≤45kg/m <sup>2</sup>	lanifibranor (oral 800mg QD) ± empagliflozin (oral 10mg QD) vs. placebo for 24 weeks	<p><b>Primary Endpoint:</b> change in A1c from baseline at 24 weeks</p> <p><u>March 2024:</u></p> <ul style="list-style-type: none"> <li>- The primary endpoint was met with lanifibranor ± empagliflozin showing sign. greater A1c reduction vs. pbo.</li> <li>- Among pts completing 24 weeks, the proportion of pts with T2D remission (A1c &lt;6.5%) and A1c-reduction ≥1% was greater with lanifibranor ± empagliflozin vs. pbo.</li> <li>- Lanifibranor ± empagliflozin sign. reduced liver fat vs. pbo. <ul style="list-style-type: none"> <li>- more lanifibranor-treated pts ± empagliflozin achieved ≥30% reduction in relative and ≥5% absolute liver fat vs. pbo.</li> </ul> </li> <li>- Lanifibranor ± empagliflozin sign. improved liver enzymes, but improvements in cT1 (<math>P=0.06</math>) did not reach sign. vs. pbo.</li> <li>- Lanifibranor ± empagliflozin showed sign. improvements in markers of dyslipidemia and insulin resistance vs. pbo.</li> <li>- Combination with empagliflozin mitigated a small weight gain with lanifibranor alone and sign. improved VAT/SAT ratio.</li> <li>- Lanifibranor ± empagliflozin was well-tolerated with no reported serious or severe TEAEs.</li> <li>- One event of mild peripheral edema was reported with lanifibranor/empagliflozin combination and deemed related to lanifibranor only; resolved without corrective treatment.</li> <li>- One event of hypoglycemia was reported with lanifibranor/empagliflozin combination and deemed related to empagliflozin only.</li> </ul>

## Ianifibranor - Clinical Trials (2 of 2)

Trial	Patients	Treatment	Endpoints
<b>NATIVE</b> Phase II - Global <a href="#">NCT03008070</a> Start: Feb. 2017 1° Completed: Feb. 2020 <b>Completed: March 2020</b>	247 patients with biopsy confirmed MASH aged ≥18 years, SAF activity score >2, SAF steatosis score ≥1, SAF fibrosis score <4, A1c <8.5 (73% of patients have NAS ≥6, 76% have F2-F3 fibrosis, 40% have T2D)	Ianifibranor (oral 800 or 1,200mg QD) vs. placebo for 24 weeks	<p><b>Primary Endpoint:</b> ≥2 point improvement in SAF score from baseline at 24 weeks</p> <p><b>Secondary Endpoints:</b> MASH resolution, change in components of SAF, change in fibrosis; change in liver enzymes, inflammatory markers, glucose metabolism, lipids, adiponectin from baseline at 24 weeks</p> <p><u>June 2020 + AASLD 2020 + ILC 2021:</u></p> <ul style="list-style-type: none"> <li>- Lanifibranor (1,200mg) met the primary endpoint sign. reducing SAF score ≥2 points from baseline in more pts vs. pbo in both the ITT and per protocol cohort.</li> <li>- More lanifibranor (both doses) treated pts resolved MASH without worsening of fibrosis vs. pbo; also in pts with baseline F2/F3 fibrosis.</li> <li>- More lanifibranor (1,200mg) treated pts improved fibrosis ≥1 stage without worsening of MASH vs. pbo.</li> <li>- More lanifibranor (both doses) treated pts achieved MASH resolution AND improvement in fibrosis vs. pbo.</li> <li>- The effect of lanifibranor on histological endpoints was similar for T2D vs. non-T2D pts.</li> <li>- Lanifibranor (both doses) sign. and rapidly (4 weeks) reduced ALT (~20U/L), AST (10-18U/L), and GGT (27-45U/L) vs. pbo which was maintained through week 24.</li> <li>- Additionally, lanifibranor (both doses) rapidly and sign. increased HDL-C (~0.1mmol/L) and reduced TG (0.5mmol/L) vs. pbo; no change in LDL-C was observed</li> <li>- While Apo-A1 did not sign. change vs. pbo, Apo-B, Apo-B/Apo-A1, and Apo-C3 were all sign. improved with lanifibranor vs. pbo.</li> <li>- Inflammation marker hs-CRP sign. decreased with lanifibranor (both doses) vs. pbo.</li> <li>- In pts with T2D at baseline, lanifibranor (both doses) sign. decreased insulin (120-130pmol/L), fasting glucose (0.7-1.7mmol/L), and A1c (~0.6%) vs. pbo.</li> <li>- AEs were generally mild to moderate and consistent with findings of previous trials of lanifibranor.</li> <li>- Consistent with known insulin sensitizing pharmacology lanifibranor (both doses) elicited a weight gain.</li> </ul>

# Lipaglyn (saroglitazar)

Status	Companies	MOA/ROA	Target Population	Next Milestone
Phase IIb non-cirrhotic MASH (US Aug. 2021) Approved non-cirrhotic MASH (India March 2020)	Zydus Cadila (Originator), Lupin (Licensee), Torrent (Licensee)	dual PPAR $\alpha/\gamma$ agonist oral (QD)	MASH with dyslipidemia or T2D	• July 2025: Expected completion of US Phase IIb trial EVIDENCES X in MASH F2-F3
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Approved for MASLD and MASH in India</li> <li>Fast Track and Orphan Drug Designation for PBC in the US</li> <li>Orphan Drug Designation for PBC in the EU</li> <li>First dual PPAR<math>\alpha/\gamma</math> agonist to be approved for hypertriglyceridemia in T2D patients in India; marketed as Lipaglyn</li> </ul>		<ul style="list-style-type: none"> <li>PPARs have had a troubled safety history with several undesirable effects including fractures and edema, consequently the majority of alpha/gamma agonists have been discontinued.</li> <li>In development by Indian company which has only just begun to build US infrastructure</li> </ul>		• <b>Jan. 2024:</b> Saroglitazar, Zydus updates primary endpoint of US Phase IIb trial EVIDENCES X and delays completion by 19 months
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Aug. 2021:</b> Zydus initiates US Phase IIb trial in MASH F2-F3</li> <li><b>Dec. 2020:</b> Saroglitazar approved for the treatment of MASLD in India</li> <li><b>March 2020:</b> Saroglitazar approved for the treatment of MASH in India</li> <li><b>Feb. 2020:</b> Saroglitazar, the DGCI approves saroglitazar for treatment of T2D in India</li> <li><b>Dec. 2019:</b> Zydus files NDA of saroglitazar with the Drug Controller General of India for MASH</li> <li><b>Oct. 2019:</b> Topline data from EVIDENCES IV of saroglitazar show improved ALT and liver fat in MASLD patients</li> <li><b>Feb. 2017:</b> Zydus initiates first US Phase II, EVIDENCES II of saroglitazar in MASH</li> <li><b>June 2016:</b> Saroglitazar safe and efficacious in T2D and prediabetics with dyslipidemia</li> <li><b>June 2016:</b> Zydus received IND approval for Phase II trial of saroglitazar in MASH</li> <li><b>May 2016:</b> Saroglitazar reduces triglycerides, A1c, ALT, and improves MASLD by FibroScan in single-center Indian study</li> <li><b>Jan. 2015:</b> Indian Phase III EVIDENCES III of saroglitazar in MASH initiated</li> <li><b>Sep. 2013:</b> Saroglitazar launched in India for dyslipidemia in T2D patients</li> <li><b>May 2012:</b> Zydus completes Indian Phase II of saroglitazar in ASH</li> </ul>		<p>Saroglitazar entered Phase III development in India in 2014, however, only very little trial information is available. In July 2019, Zydus completed enrollment of three Indian/Mexican Phase III studies of saroglitazar in patients with MASLD and MASH, in December 2019 Zydus filed New Drug Application (NDA) of saroglitazar in MASH with the Drug Controller General of India (DCGI), and saroglitazar was approved for the treatment of MASH in March 2020 and for MASLD in December 2020 in India (marketed Lipaglyn).</p> <p>Saroglitazar entered development outside India in April 2017 when Zydus initiated their first US Phase II trial, EVIDENCES IV. Topline data from EVIDENCE IV released in fall 2019, showed all investigated doses met the primary endpoint and significantly reduced ALT levels. Additionally, saroglitazar (4mg) significantly improved liver fat, measures of insulin sensitivity, and dyslipidemia.</p> <p>In August 2021, Zydus initiated a US Phase IIb trial to evaluate efficacy on MASH resolution without worsening in fibrosis in 240 MASH patients with F2-F3.</p>		

## Lipaglyn (saroglitazar) - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>EVIDENCE XI</b> Phase IV – India <a href="#">NCT05872269</a> Start: July 2023 1° Completion: Jan. 2025 Completion: June 2025	1,500 MASLD patients aged 18-80 years, LSM $\geq 8\text{kPa}$ or ALT $\geq 45\text{U/L}$ , T2D, dyslipidemia, or metabolic syndrome	saroglitazar (oral 4mg QD) for 52 weeks	<b>Primary Endpoints:</b> change in liver stiffness by VCTE and safety from baseline at 52 weeks
<b>SARONAPLUS</b> Phase II - US <a href="#">NCT05211284</a> Start: April 2022 1° Completion: Feb. 2025 Completion: March 2025	160 MASH patients with HIV aged $\geq 18$ years, NAS $\geq 4$ ( $\geq 1$ -point for each of steatosis, inflammation, and ballooning), HIV-1 RNA $<50$ copies/mL for $\geq 6$ months on ART (stable ART regimen $\geq 3$ months)	saroglitazar (oral 4mg QD) vs. placebo for 72 weeks	<b>Primary Endpoint:</b> $\geq 2$ -point improvement in NAS ( $\geq 1$ -point improvement in either ballooning or inflammation) without worsening in fibrosis from baseline at 72 weeks
<b>EVIDENCES X</b> Phase IIb - US <a href="#">NCT05011305</a> Start: Aug. 2021 1° Completion: July 2025 Completion: July 2025	240 MASH patients aged 18-75 years, BMI $\leq 45\text{kg/m}^2$ , NAS $\geq 5$ , F2-F3, stable body weight ( $\leq 5\%$ change between biopsy and randomization), if T2D A1c $\leq 9\%$ on stable dose anti-diabetic medication	saroglitazar (oral 2 or 4mg QDAM) vs. placebo for 76 weeks	<b>Primary Endpoint:</b> MASH resolution without worsening in fibrosis from baseline at 76 weeks
<b>EVIDENCES IV</b> Phase II - US <a href="#">NCT03061721</a> Start: April 2017 1° Completed: Oct. 2020 <b>Completed: Dec. 2020</b>	106 MASLD (documented by ultrasound, CT scan, or MRI) or MASH (documented by liver biopsy) patients diagnosed within 12 months of enrollment, aged 18-75 years, BMI $\geq 25\text{kg/m}^2$ , ALT $\geq 1.5$ at visit 1 and 2 ( $<30\%$ variance between visits)	saroglitazar (oral 1mg, 2mg, or 4mg QD) vs. placebo before breakfast for 16 weeks	<b>Primary Endpoint:</b> %change in ALT from baseline at 16 weeks <u>Press release October 2019:</u> - Saroglitazar (all doses) sign. reduced ALT levels and liver fat content vs. placebo. - Saroglitazar (4mg) sign. improved dyslipidemia and insulin resistance. - No weight gain or fluid retention were observed.

