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LET'S TALK ABOUT NASH

The pharma opportunity everyone's waiting for

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THE RACE TO TREAT NASH

Several promising candidates are currently competing in a multi-billion-dollar race. NASH, or non-alcoholic steatohepatitis, affects millions of patients world-wide and by 2020 is projected to replace hepatitis C as the number one reason for liver transplantation in the United States.[1]

Multiple drug developers have taken on the challenge and a variety of different approaches are currently in the pipeline to tackle this complex, silent disease. Now all eyes are on the finish line to see who will be the first to enter this lucrative and untapped market.

Understanding the bigger picture of NAFLD

Non-alcoholic fatty liver disease (NAFLD) is an umbrella of disorders characterized by the accumulation of excess fat in the liver of people who drink little or no alcohol.[2] NAFLD is the most common chronic liver condition in the world[3] with a global prevalence estimated to be 25.2.%[4] In the United States, NAFLD is the most common form of chronic liver disease, affecting about one-quarter of the population.[5,6] In 2017 the direct lifetime costs associated with NAFLD were $222.6 billion; $95.4 billion of this was just for patients with an advanced form of liver disease known as non-alcoholic steatohepatitis or NASH.[7]

Who is at risk?

A wide range of diseases and conditions can increase the risk of NAFLD including obesity, type 2 diabetes, hypertriglyceridemia, insulin resistance, and hypertension.[5]. In fact, studies have shown that NAFLD may be present in up to 70% of patients with diabetes.[8]

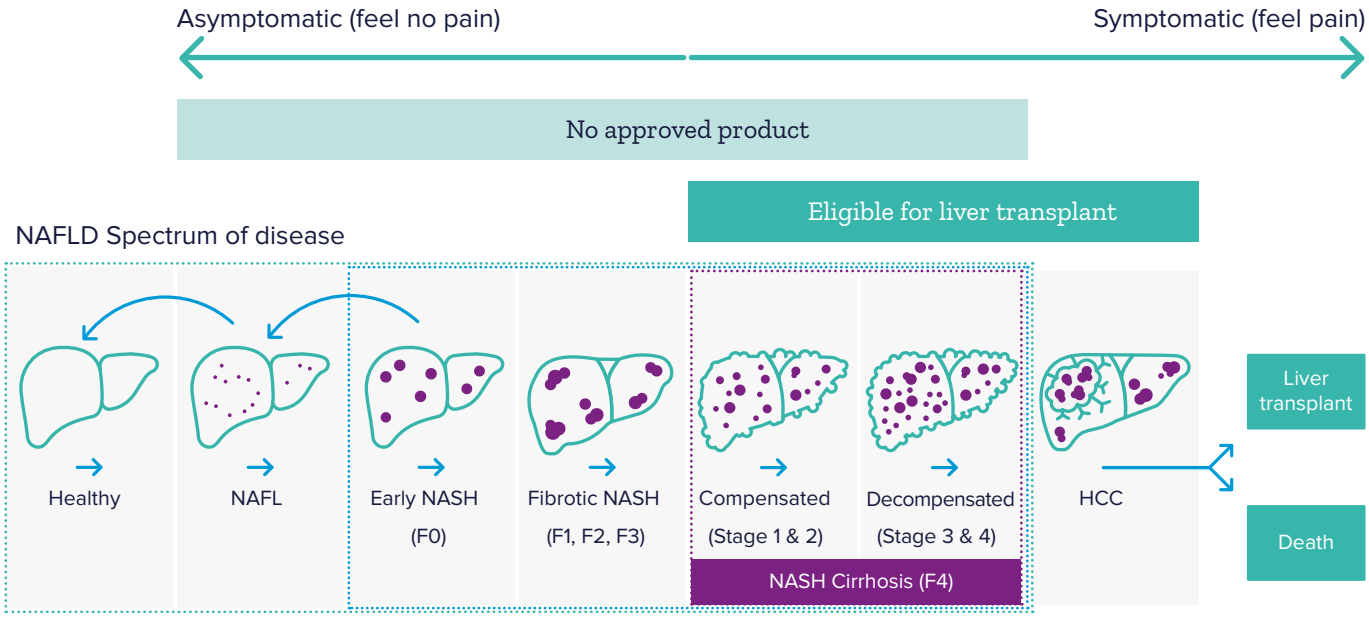
What is NASH?

Up to 30% of people with NAFLD will develop NASH, a more progressive type of liver disease.[9,10]

NASH is associated with hepatocellular ballooning and inflammation, in addition to hepatic steatosis. About 20% of people with NASH will go on to develop scarring (fibrosis) of the liver, which may become severe enough to affect the liver's function, conferring an increased risk of liver cirrhosis or liver cancer.[11]

Overall, the global prevalence of NASH is estimated to be 1.5%-6.5% and it is predicted to become the leading indication for liver transplantation in the next few years.[12]

NAFLD DISEASE SPECTRUM



Please note it is possible to skip stages, and is not always a progression through each one.

	F0	F1	F2	F3	F4 - compensated cirrhosis	F4 - decompensated cirrhosis
US # patients (2016) (Focusing on NASH)	~3.6M	~6.6M	~3.6M	~2.1M	~1.3M	~42.2K
US # patients (2030) (Focusing on NASH)	~3.9M	~9.0M	~6.1M	~4.5M	~3.4M	~105.4K

NASH is a multifactorial and multifaceted disease consisting of a complex myriad of pathogenic pathways.