# PXL065

PXL065				Next Milestone
Status	Companies	MOA/ROA	Target Population	
Phase II non-cirrhotic MASH (US June 2020)	DeuteRx (Originator), Poxel (Owner, Global)	MPC inhibitor oral (QD)	MASH with T2D	<ul style="list-style-type: none"> <li>Discussion with regulatory agencies regarding Phase III development</li> </ul>
Strengths/Opportunities		Weaknesses/Threats		2024 Sentinels
<ul style="list-style-type: none"> <li>Increased R-pioglitazone activity corresponding to 3-fold higher vs. Actos</li> <li>Pioglitazone and deuterated S-pio induce steady weight gain (~4%) while deuterated R-pio induced less than 2% weight gain</li> <li>X-Linked Adrenoleukodystrophy</li> </ul>				<ul style="list-style-type: none"> <li><b>Feb. 2024:</b> PXL065, Poxel hopes to finalize financing to progress development by end of 1Q 2024</li> </ul>
Key Milestones		CVrg Synopsis		
<ul style="list-style-type: none"> <li><b>Aug. 2022:</b> PXL065 reduces liver fat in Phase IIb trial DESTINY-1, histology data expected in Sep. 2022</li> <li><b>Sep. 2020:</b> Poxel initiates US Phase II trial DESTINY 1 in MASH patients with F1-F3</li> <li><b>Aug. 2016:</b> IND accepted for DRX-065 (DeuteRx), Phase I expected for MASH</li> </ul>		<p>Pioglitazone consists of two interconverting enantiomers, and PXL065 is deuterated R-pioglitazone, which stabilizes the drug in one form; R-pioglitazone has been shown to be more readily absorbed in humans than S-pioglitazone. Whereas S-pioglitazone in addition to inhibiting MPC is a strong PPAR<math>\gamma</math> agonist, R-pioglitazone is a potent MPC inhibitor without any effect on PPAR<math>\gamma</math>. PXL065 displays increased R-pioglitazone activity. In fall 2019, Poxel received positive feedback from the US FDA, and now plans to advance MPC inhibitor PXL065 using a 505(b)(2) regulatory pathway allowing the company to reference and in part rely on the Actos (pioglitazone label) and relevant published literature. Poxel intends to apply for Fast Track Designation for PXL065.</p> <p>Pioglitazone is one of two (the other being Vitamin E) current treatment options for MASH in addition to lifestyle interventions. Long-term treatment with pioglitazone has shown significant improvements of NAS without worsening of fibrosis and resolution of MASH, however treatment is associated with weight gain and increased risk of osteoporosis, where weight gain in particular is a problematic adverse event in patients at increased risk of cardiovascular disease.</p> <p>Data from Phase II trial DESTINY 1 showed significant reductions in liver fat and improvements in liver histology and non-invasive measures of fibrosis in patients with paired liver biopsies. Poxel plans to initiate discussion with regulators regarding future development.</p>		

## PXL065 - Clinical Trials

Trial	Patients	Treatment	Endpoints
<b>DESTINY-1</b> Phase II - US <a href="#">NCT04321343</a> Start: Sep. 2020 1° Completed: June 2022 <b>Completed: June 2022</b>	123 MASH patients aged 18-75 years, BMI $\leq 50\text{kg}/\text{m}^2$ , eGFR $\geq 45\text{mL}/\text{min}/1.73\text{m}^2$ , liver fat $\geq 8\%$ , NAS $\geq 4$ , F1-F3 fibrosis, if T2D either treatment naïve or on stable oral glucose lowering drug	PXL065 (oral 7.5, 15, or 22.5mg QD) vs. placebo for 36 weeks	<p><b>Primary Endpoint:</b> change in %liver fat from baseline at 36 weeks  <u>Aug. + Sep. 2022:</u></p> <ul style="list-style-type: none"> <li>- PXL065 (all doses) met the primary endpoint showing sign. reductions in liver fat and some non-invasive markers of fibrosis at 36 weeks</li> <li>- In 92 pts with liver biopsy at baseline and EOT, a strong trend for more PXL065-treated (15mg) pts achieving at least 1-pt improvement in MASH and <math>\geq 1</math> stage improvement in fibrosis without worsening in MASH vs. pbo was observed.</li> <li>- Numerically more pts treated with PXL065 achieved <math>&gt;2</math>-pt improvement in NAS without worsening in fibrosis, MASH resolution without worsening in fibrosis, and MASH resolution with 1 stage improvement in fibrosis vs. pbo.</li> <li>- More PXL065 treated pts achieved improvement in steatosis and fibrosis, and fewer worsened vs. pbo.</li> <li>- Changes in inflammation and ballooning were not markedly different between PXL065 and pbo.</li> <li>- PXL065 dose-dependently decreased A1c and C-peptide, which reached sign. for the 22.5mg dose vs. pbo. <ul style="list-style-type: none"> <li>- in pts with T2D pbo-subtracted change in A1c up to -0.6%.</li> </ul> </li> <li>- PXL065 sign. improved measures of insulin sensitivity HOMA-IR and Adipo-IR.</li> <li>- PXL065 modestly increased plasma adiponectin levels vs. pbo.</li> <li>- No changes in TG, total cholesterol, or LDL-C were observed with PXL065, and HDL-C increased by up to 7%.</li> <li>- No dose-dependent weight gain was observed, and while the 15mg dose elicited a 2.4kg weight gain PXL065 (22.5mg) only elicited a 0.7kg weight gain. <ul style="list-style-type: none"> <li>- changes in body weight were smaller than published data on pioglitazone.</li> </ul> </li> <li>- Incidence of edema was not increased with PXL065 vs. pbo.</li> <li>- No relevant difference was observed in incidence of TEAEs of which most were grade 1 or 2 in severity.</li> <li>- Few pts reported treatment related TEAEs (12-27%).</li> <li>- One death occurred in the pbo group.</li> <li>- One TEAE lead to discontinuation of study drug (PXL065 22.5mg - agranulocytosis).</li> <li>- Incidence of serious TEAEs was similar (3-9%) and considered unrelated to study drug.</li> <li>- No other AEs of specific interest were reported except one case of increased liver enzymes (pbo group).</li> </ul>

# MASH data on T2D Assets

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## Clinical Data on Marketed T2D Products in MASLD/MASH

**Pioglitazone** is the only option recommended by [guidelines](#) for the treatment of MASH. Pioglitazone has been shown to improve liver histology in patients with MASH, but its safety profile raises the need for safer alternatives.

**Liraglutide** and **exenatide** have been shown to improve transaminases as well as histology in patients with MASH. While liraglutide is no longer in development for the treatment of MASH, the [LEAN](#) study established that liraglutide can improve liver fat and fibrosis, as well as related metabolic parameters in overweight patients with MASH. In conjunction with recent data on Novo Nordisk's weekly GLP-1 agonist semaglutide SC showing histological improvements in MASH, the GLP-1 class including GLP-1 combinations will be interesting to follow.

**Sitagliptin** has been associated with improvement in transaminases, but there are limited studies on its effect on histology.

A [meta-analysis](#) of 12 randomized clinical trials of GLP-1 agonist **lixisenatide** (Lyxumia; Sanofi) showed that lixisenatide has potential to lower ALT in T2D patients. Further trials are needed to determine if this effect extends to MASLD patients with or without T2D, and if there is clinical benefit.

In a subgroup analysis of patients with elevated FLI, **tirzepatide** showed reductions in liver fat, SAT, and VAT in a MASLD subset of obesity study which was accompanied by improvement in PRO-C3.

The following pages summarize data from completed clinical trials of T2D drugs in MASLD/MASH.

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (SGLT-2) (1 of 2)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)
<b>luseogliflozin</b> (oral 2.5mg QD) or <b>dapagliflozin</b> (oral 5mg QD) for 6 months	115 Japanese patients with T2D and hepatic steatosis (confirmed by ultrasound)	31 → 26	<b>No histology performed</b> Some serum lipids improved ( $\Delta$ HDL +3mg/dL, P<0.01; $\Delta$ triglycerides -20mg/dL, P<0.05) but there was no significant change in total cholesterol or LDL-C	Body composition improved ( $\Delta$ BW -2kg, P<0.05; $\Delta$ waist circumference -3cm, P<0.05)	6.8 → 6.7
<b>dapagliflozin</b> (oral 10mg QD) ± exenatide (2mg SC QW) for 52 weeks	695 T2D patients <a href="#">DURATION-8</a>	Not reported	<b>No histology performed</b> Combination tx reduced MASLD and fibrosis by FLI, NLFS, FIB-4, and NFS	$\Delta$ BW -3.3kg (combi), -2.3 (dapa), -1.5 (exe)	9.3 → 7.3 (combi), 7.9 (dapa) 7.7 (exe)
<b>dapagliflozin</b> (oral 5mg QD) for 24 weeks	<a href="#">UMIN000022155</a> 57 Japanese T2D patients with MASLD on 1-3 OADs	↓ (P=0.0212)	<b>No histology performed</b> A1c (P<0.0001) and HOMA-IR (P=0.0369) were improved	Significant weight loss vs. placebo (P=0.0069).	Improved, no values reported
<b>dapagliflozin</b> (oral 5mg QD) + OADs for 24 weeks	52 Japanese T2D patients	34 → 28	Hepatic TG reduced by 5.6%	$\Delta$ BW -2.4kg, P<0.05	7.7 → 7.3
<b>empagliflozin</b> (oral 10mg QD) for 3 months	100 Indian patients with T2D and MASLD (≥grade I on ultrasound)	- 10.9	$\Delta$ Liver fat fraction -4.9% (P<0.0001)	Not reported	No change
<b>empagliflozin</b> (oral 25mg QD) for 6 months	9 Malaysian patients with T2D and MASH (biopsy confirmed) vs. historical placebo	Not reported	Metabolic plasma markers improved ( $\Delta$ FPG -30mg/dL, P<0.05; $\Delta$ total cholesterol -19mg/dL, P<0.05); Liver histology was improved: steatosis -67% vs. -26% (P=0.025), hepatocyte ballooning -78% vs. -34% (P=0.024), fibrosis -44% vs. -6% Lobular inflammation was not improved by empagliflozin	Body composition improved ( $\Delta$ BMI -0.7kg/m <sup>2</sup> , P<0.01; $\Delta$ visceral fat area -8cm <sup>2</sup> , P<0.01)	Not reported
<b>empagliflozin</b> (oral 25mg QD) ± metformin (2,000mg) for 12 weeks	<a href="#">NCT03639545</a> 40 T1D patients	Improved FLI and NFS	<b>No histology performed</b>	Body composition improved ( $\Delta$ body weight -7%, empa+met)	-0.6% (empa+met)

**Sources:** Kusunoki et al. "SGLT-2 Inhibitors ameliorate hepatic steatosis independently of visceral fat reduction or increase in basal metabolic rate in Japanese patients with T2D", Poster 137-LB ADA 2016; Mithal et al., "[Effect of Empagliflozin on Liver Fat in Patients with Type 2 Diabetes and Nonalcoholic Fatty Liver Disease: A Randomized Controlled Trial \(E-LIFT Trial\)](#)", OR27-2 ENDO 2018; Lai L.L., "A pilot study of empagliflozin for the treatment of NASH in patients with T2D", LBP-011 ILC 2018; Kishi et al., "[Dapagliflozin improves liver dysfunction in parallel with a decrease in serum soluble DPP-4/CD26 level in T2D patients with NAFLD](#)", 657-P EASD 2018, Morino K. et al., "[Dapagliflozin reduces intra-hepatic triglyceride content in Japanese patients with T2D treated with oral anti-diabetic agents](#)", Poster 1192, ADA San Francisco June 7-11 2019; C. Guja et al., "[Effect of exenatide and dapagliflozin combination on NAFLD in T2D](#)", Oral 177, EASD 2019.

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (SGLT-2) (2 of 2)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)	
<b>empagliflozin</b> (oral 10 and/or 25mg QD) for 24 -164 weeks	<a href="#">EMPA-REG OUTCOME</a> <a href="#">EMPA-REG H2H-SU</a> <a href="#">NCT01177813</a> <a href="#">NCT01159600</a> <a href="#">NCT01210001</a> T2D patients	7,020 1,545 2,477	-2U/L; all patients -4U/L; patients with high baseline ALT (both placebo controlled)	<b>No histology performed</b>	Body composition improved ( $\Delta$ Body weight -2kg, P<0.05; $\Delta$ waist circumference -2cm, P<0.05)	8.1 → 7.4
<b>empagliflozin</b> (oral 25mg QD) for 24 weeks	<a href="#">EmLiFa</a> 84 T2D patients	ALT: -20%	<b>No histology performed</b>	$\Delta$ body weight -2.7kg	6.7 → 6.6	
<b>canagliflozin</b> (RWE) <b>dapagliflozin</b> <b>empagliflozin</b>	21,338 patients from the ABCD audit program	ALT: -3U/L	<b>No histology performed</b>	ALT reduction associated with weight loss	NA	
<b>ertugliflozin</b> (oral 5 or 15mg) for 52 weeks	<a href="#">VERTIS CV</a> T2D patients	8,238	ALT: -5.0 and -8.5% AST: -1.9 and -3.4%	<b>No histology performed</b> FIB-4 index unchanged	-2.7 and -3.0kg	Not reported
<b>ertugliflozin</b> (oral 5 or 15mg) for 52 weeks	Phase III – Global <a href="#">MONO</a> , <a href="#">MET</a> , <a href="#">SITA2</a> , <a href="#">SITA</a> , <a href="#">SU</a> , <a href="#">FACTORIAL</a> , <a href="#">RENAL</a>	ALT: -3-4U/L AST: -2-3U/L	<b>No histology performed</b> HIS improved no consistent change in FIB-4 or NFS	Not reported	Not reported	
<b>ipragliflozin</b> (oral 50mg QD) for 72 weeks	Multi-center no NCT#	ALT: -20 vs. -10U/L AST: -15 vs. -10U/L GGT: -25 vs. 0U/L	Improvement in hepatocellular ballooning and fibrosis Resolution/prevention of MASH	$\Delta$ BMI: -1.5	6.7 → 6.2	
<b>tofogliflozin</b> (oral 10, 20 or 40mg QD) for 24 -52 weeks	<a href="#">CSG 003JP</a> Phase II/III – Japan <a href="#">CSG 004JP</a> Phase III – Japan <a href="#">CSG 005JP</a> Phase III – Japan <a href="#">CSG 006JP</a> Phase II – Japan	-16.7 GGT and AST improved by -18.1 and -6.6%, respectively	<b>No histology performed</b>	$\Delta$ Body weight -4.2% (P<0.001) FPG improved by -19.5%	Improved, no values reported	

**Sources:** Sattar et al., "Empagliflozin is associated with improvements in liver enzymes potentially consistent with reductions in liver fat: results from randomised trials including the EMPA-REG OUTCOME® trial", Diabetologia, July 2018; Takamura et al., "GGT levels reflect glycaemic status in T2D people treated with an SGLT2 inhibitor tofogliflozin", 1201-P EASD 2018; M. Lunder et al., "Beneficial metabolic effects of empagliflozin alone and empagliflozin on top of metformin treatment in T1D patients", 719-P EASD 2019; Kahl et al., "Empagliflozin effectively lowers liver fat content in well-controlled T2D: A randomized, double-blind, Phase 4, placebo-controlled trial", Diabetes Care Feb. 2020, Takahashi et al., "Ipragliflozin ameliorated overweight and pathological liver fibrosis in diabetic patients with NAFLD in a multicenter randomized controlled trial.", 31-OR ADA 2020; Gallen et al., "SGLT2s and ALT levels in the Associated of British Clinical Diabetologists (ABCD) audits", Short Oral 424 EASD 2021; Corbin et al., "Long-term effects of ertugliflozin on liver enzymes and indices in patients with T2D: analyses from VERTIS CV", Short Oral 425 EASD 2021

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (DPP-4i)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)
<b>sitagliptin</b> 100 mg QD for 52 weeks	15 T2D adults with histologically proven MASH; 5 patients with MASH score of 3-4 (borderline MASH), 10 patients with MASH score of $\geq 5$ (definite MASH)	65 → 40	<b>Histology - improved</b> ALT and AST improved and there was a significant reduction in hepatocyte ballooning and NASH score. The decrease in steatosis was of borderline statistical significance. In contrast, there was no significant improvement in lobular inflammation and fibrosis.	Decreased	Change not statistically significant
<b>sitagliptin</b> 50 mg QD for 4 months	30 Japanese T2D patients with MASLD diagnosed by ultrasonographic and biochemical evidence	56 → 36	<b>No histology performed</b> A significant decline in ALT and AST after 16 weeks	Change not statistically significant	8.1 → 6.8
<b>sitagliptin</b> 50-100 mg QD for ~52 weeks	T2D patients with MASLD diagnosed by ultrasonography and elevated ALT levels for more than 6 months	75 → 61	<b>Histology non-significant improvement</b> Reduction in ALT but no significant change in AST or APRI (AST to platelet counts ratio index).	Change not statistically significant	8.4 → 7.3
<b>teneligliptin</b> 20mg QD vs. metformin 1,000mg QD for 48 weeks	64 T2D patients	96 → 56	<b>No histology performed</b> Steatosis by Fibroscan decreased 15%, AST reduced 45%	Not assessed	8.8 → 7.7

**Sources:** Olaywi. M. et. al. [Novel anti-diabetic agents in NAFLD: a mini-review](#). Hepatobiliary Pancreat Dis Int Vol 12 No 6 December 15 2013

Gupta. V.K. et al., [Teneligliptin significantly reduces liver fat content and delays progression of NASH in T2D patients](#). Poster 1029, ADA San Francisco June 7-11 2019

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (GLP-1)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)
<b>exenatide</b> 5-10 µg BID for 7 months	8 T2D patients with biopsy proven MASLD	69 → 45	<b>Histology - improved</b> <ul style="list-style-type: none"><li>NAS improved in 5 patients, unchanged in 2 and worsened in 1</li><li>Fibrosis improvement was seen in 50%, no change in 38%, and worsening fibrosis in 12% of the patients.</li><li>Hepatocyte ballooning improved in 50% of the patients. One subject developed hepatocyte ballooning on follow-up biopsy.</li></ul>	Decreased (mean 4.9 kg)	7.1 → 6.1
<b>exenatide</b> 10ug BID and <b>insulin glargine</b> vs. insulin aspart and insulin glargine for 12 weeks	60 newly diagnosed Chinese patients with T2D, MASLD (ALT or AST >100U/L or γGGT > 125U/L), and obesity (BMI ≥ 28kg/m <sup>2</sup> )	170 → 43 ALT, AST, γGGT all improved more with exenatide	<b>No histology performed</b>	BMI decreased (-2.75kg/m <sup>2</sup> ) and mean body weight change correlated with change in ALT, AST, γGGT	7.7 → 6.3
<b>liraglutide</b> 0.3-0.9 mg QD for ~8 months	T2D patients with MASLD diagnosed by ultra-sonography, elevated ALT levels for more than 6 months	65 → 48	<b>Histology - improved</b> significant decrease in ALT, AST, and APRI.	Decreased	7.7 → 6.9
<b>liraglutide</b> (1.8 mg SC QD) vs. placebo for 48 weeks Phase II <u>LEAN</u>	52 overweight/obese patients (mean age 51 years; 60% male, 33% T2D; 52% F3/F4 Kleiner fibrosis stage; BMI≥25 kg/m <sup>2</sup> ) patients aged 18-75 (patients with T1D A1c<9.0%) with biopsy-confirmed MASH	77 → 50 P=0.164 vs. placebo	<b>Histology - improved</b> 9/23 patients (39%) on lira had resolution of definite MASH vs. 2/22 patients (9%) on placebo (P=0.019) 2 patients (9%) on lira had worsening of fibrosis vs. 8 patients (36%) on placebo (P=0.026) 19 patients (82.6%) on lira had improvement in steatosis vs. 10 (45.5% on placebo (P<0.05) There was no significant change in hepatocyte ballooning or inflammation between treatment groups	Decreased -1.84 kg/m <sup>2</sup> with liraglutide vs. -0.27kg/m <sup>2</sup> with placebo P=0.005	5.9 → 5.4 Trend towards decrease P=0.074 vs. placebo
<b>liraglutide</b> (1.2mg SC QD) for 6 months UK academic trial (EASD 2015)	53 T2D patients not on DPP-4s or TZDs (mean age 56 years; BMI 36.1kg/m <sup>2</sup> ; A1c 9.9%; liver fat 17.9%)	46.9 → 40.7 (P=0.016)	<b>No histology performed</b> Liver fat assessed by MRS After 6 months, liver fat content had dropped by 33% from 17.9% to 12% A1c, weight, and ALT also decreased significantly from baseline	Decreased significantly from baseline (-4kg, P<0.001)	9.9 → 7.1 P<0.0001

**Sources:** Olaywi. M. et. Al. [Novel anti-diabetic agents in NAFLD: a mini-review](#). Hepatobiliary Pancreat Dis Int. Vol 12, No 6 December 15, 2013; Shao N. et al. [Benefits of exenatide on obesity & NAFLD with elevated liver enzymes in pts with T2D](#). Diabetes Metab Res Rev. 2014 Sep;30(6):52; Loomba R. et al. Liraglutide is effective in the histological clearance of NASH in a multicentre, double-blinded, randomised, placebo-controlled Phase II trial. Oral G01, ILC 2015; Verges B. Treatment with liraglutide leads to an important reduction in liver fat content, assessed by MR spectroscopy, in people with T2D. Oral 13, EASD 2015

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (GLP-1/GIP)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)
tirzepatide 5-15mg QW for 52 weeks	<p><a href="#">SURPASS-3 MRI</a></p> <p>296 T2D patients with elevated FLI (mean age 56 years; A1c 8.2%; T2D duration 8.3 years; body weight 94.4kg; BMI 33.5kg/m<sup>2</sup>; liver fat 15.7%; VAT 6.6L; SAT 10.4L)</p>	-32U/L	<p><b>No histology performed</b></p> <p>Absolute reduction in liver fat -8.1%</p> <p>Up to 81.4%pts with ≥30% reduction in liver fat</p> <p>Significant reductions of SAT and VAT</p> <p>Change in liver fat correlated with improvements in BW, WC, A1c, and HDL-C</p>	Decreased (up to -11.2kg)	8.2 → 5.9

**Sources:** Gastaldelli A. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in patients with T2D, Short Oral 426, EASD 2021; Cusi K. The effects of tirzepatide on liver fat content and abdominal adipose tissue in patients with T2D, S42a Symposium EASD 2021

## Completed trials of approved anti-diabetic drugs for MASLD/MASH (TZD)

Anti-diabetic agents (dose/duration)	Patients & Tx	ALT (U/L)	Histology (inc. steatosis, lobular inflammation, hepatocyte ballooning, and fibrosis)	BMI or weight (If BMI not reported)	A1c (%)
<b>pioglitazone</b> 15mg QD for ~41 months	T2D patients with MASLD diagnosed by ultrasonography and elevated ALT levels for more than 6 months.	87 → 53	<b>Histology - improved</b> significant decline in ALT, AST, and APRI.	Increased	7.7 → 6.9
<b>pioglitazone</b> 30mg QD PO for 36 months Phase IV <a href="#">NCT00994682</a>	101 MASH patients with or without T2D	-	<b>Histology</b> <ul style="list-style-type: none"> <li>- At 18 months, 58% of pioglitazone treated patients achieved the 1° outcome of &gt;2 point reduction in NAS score without worsening of fibrosis vs. 17% in placebo group (<math>P&lt;0.001</math>)</li> <li>- 51% of patients in the treatment group experienced resolution of MASH vs. 19% in placebo group (<math>P&lt;0.001</math>)</li> <li>- Fibrosis score was improved with pioglitazone vs. placebo</li> <li>- Hepatic triglyceride content was reduced from 19% to 7% (<math>P&lt;0.001</math>) with pioglitazone treatment</li> </ul>	Increased	-
<b>lobeglitazone</b> 0.5mg PO QD for 24 weeks Phase IV <a href="#">NCT02285205</a>	43 T2D patients with hepatic steatosis (as assessed by Fibroscan) who had either never been treated with drugs for T2D or were on metformin	44 → 39	<b>No histology performed</b> <ul style="list-style-type: none"> <li>- Significant reduction in fibroscan CAP</li> <li>- Significant improvements in triglycerides and HDL but not LDL</li> </ul>	Increased	7.5 → 6.6

**Sources:** Olaywi. M. et. Al. [Novel anti-diabetic agents in NAFLD: a mini-review](#). Hepatobiliary Pancreat Dis Int. Vol 12, No 6 December 15, 2013; Shao N. et al. [Benefits of exenatide on obesity & NAFLD with elevated liver enzymes in pts with T2D](#). Diabetes Metab Res Rev. 2014 Sep;30(6):52; Loomba R. et al. Liraglutide is effective in the histological clearance of NASH in a multicentre, double-blinded, randomised, placebo-controlled Phase II trial. Oral G01, ILC 2015; Verges B. Treatment with liraglutide leads to an important reduction in liver fat content, assessed by MR spectroscopy, in people with T2D. Oral 13, EASD 2015

# Emerging Trends

While the first drug is now approved for MASH and multiple assets showing promise in late-stage trials, the growing prevalence of the disease is driving an increasing amount of academic and industrial research on MASH.

This section highlights the following emerging trends:

- New insights into the pathogenesis of MASLD/MASH
- Increasing interest by large Pharma

## Insights into Pathogenesis

### Insights into the pathogenesis of MASLD and MASH

MASLD is a complex disease, with considerable variation in severity amongst patients. The growing prevalence of the disease is driving an increasing amount of academic and industrial research on MASLD/MASH. Interaction of genetic variation, commensal bacteria, and diet might account for the heterogeneity in disease phenotype and progression.

Certain single nucleotide polymorphisms (**SNPs**) have been linked to disease progression of MASH and fibrosis, and [five loci](#) linked to MASH, fibrosis, and HCC have been identified in MASLD patients: patatin-like phospholipase domain-containing 3 (**PNPLA3**) rs738409, transmembrane 6 superfamily member 2 (**TM6SF2**) rs58542926, 17-β hydroxysteroid dehydrogenase 13 (**HSD17B13**) rs72613567, membrane bound O-acyltransferase domain-containing 7 (**MBOAT7**) rs641738, and mitochondrial amidoxime-reducing component 1 (**MARC1**) rs2642438.

- rs738409 C>G (I148) in [PNPLA3](#) increases hepatic lipid accumulation and is the genetic variant most strongly associated with liver outcomes in MASLD; multiple programs are targeting PNPLA3 for the treatment of MASH including Phase II asset **AZD2693** (AZ/Ionis) and Phase I assets **ALN PNP** (Alnylam/Regeneron), **ARO-PNPLA3** (Arrowhead), **LY3849891** (Lilly), and **PF-07853578** (Pfizer). - a [study](#) investigating the relationship between PNPLA3 rs738409, nutrient intake, and disease severity in MASLD patients found that high carbohydrate intake (>48% of energy) was associated with increased risk of significant fibrosis while higher n-3 PUFA, isoflavone, and methionine intake were associated with reduced risk of significant fibrosis. These dietary findings tended to be intensified in rs738409 G-allele carriers.
- [HSD17B13](#) is localized to lipid droplets in hepatocytes and involved in metabolism of hormones, fatty acids, and bile acids. A loss-of-function mutation has been shown to reduce the risk of development of MASLD; RNAi therapeutics aiming to potentially mimic a natural loss-of-function genetic variant by silencing the HSD17B13 gene in clinical development for the treatment of MASH include Phase IIb assets **rapirociran sodium** (ALN HSD) (Alnylam/Regeneron), **GSK4532900** (GSK/Arrowhead) and **VSA006** (Visirna), and Phase I assets **AZD7503** (AZ) and **IN1822** (Inipharm).
- [MARC1](#) is a protein anchored to the outer mitochondrial membrane and catalyzes the reduction of N-oxygenated substrates. A common variant rs2642438 G>A in MARC1 [protects](#) against all-cause cirrhosis, the A allele of rs2642438 is associated with decreased liver fat, enzymes, plasma cholesterol, and risk of MASLD, and finally low-frequency coding variant rs17850677 T>A and rare stop codon variant rs139321832 C>T are associated with lower plasma cholesterol and protection from cirrhosis. In November 2022, Novo Nordisk initiated Phase I development of MARC1 siRNA **NN6581**.
- In July 2022, Regeneron announced discovery of a rare loss-of-function (LoF) mutation in the Cell Death Inducing DFFA Like Effector B (**CIDEB**) gene, the most highly expressed gene in human liver cells. A multi-stage sequencing analysis based on >540,000 individuals across five ancestry groups and multiple cohorts showed that LoF mutations in one or two copies of the CIDEB gene was associated with a ~53% reduction in risk of MASLD and ~54% risk reduction of MASH cirrhosis. Additionally, CIDEB mutations had greater protective effects in patients with obesity or T2D. Based on these findings, Regeneron in collaboration with partner Alnylam has already initiated a new therapeutic program to target CIDEB utilizing Alnylam's siRNA technology that could enter clinical development in 2023.

A number of [environmental factors](#) have been identified as significant modifiers of disease activity. These include diets high in fat and/or fructose (widely adopted as animal models for MASFLD research). There is also mounting evidence that the microbiome contributes to MASLD pathogenesis throughout its progression from insulin resistance and abdominal obesity, through to fibrosing MASH. Small bowel bacterial overgrowth is more prevalent in patients with MASH than controls and is associated with more severe steatosis. Perhaps most intriguing are reports demonstrating the close interactions between the host innate immune system and the microbiome.

## Interest by Large Pharma (1 of 2)

### Increasing interest by large Pharma of the MASH market

Initially, MASH research was left mostly to small, unpartnered biotech who were leading the field. Intercept looked set to gain an early foothold in the MASH market space being the first to achieve positive clinical Phase III data from FXR agonist **obeticholic acid** (OCA) followed by further positive Phase III data with **resmetirom** (Madrigal). While obeticholic acid received a CRL and Intercept disbanded further development, in March 2024 Madrigal won the race getting the first MASH drug to market. While other late-stage assets including Genfit's **elafibranor**, AbbVie's **cenicriviroc**, Gilead's **selonsertib**, and Conatus' **emricasan** have failed, Big Pharma have now realized the potential market opportunity in MASH, touted to be the next global epidemic. Companies showing increasing engagement in the MASH space include AZ, BI, GSK, Merck, and Novo Nordisk, while several leading Pharma including AbbVie, BMS, Gilead, and Novartis have reduced their presence.

#### AstraZeneca:

In April 2015, AZ and Regulus announced that the GalNAc-conjugated dual anti-miR 103/107 RG-125 (**AZD4076**) had been chosen for collaborative development for MASH patients with pre-diabetes/T2D. Preclinical studies of RG-125 showed sustained reduction in fasting glucose, fasting insulin levels, liver triglycerides, and liver steatosis. In July 2017, a US Phase I/II trial was initiated in 51 T2D patients with MASLD, however, in June 2017, AZ informed Regulus that it intended to terminate the clinical program for AZD4076 for the treatment of MASH in T2D and returns rights to Regulus. In April 2018 AZ and Ionis expanded upon an R&D agreement of novel antisense therapeutics to include antisense against PNPLA3 ION838 (**AZD2693**). In March 2023, AZ initiated [Phase II](#) development, making AZD2693 the first asset targeting PNPLA3 to enter late-stage development.

In January 2020, AZ entered an agreement with MiNA to develop saRNA based therapies against undisclosed targets for the treatment of metabolic disease, and in March 2020, AZ entered an agreement with Silence Therapeutics to develop siRNA-based therapies against undisclosed targets for the treatment of cardiovascular, renal, metabolic, and respiratory diseases.

In November 2020, AZ licensed antisense ION455 (now **AZD7503**) against HSD17B13 that is now in Phase I development for MASH. Additionally, AZ has Phase II myeloperoxidase inhibitor mitiperstat and Phase I/II QW dual GLP-1/GRA AZD9550 in development for the treatment of MASH.

#### Boehringer Ingelheim:

In June 2011, Boehringer Ingelheim and Zealand entered an agreement to develop dual GLP-1/GRAs for the treatment of T2D and obesity, and in June 2017, the first clinical trial of weekly dual GLP-1/GRA **survotudide** (formerly BI 456906) was initiated. The asset remains in late-stage development for MASH, T2D, and obesity – [data from a global Phase IIb trial released January 2024 showed survotudide met all endpoints including significant improvements in MASH and fibrosis; a Phase III trial was initiated in March 2024](#).

In March 2015, Boehringer Ingelheim and Pharmaxis (now Syntara) signed an Option and Asset Purchase Agreement granting BI an exclusive option to acquire world-wide rights to Pharmaxis' semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1) agent, PXS4728A (now **BI 1467335**), and related SSAO/VAP-1 inhibitor molecules. In May 2015, BI exercised its option to purchase BI 1467335 to develop it for MASH. Interim results from Pharmaxis' Phase I study of BI 1467335, presented at ILC 2015 in April, showed that a single dose was safe and tolerable; subsequently, BI 1467335 was found to be safe and tolerable in a Phase Ib MAD study (disclosed September 2015). In June 2017, BI initiated a proof-of-mechanism Phase II trial of BI 1467335 in overweight/obese MASH patients, however, in December 2019, BI discontinued development of BI 1467335 due to risk of drug interactions in MASH patients.

In October 2017, BI entered an agreement with Dicerna to develop GalXC RNA interference (RNAi) based therapy in MASH, followed in November 2017 by an agreement with MiNA Therapeutics to develop small activating RNA (saRNA) for the treatment of fibrotic liver disease. In June 2019, BI entered an agreement with Yuhan to develop dual GLP-1/FGF21 **YH25724** for MASH.

In January 2020, BI acquired global exclusive rights to Enleoven's anti-IL-11 platform with the aim to develop therapies for multiple fibro-inflammatory disorders including MASH.

In March 2022, BI announced Phase II trial to evaluate combination therapy of SGLT-2 inhibitor empagliflozin and sGC activator avenciguat (BI 685509) in MASH with F4.

In January 2024, BI entered a collaboration with Ribo to develop novel therapeutics for MASH utilizing Ribo's RNAi platform RIBO-GalSTAR. Additionally, BI announced a £30 million observational study **ADVANCE** to improve understanding of MASH cirrhosis.

*Continued*

## Interest by Large Pharma (2 of 2)

### Increasing interest by large Pharma of the untapped MASH market

#### GlaxoSmithKline:

In November 2021, GSK entered an exclusive license agreement to develop and commercialize Arrowhead's HSD17B13 RNAi ARO-HSD (**GSK4532990**) for the treatment of MASH. First-in-human data presented at AASLD 2021 showed ARO-HSD was well tolerated and elicited robust inhibition of hepatic HSD17B13 associated with reduction in ALT (see CVrg's AASLD 2021 Conference report for further details). GSK4532990 was the first RNA technology targeting HSD17B13 to clinical development for the treatment of MASH and is now in late-stage development in Phase IIb trial [HORIZON](#) that will evaluate efficacy of GSK4532990 on liver histology in ~250 MASH F3 patients.

#### Merck:

In February 2015, Merck announced that it has entered a five-year collaboration with NGM Biopharmaceuticals Inc. to research and develop drugs for diabetes and obesity. The deal included preclinical agents **NGM386** and **NGM395** (GDF15 analogs), and **NGM313** (insulin sensitizer), which was being developed for diabetes, obesity, and MASH. NGM was to lead research efforts, and Merck would license resulting programs and lead global product development and commercialization. In January 2019, Merck exercised its option on NGM313 (**MK3655**) following positive [Phase I](#) data showing reductions in liver fat and improved glycemic control as well as plasma lipids 28 days after a single dose. In March 2019, Merck extended their collaboration with NGM for additional five years but terminated its license to GDF15 analogs NGM386 and NGM395. In November 2020, Merck initiated a [Phase IIb](#) trial of MK3655 in MASH patients with/without T2D to evaluate histology endpoints at 52 weeks, however, due to lack of efficacy the Phase IIb trial was discontinued.

In August 2020, Merck acquired exclusive rights (ex S. Korea) to Hanmi's dual GLP-1/GRA **efinopegdutide**. The asset was in Phase II development in a collaboration with J&J, but in July 2019 rights were returned to Hanmi due to lack of A1c lowering efficacy; Merck is pursuing development of efinopegdutide in MASH and data presented at EASL 2023 showed greater improvements in liver fat despite similar weight loss magnitude, indicating a specific contribution from glucagon receptor agonism. In June 2023, Merck initiated a Phase IIb trial in patients with MASH F2-F3. In December 2020, Merck entered a collaboration with Aligos to discover and develop oligonucleotide therapies for the treatment of MASH and up to one additional target of interest in the cardiometabolic/fibrosis space.

#### Novo Nordisk:

In December 2017, Novo Nordisk entered a collaboration to University of Leuven spin-off reMYND to develop an undisclosed preclinical small molecule **ReS39** with therapeutic potential for diabetes, MASH, and metabolic diseases. In April 2019, Novo Nordisk entered a collaboration agreement with Gilead to investigate in-house GLP-1 agonist semaglutide SC in combination with Gilead's ACC inhibitor firsocostat and FXR agonist cilofexor for the treatment of MASH. In March 2021, the two Pharma announced a [Phase IIb](#) trial to evaluate the combination on histology endpoints in MASH F4 patients.

In November 2019, Novo Nordisk and Dicerna entered an agreement to discover and develop RNAi therapies for liver-related cardio-metabolic diseases with plans to explore >30 liver cell targets with potential to deliver multiple clinical candidates for indications including chronic liver disease, MASH, T2D, obesity, and rare diseases. While several other Pharma have collaborations with Dicerna, this deal granted Novo Nordisk rights to any targets not already included in Dicerna's previous agreements. In November 2022, Novo Nordisk initiated clinical development of two assets originating from this collaboration; MARC1 siRNA **NN6581** and LXR $\alpha$  siRNA **NN6582**.

In September 2022, Novo Nordisk licensed Ventus' peripherally-restricted NLRP3 inhibitors including preclinical asset **VENT-01**.

In January 2024, Novo Nordisk entered research collaborations with Omega Therapeutics and Cellarity on novel treatment approaches to cardiometabolic diseases. The Cellarity collaboration will build upon initial work from a collaboration, initiated September 2022, utilizing the Company's platform to investigate novel biological drivers of MASH aiming to develop a small molecule therapy for MASH.

# Market Landscape

The outlook for the MASH market looks robust due to the magnitude of the global MASH epidemic resulting from the ageing population and the continuing high rates of obesity and T2D. Projections indicate that as many as 8 million US adults (22 million globally) could have MASH F3-F4 by 2030.

According to the FDA, pharmacotherapies should focus on patients with MASH with advanced fibrosis, and as of March 2024, resmetirom (marketed Rezdiffra, Madrigal) was approved became the first treatment for MASH F2-F3 in the US.

This section includes:

- Target Product Profile for MASH drugs
- Commercial opportunities
- Launch forecast
- Latest news on leading assets

## Target Product Profile

According to the FDA, until criteria that can reliably identify which MASLD patients will progress to MASH are established, **focus should be on developing treatments targeting MASH with fibrosis.** For a drug to be considered for accelerated approval for MASH the FDA requires achievement of endpoints based on improvement in liver histology, likely to predict clinical benefit including:

- **resolution of MASH (overall histopathological reading) and no worsening of fibrosis (CRN fibrosis score) and/or**
- **≥1 stage improvement in fibrosis without worsening of MASH**
  - Composite endpoint of complete resolution of steatohepatitis AND/OR no worsening of fibrosis
  - Composite endpoint of at least one point of improvement in fibrosis with no worsening of steatohepatitis (steatosis, ballooning, or inflammation)

Full approval requires demonstration of benefit on clinical outcomes – see “Regulatory Considerations” for further details.

Resmetirom (Rezdiffra, Madrigal) received accelerated approval from the US FDA based on data from registrational Phase III trial [MAESTRO-NASH](#) showing more resmetirom (80 or 100mg) treated patients achieved **≥1 stage improvement in fibrosis without worsening in MASH** vs. placebo (24 and 26 vs. 14%, respectively) and **MASH resolution without worsening in fibrosis** (28 and 34 vs. 16%, respectively). These data will be a benchmark for future MASH therapies to match to be successful.

MASH is largely an asymptomatic disease and will likely require **long-term treatment** to promote and sustain remission of MASH and fibrosis, thus a benign **safety** profile is important.

**Cost** does factor highly in treatment choices; however, premium pricing might be acceptable if a drug is significantly better in terms of its efficacy and/or its safety, especially if a cost-effectiveness analysis shows that such efficacy or safety can lower overall costs.

Several KOLs are convinced that an injectable formulation will not in practice be as big a drawback as once thought. Since treatment options remain limited, **route of administration** may not play as big a role for the treatment of MASH as for example for T2D. Resmetirom, the **only drug currently approved for the treatment of MASH F2-F3 is a once-daily oral.**

### Combinations

Combination therapy may be the most effective strategy to treat MASH. A workgroup under the [Liver Forum](#) is exploring the regulatory landscape for MASH combination therapies and working on a consensus statement considering different risk phenotypes, mechanistic rationales for combination therapies, and exploring the inventory of MOAs to build consensus around prioritized combinations. A draft available for broader comments is expected by end of June 2024. Demonstrated safety in combination therapy will be necessary, since many MASH drugs will be used in combination to target different aspects of the disease. The FDA does not have a clear approach to approval of combination drugs, but if the components are already marketed, established data on their safety profiles will be available.

## Commercial Opportunity – Market Opinion, Barriers/Drivers of Opportunity

### Market opinion

A 2014 [Deutsche Bank](#) industry report titled “*NASH – the next big global epidemic in 10 years?*” estimated a peak MASH market of \$35–40 billion by 2025 with ~1 million patients receiving various MASH therapies. While several analysts reported figures approaching similar heights ([Reuters 2017](#), [Financial Times 2017](#)), getting the first drug to market took longer than expected at the time and a 2023 report by [Research and Markets](#) valued the 2022 market at \$1.95 billion projected to grow to \$15.04 billion by 2027.

- CVrg considers \$40-50 billion unlikely, even for a novel therapy in an area of high unmet need

For example, Gilead's hepatitis C drug Sovaldi has been touted as the most successful drug launch ever and could be viewed as a model for the most optimistic scenario possible for a drug for MASH and yet worldwide consensus estimates were, that Sovaldi would reach global sales of \$13 billion in 2018. Like MASH, hepatitis C ultimately leads to liver transplant or death.

- Costing \$84,000 (~\$1,000/dose) for 12 weeks of therapy, the drug achieved [\\$2.27 billion](#) in revenue in its first quarter on the market.
- \$2.1 billion of the \$2.27 billion of Sovaldi's revenues in the first quarter came from US sales.

In reality, Sovaldi achieved global sales of [\\$5.2 billion in 2015 declining to \\$4 billion in 2016](#) due to pricing pressure and competition from [Merck's Zepatier priced at \\$54,600 for 12 weeks of therapy](#).

### Major obstacles to a MASH drug achieving success remain

- While liver biopsy has largely been replaced by non-invasive diagnostic tools in clinic, due to lack of definitive screening recommendations and the largely asymptomatic nature of the disease **diagnosis rates of MASH remain low**.
- Continued challenges regarding histology endpoint requirements in clinical trials as biopsy is rarely done outside trial settings.
- New drugs for MASH are unlikely to provide a cure, but rather **will be taken long-term** to delay or prevent clinical outcomes such as death/liver transplant, analogous to diabetes, obesity, or dyslipidemia medications.
- It is unclear what proportion of patients with MASH would benefit from a disease specific treatment vs. risk factor modification.

### Key upside factors driving the excitement for the indication

- Huge patient population driven by continued growth of the obesity and diabetes epidemic.
- Heterogeneous patient population and complex disease pathophysiology may call for engagement of several targets to obtain clinically meaningful improvements.
- Significant unmet need: only one approved therapy and dismal outcomes among severely affected patients.

# Commercial Opportunity – Current Market, Pricing Assumptions, Treatment Uptake

## Current Market

In addition to THR $\beta$  agonist resmetirom (Rezdiffra, Madrigal) launched in the US in April 2024, lifestyle changes including diet and exercise to reduce weight, Vitamin E supplementation, as well as treatment of comorbidities including obesity, diabetes, and dyslipidemia, are routinely accepted as the standard of care for MASLD and MASH.

Various drugs used off-label for the treatment of MASH, include vitamin E, metformin, statins, GLP-1 agonists, and SGLT-2 inhibitors, but none have been approved by the FDA or EMA as a treatment for MASH.

It is very difficult to estimate the current market for MASH since all drugs but resmetirom are used off-label (e.g., metformin is primarily used for diabetes), and it is challenging to estimate the percentage of sales that are for MASH; some of these agents are available as low-cost generics.

## Pricing Assumptions: Agents with disease modifying potential

- Resmetirom targeting patients with MASH F2-F3 is priced at a premium (~\$131/day) compared to Zetia for dyslipidemia (~\$11 per day) and SGLT-2i inhibitors for T2D (~\$10-20 per day).
- Therapies for the treatment of MASH with fibrosis are generally believed to be priced in line with the novel **PCSK9 inhibitors** used for the chronic treatment of familial hypercholesterolemia or injectables used in obesity/T2D (**GLP-1 agonists**). The price of GLP-1 agonists range between **\$8,000-11,000 per year in the US** while the list price of PCSK9 inhibitors dropped by ~60% in late 2018 to **~\$6,000 per year in the US**. Prices of PCSK9i in the EU are currently ~€4,500 (~\$5,000), which is not much lower than the US prices, but may decrease further in the future given that there is often a large cost differential between the EU and US; for example, there is at least a five-fold price difference of leading T2D drugs between the US and the UK.
- Pricing at these levels may require clinical outcomes data, such as prevention of transplant and/or death. Given the cost of a liver transplant exceeds \$800,000, any novel drug treatment that can reverse the fibrotic damage of MASH could have a major positive impact on healthcare costs.

## Treatment uptake

In 2030 ~100 million US patients are expected to have MASLD, 25-30 million are expected to have MASH, of which ~8 million will have F3-F4. For T2D, ~50% of patients are diagnosed and 50% of those diagnosed are treated; given a more challenging diagnosis of MASH fibrosis/cirrhosis these proportions would be expected to be lower for MASH.

Cost will ultimately have an impact on the market traction of any novel drug, since cost of treatment will affect reimbursement and subsequent patient penetration, as has been the case for the PCSK-9 inhibitors. While there is huge market potential, the bar is high for a novel drug to be safe and prove highly effective on meaningful endpoints. Adoption and penetration rate are currently one of the biggest unknown factors that will influence the size of the market.

An April 2024 survey of 81 gastroenterologists performed by Spherix Global Insights revealed 82% of respondents were aware of Rezdiffra's approval, and despite the potential drawbacks (non-responders and cost were mentioned), rapid adoption of Rezdiffra is anticipated, with more than three-quarters expecting to trial the brand within six months of its launch. Respondents indicated that >1/3 of MASH patients under their care would be suitable candidates for Rezdiffra.

- Resmetirom, (Rezdiffra, Madrigal) has an initial list price of \$47,000/year targeting ~315,000 diagnosed MASH F2-F3 patients that are seen by specialists. Leerink Partners has touted resmetirom to generate annual revenues upwards of \$3.5 billion before the end of the decade.

## Commercial Opportunity – MASLD/MASH Competitive Landscape

Updated March 2024

Madrigal completed the rolling submission of an NDA for resmetirom in MASH in July 2023 and on March 14, 2024, resmetirom (Rezdifra) became the first drug to make it to the US market for MASH with fibrosis. With the new guidance for MASH cirrhosis from the US FDA requiring improvement in hard clinical endpoints, the expected trial duration of MASH cirrhosis trials is likely going to increase, pushing a potential launch further into the future (it is not clear how this guidance will impact ongoing trials in MASH cirrhosis).

Currently, seven drugs are in Phase III development for the treatment of MASH; below are the earliest potential launch dates for the leading agents in development, estimated based on company press releases, trial completion dates, and special regulatory status. The latest development details on leading agents are included in the following pages.

### MASLD/MASH Launch Forecast – US/EU

Current Phase:

Approved	For MASH with fibrosis
Pre-reg	*For MASH with cirrhosis
Phase III	



## Leading Assets - MASH fibrosis (resmetirom)

### Resmetirom (THR $\beta$ agonist, Madrigal)

Resmetirom is a thyroid hormone receptor (THR)  $\beta$  that was originally developed by Roche, then licensed to VIA Pharmaceuticals along with additional lipid modulators from Roche's DGAT1 program. In September 2011, Madrigal acquired VIA's assets and in mid-2016 initiated a [Phase II](#) trial of resmetirom in patients with MASH. Top-line 12-week data from this trial presented at ILC 2018, showed potent anti-steatotic effects of resmetirom and additional beneficial effects on LDL-C and triglycerides. Top-line [36-week data](#) released in May 2018 demonstrated that more patients with  $\geq 30\%$  reduction of liver fat at 12 weeks had resolution of MASH at 36 weeks, emphasizing the correlation between this non-invasive measure and biopsy related outcomes.

In March 2019, Madrigal [announced](#) a Phase III trial, [MAESTRO-NASH](#), of resmetirom in 2,000 MASH patients with fibrosis investigating two doses (80 and 100mg) with primary endpoints of MASH resolution without worsening of fibrosis *OR*  $\geq 1$  stage improvement in fibrosis without worsening in MASH at 52 weeks in an interim cohort of 900 patients and a composite clinical outcome in the full population of 2,000 patients at 54 months. In November 2019, resmetirom was granted **Fast Track Designation** for MASH by the US FDA and in April 2023 resmetirom was granted **Breakthrough Therapy Designation** for MASH with fibrosis by the US FDA. A second Phase III trial, [MAESTRO-NAFLD1](#), of resmetirom initiated December 2019 evaluated safety and efficacy of two doses (80 and 100mg) in 700 MASLD/MASH patients with dyslipidemia including secondary endpoints of atherogenic lipids and non-invasive markers of fibrosis.

Topline data from MAESTRO-NASH [released](#) in December 2022 showed **significant improvements in both primary histology endpoints, making resmetirom the first drug to show benefit on both MASH and fibrosis in a Phase III trial**. Additionally, resmetirom showed improvement in atherogenic lipids, and was generally safe and well-tolerated.

On June 30<sup>th</sup>, 2023, Madrigal initiated a rolling submission of a New Drug Application (NDA) to the US FDA seeking accelerated approval of resmetirom for the treatment of MASH with fibrosis. Breakthrough Designation allowed Madrigal to submit individual sections of the NDA when completed rather than waiting until the entire application was complete. The submission was based on data from ~1,000 patients in the global Phase III trial [MAESTRO-NASH](#) showing significantly more resmetirom-treated (80 and 100mg) patients met both histology endpoints of MASH resolution without worsening in fibrosis and improvement in fibrosis without worsening in MASH, data from real-world Phase III trial [MAESTRO-NAFLD1](#), and Phase III trial [MAESTRO-NAFLD-OLE](#), plus data from earlier trials. [In March 2024, the US FDA approved resmetirom for the treatment of MASH F2-F2 in conjunction with diet and exercise under subpart H making resmetirom the first drug approved for the treatment of MASH](#). Full approval is contingent on demonstration of clinical benefit in ongoing Phase III trials. In the same month, the EMA accepted a Marketing Authorization Application (MAA) for resmetirom for the treatment of MASH with fibrosis and the drug is now under evaluation with the Committee for Medicinal Products for Human Use (CHMP).

In May 2022, Madrigal announced an additional Phase III trial [MAESTRO-NASH Outcomes](#) in 700 MASH patients with early cirrhosis. The FDA has publicly stated that an outcomes trial in this patient population can also support full approval in non-cirrhotic MASH, and following a meeting with the FDA, Madrigal decided to pursue this approach for resmetirom.

## Leading Assets - MASH fibrosis (semaglutide)

### Semaglutide (GLP-1, Novo Nordisk)

Novo Nordisk's semaglutide SC is a long-acting GLP-1 agonist is approved for T2D in the EU, US, and Japan, approved for obesity in the US and EU, and Phase III development for MASH with fibrosis. Like once-daily liraglutide, once-weekly semaglutide improves weight loss and A1c control in T2D, and data from the CVOT [SUSTAIN 6](#) presented at EASD 2016 showed a significant 26% reduction in CV risk. In May 2020, topline data from a global [Phase IIb](#) trial of semaglutide in MASH F2-F3 patients showed semaglutide met the primary endpoint of resolution of MASH without worsening of fibrosis at 72 weeks for doses ranging 0.1-0.4mg QD and improved histological and non-invasive markers of fibrosis. Further data from the full cohort (including F1 patients) presented at digital AASLD 2020, confirmed a significant effect on MASH resolution without worsening in fibrosis, and despite the proportion of patients achieving fibrosis improvement without worsened MASH was not significantly different from placebo, fewer semaglutide treated patients experienced fibrosis progression. Further data presented at ILC 2021 (PO-1575) showed that when assessed by ELF and liver stiffness by FibroScan, more semaglutide treated patients achieved improvement in fibrosis and fewer patients experienced worsening in fibrosis vs. placebo.

In October 2020, semaglutide SC received **Breakthrough Therapy Designation** from the US FDA in MASH.

In January 2021, Novo Nordisk announced a 72-week Phase III trial [ESSENCE](#) of semaglutide (SC 2.4mg QW) in 1,200 MASH F2-F3 patients with primary endpoints: MASH resolution without worsening of fibrosis and improvement in fibrosis without worsening of MASH at 72 weeks, and cirrhosis-free survival at 240 weeks – topline data expected end of 2024/early 2025.

In May 2019, Novo Nordisk initiated a [Phase II](#) trial of semaglutide SC in 71 MASH F4 patients with overweight/obesity evaluating efficacy on primary endpoint  $\geq 1$  stage improvement in fibrosis without worsening in MASH. Data presented at ILC 2022 (LB001), showed semaglutide failed to meet the primary endpoint of  $\geq 1$  stage improvement in fibrosis without worsening in MASH in MASH F4, but significantly improved BW, A1c, liver fat, and PRO-C3, but not MRE.

In April 2019, Novo Nordisk entered a collaboration with Gilead, and in August 2019 a 24-week [Phase II](#) trial in MASH F2-F3 patients testing semaglutide SC QW in combination with Gilead's non-bile FXR agonist cilofexor (30 or 100mg) and/or ACC inhibitor firsocostat (20mg) was initiated. At digital AASLD 2020, topline data revealed no new safety concerns of combination therapies, and exploratory efficacy endpoints showed additive effects of combination therapy on liver fat and liver enzymes. In March 2021, Novo Nordisk and Gilead announced an expansion to their collaboration in MASH and in August 2021 initiated Phase IIb trial [WAYFIND](#) investigating safety and efficacy semaglutide SC alone and in combination with a fixed-dose combination of ACC inhibitor firsocostat and non-bile FXR agonist cilofexor in 457 MASH F4 patients.

In August 2021, Novo Nordisk initiated a global [Phase IIb](#) trial to investigate semaglutide SC in combination with in-house FGF21 analog NN9500 and amylin analog cagrilintide in MASH patients with F2-F4 fibrosis.

## Leading Assets - MASH fibrosis (efruxifermin, pegozafermin)

### Efruxifermin (FGF21, Akero)

Akero's efruxifermin is a long-acting FGF21 exclusively licensed to Akero from Amgen; efruxifermin targets FGFR1c (adipose tissue), 2c, and 3c (both liver) but not FGFR4. Phase II trial [BALANCED](#) in MASH F1-F3 patients with overweight/obesity was initiated in May 2019 and in January 2020, Akero expanded the trial to include a cohort of MASH F4 patients. Efruxifermin met the primary endpoint showing significant reduction in liver fat and impressive histological improvements in liver fat responders.

In October 2020, efruxifermin received **PRIME Designation** in the EU, and in October 2021 efruxifermin received **Fast Track Designation** from the US FDA in MASH.

Phase IIb trial [HARMONY](#) was initiated in February 2021, and topline data released in September 2022 showed impressive histological improvements on both fibrosis and MASH in patients with F2-F3, already at 24 weeks which were sustained at 96 weeks.

In Phase IIb trial [SYMMETRY](#) in MASH F4, efruxifermin failed to meet the primary endpoint of improvement in fibrosis without worsening in MASH but showed significant improvements in non-invasive markers of fibrosis. The trial will continue in a long-term safety follow-up for 96 weeks of treatment including a 96-week biopsy. Data from a cohort in SYMMETRY (Cohort D) of non-cirrhotic MASH patients on a stable dose of GLP-1 showed greater improvements in liver fat, markers of liver injury and fibrosis, glycemic control, and dyslipidemia with addition of efruxifermin than GLP-1 therapy alone.

Phase III program, SYNCHRONY was initiated in December 2023 consisting of [SYNCHRONY Real-World](#) evaluating efruxifermin in non-invasively diagnosed MASLD/MASH patients, registrational [SYNCHRONY Histology](#) in 1,000 MASH F2-F3 patients evaluating efficacy of two dose levels (SC 28 and 50mg QW) on MASH resolution AND ≥1 stage improvement in fibrosis from baseline at 52 weeks, and finally a FDA Type B end-of-Phase II meeting has been scheduled for 1Q 2024 to review the design of SYNCHRONY Outcomes of efruxifermin in MASH F4.

### Pegozafermin (FGF21, 89bio)

89bio's pegozafermin is a site-specific glycoPEGylated analog of FGF21 in Phase III development for MASH and severe hypertriglyceridemia (SHTG). Data from a Phase I/II trial showed significant dose-dependent improvements in liver fat, serum lipids, and liver enzymes in MASH patients, and in an expansion cohort, pegozafermin showed corresponding impressive improvements in histological measures of MASH and fibrosis. Additionally, pegozafermin improved cardiometabolic risk factors including A1c, triglycerides, LDL-C, HDL-C, and body weight.

In June 2021, Phase IIb trial [ENLIVEN](#) in MASH F2-F3 was initiated and topline data released in March 2023 showed impressive improvements in both histology-based primary endpoints accompanied by improvements in non-invasive markers of fibrosis. In a small cohort of F4 patients, pegozafermin improved histological fibrosis as well as non-invasive markers of fibrosis.

In September 2023, pegozafermin was granted **Breakthrough Therapy Designation** for MASH.

A [Phase III](#) trial of pegozafermin in SHTG initiated in June 2023, and in March 2024, 89bio initiated Phase III trial [ENLIGHTEN-Fibrosis](#) in MASH F2-F3; ENLIGHTEN-Cirrhosis in MASH F4 is expected in 2Q 2024.

In March 2024, pegozafermin received **PRIME Designation** in the EU.

## Leading Assets - MASH fibrosis (aramchol)

### Aramchol

Galmed's aramchol, a conjugate of cholic acid and arachidic acid, is also a leading contender; this agent was accidentally discovered to reduce liver fat infiltration in animal models with high-fat diets during research to solubilize bile stones. Aramchol was granted **Fast Track Designation** in MASH in September 2014. A Phase II study showed aramchol to be safe and effective in reducing liver fat content and improve metabolic parameters associated with MASLD.

In February 2018, Galmed released data from Phase II trial [ARRIVE](#) of aramchol in patients with HIV-associated lipodystrophy and MASLD, showing no effect of aramchol on MRI-PDFF vs. placebo. In Galmed's Q4 2017 call, it was discussed that MASLD in HIV lipodystrophy patients is associated with underlying fat destruction, thus different signaling pathways may be involved compared to non-HIV MASH. In June 2018, Galmed released topline results of [ARREST](#), a global dose-ranging Phase II/III trial of aramchol in 240 MASH patients which met the primary endpoint of reduction in liver fat at 52 weeks. The 600mg dose significantly resolved MASH and more patients achieved MASH resolution without worsening of fibrosis, one of two surrogate endpoints recommended by the FDA for pre-cirrhotic MASH; additionally, in a *post hoc* analysis fewer patients progressed to cirrhosis.

In May 2019, Galmed announced global Phase III/IV trial ARMOR investigating BID oral doses of 300mg aramchol for 52 weeks in MASH patients with F2-F3 fibrosis, overweight/obesity, and prediabetes/T2D. The trial was initiated in September, and primary endpoints of the Phase III part are MASH resolution without worsening of fibrosis and/or improvement in fibrosis without worsening of MASH at 52 weeks in a 1,200-patient interim cohort, and for the Phase IV part: clinical efficacy endpoints. In December 2020, an open-label arm was added to ARMOR to evaluate treatment response kinetics, PK, and safety of aramchol at various time points including a second liver biopsy at 24 weeks after treatment initiation. In January 2021, Galmed announced that due to the COVID-19 pandemic, randomization of patients to the registrational part of ARMOR was temporarily suspended and currently enrolled patients were transitioned to the open-label cohort. The time to evaluation of the histological primary interim endpoints was expanded from 52 to 72 weeks, and trial completion as well as primary completion were delayed. Early findings from the first 20 patients in the open-label cohort presented at AASLD 2021, showed 60% of patients treated with aramchol exhibited histological fibrosis improvement accompanied by improvements in non-invasive markers of liver injury and fibrosis, with the antifibrotic effect occurring as early as 24 weeks.

In August 2021, the US FDA and UK Medicines and Healthcare products Regulatory Agency (MHRA) agreed that Galmed can proceed with plans to use aramchol meglumine (in lieu of aramchol free acid) in the double-blind placebo-controlled part of registrational Phase III trial [ARMOR](#) without needing to conduct additional non-clinical and clinical studies other than planned limited pharmacology studies relating to aramchol meglumine. Aramchol meglumine contains the same active pharmaceutical ingredient (API) as aramchol free acid but displays a markedly higher (30,000 times) solubility, leading to a reduced variability in exposure; exposure with aramchol meglumine (oral 338mg QD) corresponds to that obtained with aramchol free acid (oral 300mg BID). According to Galmed CEO Allen Baharaff, this means Galmed "*can potentially significantly reduce our target marketing price once Aramchol is approved via the potential saving of approximately 50% of cost of goods*".

In May 2022, Galmed discontinued the open-label arm of ARMOR since it was deemed the open-label part of the study met its objective showing anti-fibrotic effects as early as 24 weeks, and initiation of the double-blind placebo-controlled part of ARMOR was postponed to 2H 2023, subject to "data from the open-label part of the trial, sufficient funding, and clarification of the regulatory approval process for MASH drugs". Additionally, the Company discussed plans to expand development aramchol into new undisclosed anti-fibrotic indications with high unmet need and potentially faster development for regulatory approval. The shift in strategy involves a cost reduction effort that will enable focus on new indications as well as preparation for the registrational part of ARMOR; Galmed is hoping to leverage clinical data from the ARMOR study to rapidly progress aramchol into Phase II and III development for new indications. Galmed is actively looking for partnering opportunities to continue aramchol's clinical development.

## Leading Assets - MASH fibrosis (lanifibranor)

### Lanifibranor

Phase IIb development of Inventiva's leading agent panPPAR lanifibranor in MASH was initiated in February 2017 ([NATIVE](#)), and in September 2019, lanifibranor was granted **Fast Track Designation** from the US FDA for the treatment of MASH. Since some single and dual PPAR agonists have been associated with toxicity and adverse effects on heart, kidney, skeletal muscle, bladder, body weight, water retention, and bone mineral density, the US FDA requires two-year carcinogenicity and one-year *in vivo* toxicity studies of PPAR class compounds to be performed prior to agents entering clinical trials of a duration >6 months. In May 2019, the US FDA lifted the partial clinical hold on lanifibranor following review of two-year carcinogenicity studies.

In June 2020, topline data from NATIVE showed lanifibranor met the primary endpoint and improved histological features of MASH and fibrosis in significantly more patients vs. placebo and generally found to be safe and well tolerated. In August 2021, Inventiva initiated pivotal Phase III trial [NATiV3](#) of lanifibranor in 2,000 MASH patients with F2-F3, planning to request accelerated approval based on an interim histology analysis. In January 2023, Inventiva announced changes to the clinical development program of lanifibranor, planning a new Phase III trial in ~800 MASH F4 patients in place of the outcomes part of NATiV3. Additionally, a placebo-controlled 72-week exploratory cohort will be added to NATiV3 Part 1, including ~200 screen failed patients from Part 1, to generate safety data and efficacy data based on NITs. All patients enrolled in NATiV3 Part 1 will be offered participation in a 48-week active treatment extension study.

In February 2022, Inventiva initiated a proof-of-concept Phase II trial ([LEGEND](#)) of lanifibranor in combination with empagliflozin in patients with non-cirrhotic MASH and T2D. The trial will enroll 63 patients and topline data are expected in 2H 2023.

In September 2022, Inventiva and Sino Biopharm announced a licensing and collaboration agreement for Sino to develop and commercialize lanifibranor for the treatment of MASH and potentially other metabolic diseases in Greater China (mainland China, Hong Kong, Macau, and Taiwan). Sino will through subsidiary Chia Tai-Tianqing Pharmaceutical Group (CTTQ) oversee the development and commercialization of lanifibranor in Greater China. In May 2023, Sino received investigational new drug (IND) approval from the Chinese National Medical Products Administration (NMPA) to initiate clinical development of pan PPAR agonist lanifibranor for the treatment of MASH in mainland China. Sino will participate in ongoing registrational Phase III trial NATiV3 and in parallel conduct a Phase I clinical pharmacology study.

In September 2023, Inventiva and Hepalys announced a licensing and collaboration agreement for Hepalys to develop and commercialize lanifibranor in Japan and S. Korea. Hepalys is expected to initiate clinical development, conducting two Phase I studies in Japanese patients and healthy volunteers to support initiation of a dedicated pivotal trial in Japanese and Korean patients with MASH, which is planned to start once the results of global pivotal Phase III trial NATiV3 are available.

In December 2023, lanifibranor was granted **Breakthrough Therapy Designation** from the Chinese NMPA.

## Leading Assets - MASH with cirrhosis (belapectin)

### Belapectin

Galectin is developing galectin 3 inhibitor belapectin for MASH with advanced fibrosis and MASH with cirrhosis. It is not possible to determine which NAFL patients will advance to MASH and cirrhosis, so while halting the accumulation of fat is clearly important, reversing the damage would be a game changer in the treatment of this disease. Preclinical evidence suggests, galectin-3 is essential for development of liver fibrosis, hence belapectin prevents fibrosis by inhibiting galectin-3. In 2013, Galectin received **Fast Track Designation** from the FDA to expedite development of belapectin for MASH patients with advanced hepatic fibrosis.

In January 2015, Galectin released final data from FibroScan analysis, a noninvasive measure of liver stiffness, which was performed for a subset of the third cohort of its Phase I trial. 3 of 5 patients on belapectin had reduction of liver stiffness, which further bolsters Galectin's assertion that belapectin can reverse hepatic fibrosis.

In March 2015, the company submitted the protocol to the FDA for its new Phase II trial NASH-CX for a Special Protocol Assessment (SPA). If positive, Galectin hoped to use results from this trial to be included in an eventual NDA of belapectin. In May 2015, Galectin disclosed that the FDA did not grant the SPA; however, Galectin opted to take the FDA's feedback and proceed with this trial as a Phase II trial [NCT02462967](#), rather than resubmit the SPA in an attempt to obtain Phase III status for NASH-CX.

In September 2016, Galectin disclosed that belapectin did not improve fibrosis vs. placebo as assessed by LiverMultiScan, FibroScan, or MRE, in the Phase II NASH-FX [NCT02421094](#). While Galectin emphasized the short nature of NASH-FX (4 months treatment) made it unlikely to see benefit in fibrosis, and the company is now stating that belapectin's primary indication is MASH with cirrhosis, these results are a blow for Galectin, as previously, belapectin had been touted as the only agent which could reverse fibrosis. While Galectin officials did not rule out additional studies in MASH with fibrosis, such studies would not be initiated till results from NASH-CX (which includes liver biopsy as a secondary endpoint) are available.

In December 2017, Galectin released top-line results of NASH-CX, and although NASH-CX did not meet its primary endpoint, a distinct patient population with well-compensated cirrhosis and no esophageal varices who may benefit from belapectin treatment was identified. Since more than 90% of cirrhotic patients develop esophageal varices, the reduction in development of new esophageal varices in patients with no baseline varices with belapectin seems promising. The effect of belapectin was consistently greater in the 2mg/kg treatment group vs. 8 mg/kg group, which is consistent with previous findings in animal models. This was most apparent in the responder analysis; therefore, increasing treatment duration rather than drug dose for a greater effect is likely to be the strategy in future studies. Galectin will explore the design of a Phase III program of belapectin in cirrhotic MASH patients without varices, where change in HPVG expressed as percent change/absolute reduction or as a responder analysis has been suggested as a possible acceptable surrogate endpoint by the US FDA. Development of varices in patients without varices at baseline may be considered a clinical outcome measure. In May 2018, Galectin met with the US FDA and despite the FDA rejecting Breakthrough Therapy Designation for belapectin for MASH with cirrhosis without esophageal varices, Galectin proceeds with plans for a Phase III trial. At a Type C meeting in February 2019, the FDA confirmed to be supportive of the use of progression to varices as a potential surrogate endpoint and progression to large varices as a component of a composite clinical benefit endpoint in the planned Phase III trial of belapectin, NAVIGATE. In December 2019, Galectin presented design refinements to NAVIGATE based on feedback from discussion with the FDA in November and revealed the trial will be an adaptive Phase IIb/III trial investigating 2 doses (2 or 4mg) of belapectin in MASH cirrhosis patients with portal hypertension and risk of developing esophageal varices. The full protocol was posted in April 2020, and enrollment was initiated in June 2020. In April 2021, Galectin launched [NAVIGATEnash.com](#) dedicated to Phase IIb/III trial [NAVIGATE](#). The website intends to educate patients and physicians about liver cirrhosis related to MASH and provides information on the trial.

Galectin is ongoing discussions with several pharmaceutical companies regarding potential partnerships to ensure cost-effective and efficient development of belapectin.

# Regulatory Considerations

The lack of well-defined and validated endpoints is a major hindrance to drug development for MASH and a key question is:

## **What endpoints will be required for a drug to be approved for MASH?**

While the first drug has been approved for the treatment of MASH F2-F3 a **high unmet need** to develop therapeutic strategies targeting early stage MASLD through to advanced liver fibrosis remains. The long asymptomatic period in the development and progression of MASLD to non-cirrhotic MASH to MASH with cirrhosis and ultimately liver failure presents a challenge in terms of trial design and choice of endpoints. Validation of relevant endpoints that reflect the progression of MASLD /MASH is key to identifying patients at risk. The FDA has suggested including unvalidated measures as secondary endpoints, particularly in later stage placebo-controlled trials, for validation. It remains to be seen if upcoming trials can validate these endpoints which for now are relegated to secondary endpoints. Until additional surrogate endpoints have been validated, various suggestions have been made regarding patient selection and potential surrogate endpoints at a 2013 FDA [workshop](#), at subsequent Liver Forum meetings ([November 2015](#)), and most recently in a draft [Guidance for Industry](#) regarding drug development for non-cirrhotic MASH issued by the US FDA; the latter is summarized in the following pages.

## US Regulatory Considerations - Background and Patient Selection Criteria

In December 2018, the FDA released a draft guidance for industry regarding drug development for the treatment of MASH. The [FDA guidance](#) is not a formal guideline document but intended as guidance describing the FDA's current thinking on trial design in MASH with fibrosis. Since MASLD can exist for years without progressing to MASH, the FDA guidance focuses on therapies that will slow progress, halt, or reverse MASLD and/or MASH. Fibrosis is considered the strongest predictor of adverse clinical outcomes, and until criteria that can reliably identify which MASLD patients will progress to MASH are established, **focus should be on developing treatments targeting MASH with fibrosis.**

Although liver biopsy at this time remains the most reliable method for diagnosing and staging of MASH, due to limitations and logistical challenges associated with biopsy, non-invasive markers providing accurate diagnosis of various grades of MASH and fibrosis are needed to replace biopsy. The FDA encourages trial sponsors to develop and validate non-invasive biomarkers for diagnosis and staging of MASH and fibrosis.

The current US guidance is not intended to cover drug development for treatment of cirrhotic MASH or development of *in vitro* diagnostics.

The focus of the guidance is on developing treatments targeting MASH with fibrosis, and early-stage Phase II trials should include a patient population similar to that planned for the Phase III development program. In December 2018, the EMA released a [reflection paper](#) including guidance for drug development in MASH, PBC, and PSC. Guidance was largely similar to the FDA guidance, recommending enrolling patients with late-stage disease (F2-F4) and using similar surrogate endpoints for accelerated approval. Additionally, the EMA reflection paper includes guidance for patients with F4 fibrosis (cirrhosis), which is outlined later in this chapter.

Type of trial	FDA guidance
Patient Population	
Proof of concept (Early Phase II)	<ul style="list-style-type: none"> <li>Preferred: patients with biopsy-proven MASH</li> <li>Acceptable: patients at high risk of MASH; <i>historical diagnosis of MASH OR combination of biochemical criteria and/or imaging evidence of steatosis/MASH/fibrosis in addition to known risk factors for MASH</i></li> </ul>
Treatment effect on histological endpoints (Late Phase II)	<ul style="list-style-type: none"> <li>Patients with biopsy proven MASH (<math>NAS \geq 4</math>) and fibrosis</li> <li>Inclusion of patients with comorbidities reflective of target population</li> </ul>
Registrational (Phase III)	<ul style="list-style-type: none"> <li>Histological diagnosis of MASH (<math>NAS \geq 4</math> with <math>\geq 1</math> point each in inflammation and ballooning) AND Clinical Research Network (CRN) fibrosis score <math>\geq 1</math> but <math>&lt; 4</math></li> <li>Patients with Model for End-Stage Liver Disease (MELD) score <math>\leq 12</math></li> </ul>

## US Regulatory Considerations –Trial Design, MASH with fibrosis (1 of 2)

### Early Phase II studies:

- Proof-of concept (POC) trials can enroll patients without histological evidence of MASH and use non-invasive biomarkers as endpoints provided they are scientifically justified.
- Should capture a **patient population similar to that planned for the Phase III development program.**

### Late Phase II studies:

- **Evidence of efficacy on a histological endpoint.**
- Adequate characterization of treatment effect size, dose-response information, and time course of treatment response to inform Phase III design.
- Trial duration should be **≥12-18 months.**

### Phase III studies:

- Enrolled patients should have a **histological diagnosis of MASH with fibrosis** (F1-F3, ≤6 months prior to enrollment) and NAS ≥4 (**≥1pt in inflammation and ballooning**)
- T2D patients should be on stable doses of anti-diabetic medication **≥3 months** prior to enrollment; randomization should be stratified by presence/absence of T2D
- Treatment with vitamin E and pioglitazone should be discontinued if not on stable dose 6-12 months prior to enrollment
- Body weight should be stable **≥3 months** prior to enrollment
- Study should be double-blind and placebo-controlled
- Endpoints should be based on improvement in liver histology, likely to predict clinical benefit including:

- **resolution of MASH (overall histopathological reading) and no worsening of fibrosis (CRN fibrosis score) and/or**
- **≥1 stage improvement in fibrosis without worsening of MASH**
  - Composite endpoint of complete resolution of steatohepatitis AND/OR no worsening of fibrosis
  - Composite endpoint of at least one point of improvement in fibrosis with no worsening of steatohepatitis (steatosis, ballooning, or inflammation)

For treatments granted accelerated approval based on histology outcomes, randomized, double-blind placebo-controlled trials to verify clinical benefits should be underway upon IND submission.

Clinical benefits need to be demonstrated in:

- Histological progression to cirrhosis
- Reduction in hepatic decompensation events
- Change in MELD score from **≤12 to >15**
- Liver transplant
- All-cause mortality

## US Regulatory Considerations –Trial Design, MASH with fibrosis (2 of 2)

The FDA's thinking on drug development for MASH with fibrosis from a regulatory standpoint was further discussed at a webinar on January 29, 2021:

- While **non-invasive biomarkers** (NITs) are under study for consideration as surrogate markers, **none have to date demonstrated reliability and consistency to be reasonable likely to predict clinical benefit**; to be used as a surrogate efficacy endpoints for accelerated approval while post-marketing trials confirm clinical benefit based on how a patient feels, functions, or survives.
  - sponsors are encouraged to use NITs to demonstrate proof-of-concept in early Phase II studies and as secondary/exploratory endpoints in late-stage trials.
- **The FDA recognized challenges associated with use of liver biopsy** including sampling issues and pathologist reading discordance (inadequate inter- and intra-reader); possible solutions:
  - having an adjudication committee of central pathologists read baseline and treatment slides together
  - ≥2 pathologists; if discordant 3<sup>rd</sup> pathologist
- Sponsor should pre-specify the details of liver biopsy interpretation**
- The recommended duration to evaluation of surrogate histology endpoints in registrational Phase III trials is 12-18 months, but a 24-month evaluation timepoint can be considered by sponsors given the slow gradual progression/improvement of the disease, which would allow for more time to gather safety data.

In the webcast it was clarified that the FDA continues to support accelerated approval of drugs for the treatment of MASH with fibrosis based on surrogate histology endpoints, and discussion in the Q&A session concluded that for investigational drugs with a very large benefit over placebo a greater risk for safety events would be acceptable. According to the panel (Drs. Toerner, Matsubayashi, and Anania) hundreds of questions were posed in the chat indicating great interest from the audience in understanding the FDA's thinking on trial design, approvable endpoints, and use of non-invasive biomarkers. Particular discussions of interest included clear guidance accepting use of digital pathology to make it easier for multiple pathologists to analyze the same slides, which has been a huge topic of debate. Other hot topics of discussion were use of AI to analyze pathology and use of non-invasive tests (NITs) as endpoints in clinical trials and the potential to eventually move towards NITs being used as approvable surrogate endpoints for accelerated approval. While the FDA were seeking dialogue on these topics, it was clear more data demonstrating improvement in biomarkers is associated with improvements in survival and/or reduction in morbidity is needed to consider NITs as approvable surrogate endpoints

The FDA is still reviewing comments to the draft guidance documents and working on issuing final guidance documents for both MASH with fibrosis and cirrhosis. Although the official docket comment period has expired it is possible to comment on a guidance document at any time.

# Disease Assessment Strategies to Accelerate Drug Development

The **Liver Forum** is a platform for ongoing multi-stakeholder dialogue to identify barriers, prioritize research, and identify solutions to accelerate development of therapies for MASLD/ASH. The Liver Forum aspires to provide a neutral, independent, and safe space for discussion and deliberation across stakeholder groups that include professional societies, academic researchers/clinicians, foundations/consortia, patient advocates, industry partners, and regulatory agencies, to focus on developing consensus, increasing synergy and collaboration, and reducing duplication and uncertainty. Meetings are closed to marketing and press.

[Liver Forum 12](#) (4/2022) focused on the **progress to non-invasive biomarkers** to review existing data on diagnostic and prognostic markers, assess gaps, and collaborate to fill gaps, and [Liver Forum 16](#) (3/2024) concentrated on anticipated marketing approvals and how that might impact drug development programs and standardizing NITs and outcomes assessments. Key news summarized below:

## Histology evaluation - improving the reference standard

Need for improved reproducibility and standardization of central reading to improve screen fail rates in late-stage trials and improve upon placebo-effect. Suggestions included:

- **Refine MASH diagnosis and utilize panel review**
  - standardized definitions of morphological lesions and standardized rules for semiquantitative assessment
  - hepatocyte ballooning is THE key to distinguishing MASH, but due to broad divergence in assessment among pathologists achieving ballooning score of 0 is possibly unrealistic
- Utilize **AI pathology** to augment ordinal scale pathology reads
- Focus on development of NITs linked to long-term outcomes including ELF, MRI cT1, MRE

## Impact of first drug approval on clinical development programs

Approval of the first drug for MASH raises potential ethical and practical challenges to continuing and new trials now that a treatment is available. Key questions include:

- Are placebo-controlled RCTs an appropriate trial design or should the approved therapy be considered SOC and trial design change to superiority/non-inferiority design
  - it could be challenging to retain patients in long-term placebo-controlled studies
- Will liver biopsy remain a requirement for surrogate endpoints – when can we transition to NITs and do NITs need to be validated against histology

## Placebo Arm Database Project

The Liver Forum's "Placebo Arm Database Project" includes patient-level data from completed Phase IIb and Phase III trials that is serving Liver Forum sponsors and regulators; currently includes ~2,800 placebo-treated patients from Phase IIb trials and ~2,400 patients from Phase III trials.

- Natural history cohort representing patients eligible for RCTs across the spectrum of MASH stages
- Allows for identification of predictors of "placebo response" vs. disease regression to reduce placebo-arm burden in future trials and increase specificity of patient selection
- Potential for shared placebo arm for future trials

## US Regulatory Considerations –Trial Design, MASH with cirrhosis

The goals for treatment of compensated MASH cirrhosis are to:

- Halt or slow progression of fibrosis
- Prevent clinical decompensation
- Reduce the need for liver transplantation
- Improve survival

### Phase III studies:

#### *Patients:*

- Enrolled patients should have a **histological diagnosis of MASH cirrhosis**; excluding cirrhosis due to other etiologies
  - Diagnosis of cirrhosis should be supported by histology (NASH CRN F4); the sponsor can propose non-histological diagnostic criteria that could be acceptable if scientifically supported
  - The FDA encourages sponsors to identify non-invasive biomarkers that can replace liver biopsy
- Patients with decompensated cirrhosis should be excluded based on evidence of portal hypertension, elevated bilirubin, and elevated INR or prolonged prothrombin time
- T2D patients should be on stable doses of anti-diabetic medication  $\geq 3$  months prior to enrollment; randomization can be stratified by presence/absence of T2D
- Treatment with vitamin E and pioglitazone should be discontinued if not on stable doses 6-12 months prior to enrollment
- Patients with MELD  $>12$ , Hx of HCC, or listed for liver transplant should be excluded

#### *Design and Endpoints:*

- Study should be double-blind and placebo-controlled, and can use stratification of patients based on diabetes status and use of vitamin E or pioglitazone
- Endpoint should be **time to first occurrence** of one of the following:
  - **Complication of ascites**
  - **Variceal hemorrhage**
  - **Hepatic encephalopathy**
  - **Worsening of MELD  $\geq 15$  (criteria for listing for liver transplant)**
  - **Liver transplant**
  - **All-cause mortality**
- Histological improvement in fibrosis can be proposed, however, due to insufficient evidence to support an association between histological endpoints and clinical benefit the FDA expects to evaluate agents for the treatment of MASH with compensated cirrhosis to be evaluated under the traditional approval pathway

#### *Safety:*

- Trial protocols should specify guidelines for monitoring liver function in this patient population with abnormal liver function at baseline
- CV safety should be monitored during the trial

## EU Regulatory Considerations

The EMA considerations differ slightly from the US FDA guidance in points summarized below:

The EMA [reflection paper](#) considers **three** broad categories of MASH:

- Histological **MASH with F2-F3 fibrosis**, NAS  $\geq 5$  (or NAS  $\geq 4$  with a score  $>1$  in all components)
- Histological **MASH with compensated cirrhosis**, NAS  $\geq 5$  (or NAS  $\geq 4$  with a score  $>1$  in all components) or historical histological MASH diagnosis, non-invasive tests indicating NSH, and relevant risk factors (obesity and T2D)
- Histological **MASH with decompensated cirrhosis**, historical histological MASH with cirrhosis diagnosis and symptoms of decompensation

### Phase III studies - endpoints:

Similar to the US guidance the EMA recommends that endpoints for **MASH patients with F2-F3 fibrosis** should be based on improvement in liver histology, likely to predict clinical benefit including:

- **resolution of MASH (overall histopathological reading) and no worsening of fibrosis (CRN fibrosis score) and**
- **$\geq 1$  stage improvement in fibrosis without worsening of MASH**
  - Composite endpoint of complete resolution of steatohepatitis AND/OR no worsening of fibrosis
  - Composite endpoint of at least one point of improvement in fibrosis with no worsening of steatohepatitis (steatosis, ballooning, or inflammation)

For **MASH patients with cirrhosis** possible acceptable endpoints include:

- Composite of all-cause death and liver decompensation events
- Lowering of MELD score below a certain (undefined) threshold
- Lowering of hepatic venous pressure gradient (HVPG)  $<10\text{mmHg}$

At [Liver Forum 10](#) held September 19-20, 2019, in Bethesda, Maryland, content and comments on the current EMA reflection paper regarding trial design were discussed.

Content to be reflected includes:

- Abandonment of co-primary endpoint requirement

In April 2023, the reflection paper was adopted by the Committee for Medicinal Products for Human Use (CHMP) - the paper on regulatory requirements for MASH will go into effect on October 1st, 2024.

## Pediatric Considerations

Since pediatric MASH appears to have different histological characteristics and a different natural history compared to adults, disease characteristics and progression may also be different and extrapolation of efficacy from adults is not currently appropriate.

Current (2018) [considerations](#) from the **US FDA**:

- Extrapolation of efficacy from adults to pediatric patients based solely on PK/PD is not appropriate at this time.
- Longitudinal natural history data are needed to better characterize disease progression and support choice of endpoints.
- Sufficient information about dosing, safety, and efficacy in adults should be obtained prior to initiation of pediatric studies.

The FDA plans to address challenges related to pediatric MASH in an upcoming guidance.

In 2019, The **Liver Forum's Pediatric Working Group** published a [paper](#) discussing factors to consider in drug development for pediatric MASLD recommending:

- Therapeutics are needed for children with MASLD and regulations in place protect children that balance the need for pediatric studies.
- Long-term longitudinal studies are essential to better define the natural history of MASLD with early onset.
- While change in NAS of 2 points has been used in pediatric MASLD trials, other histologic criteria may be considered in pediatric trials owing to the unique portal-predominant pattern in many children.
- Early phase and dose-ranging trial endpoints should be based on the mechanism of action of the drug and the target population.
- Clinical trials designed with liver biopsies should have concurrent non-invasive tests to advance validation of non-invasive biomarkers.
- Children with MASLD who have inflammation and fibrosis may benefit the most from pharmacotherapies and thus are preferred for inclusion in trials.
- Formal pharmacokinetic studies are recommended to establish evidence-based dosing.
- For early phase studies, reduction of elevated serum ALT is a reasonable primary outcome.
- Although steatosis can be measured accurately with MRI, there is inadequate data to support that steatosis reduction will lead to clinically meaningful benefit or changes in other pertinent features related to MASH.
- Endpoints "reasonably likely to predict clinical outcomes" by the regulatory authorities for adults are as follows, and pediatric trials may use similar endpoints in those with MASH:  
FDA/EMA: Biopsy based resolution of steatohepatitis and no worsening of fibrosis or at least a 1-point improvement in fibrosis with no worsening of steatosis, ballooning or inflammation.
- Histology endpoints in children should recognize and account for the unique periportal pattern of inflammation without ballooning in a significant subset of pediatric MASLD patients.

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