Harnessing unmet needs and drivers

The NASH therapeutic area is facing several challenges and unmet needs for pharma to conquer if they wish to find success and create significant value in the NASH space.

UNMET NEED 1: Lack of approved therapies
Physicians can recommend weight loss through lifestyle changes such as a healthy diet and daily exercise to help reduce the features of NASH.[13] However currently there are no approved specific treatments. With potentially millions of patients who may benefit from a treatment for NASH this presents pharma companies with a huge opportunity.

DRIVER: Approval of novel therapies
Several therapies are already at various stages of development to help overcome this major unmet need. The competition is fierce as the first entrants into the NASH market will have a clear advantage. However, further barriers make the road ahead a challenging one.

UNMET NEED 2: Complex pathophysiology
The pathophysiology of NASH is complex, making an understanding of the disease extremely important.[14]

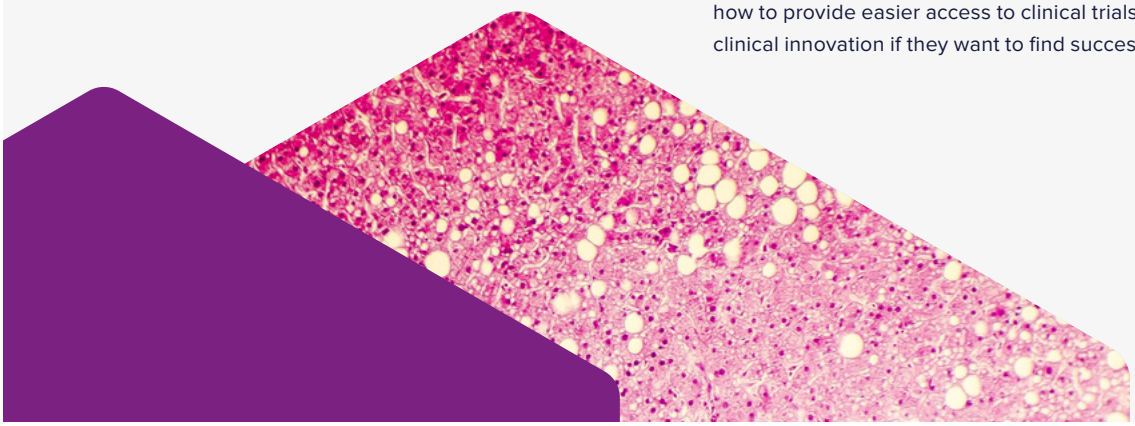
DRIVER: Awareness and education
Awareness and education are key to helping advance understanding of the disease. Many may face challenges in demonstrating the efficacy of treatments in cirrhotic patients, due to the intractable nature of NASH. All pharma companies will need to generate strong awareness of the disease and their treatment's role in stopping its progression.

UNMET NEED 3: Low disease awareness
Behind patient education lies the barrier of physician understanding. Physicians have a low awareness of the NASH condition, resulting in some patients not being referred to specialty care.

DRIVER: Access to care
Greater education to help raise awareness of NASH is growing. Pharma companies with an interest in NASH are already paving the way through conferences and initiatives to help physicians diagnose more patients. An example is the NASH Education Program™ - a public health initiative developed by Genfit which educates on NASH under the supervision of a scientific committee.

UNMET NEED 4: Difficulties in patient recruitment
The NASH patient population is heterogeneous, making patient retention a challenge.[15] NASH is asymptomatic until its later stages, so few patients are even aware of their condition, or seek a diagnosis.

DRIVER: Multidisciplinary team approach
It is vital for pharma companies to engage with the wider multidisciplinary team including primary care physicians, endocrinologists and hepatologists so there is greater awareness of NASH amongst all healthcare professionals at every stage of the disease. Pharma will also need to explore how to provide easier access to clinical trials to help drive clinical innovation if they want to find success in the market.



UNMET NEED 5: Lack of NASH-specific diagnostics

Currently, liver biopsy is the gold standard to diagnose NASH based on standardised universally accepted scoring systems such as METAVIR and the Ishak score that can be interpreted regardless of comorbid disease. However, liver biopsy is expensive, painful and requires extensive medical expertise to perform and interpret the data. The limited number of specialized clinicians vs. the huge number of patients represent a significant barrier. Several non-invasive methods are also used (see table), however none are specific for NASH.

Non-invasive diagnosis of NAFLD and NASH

Lab tests

- NAFLD fibrosis score
- FIB 4 index
- BARD score
- AST: ALT ratio
- AST platelet ratio index
- Fibrotest
- Hepascore
- Fatty liver index
- Index of NASH

Imaging

- Ultrasound
- CT
- MRI
- MRS
- Transient elastography
- Acoustic Radiation Force Impulse (ARFI)
- Magnetic Resonance Elastography (MRE)

Biomarkers

- Hyaluronic acid
- CK 18
- Serum Fucosylated
- Haptoglobin
- Mac 2 binding protein
- ELF score
- FIBROSpect ®

DRIVER : Novel non-invasive diagnostics

There is an urgent need for non-invasive biomarkers for staging NAFLD as well as identifying those at risk of progressing to end stage liver disease so they can be treated early and aggressively in order to prevent progression. Until novel non-invasive diagnostic tools are developed, validated, and approved, the combination of non-invasive techniques such as FibroScan®, MRE, and serum-based fibrosis biomarkers may be the optimal tools to stratify risk of advanced fibrosis.

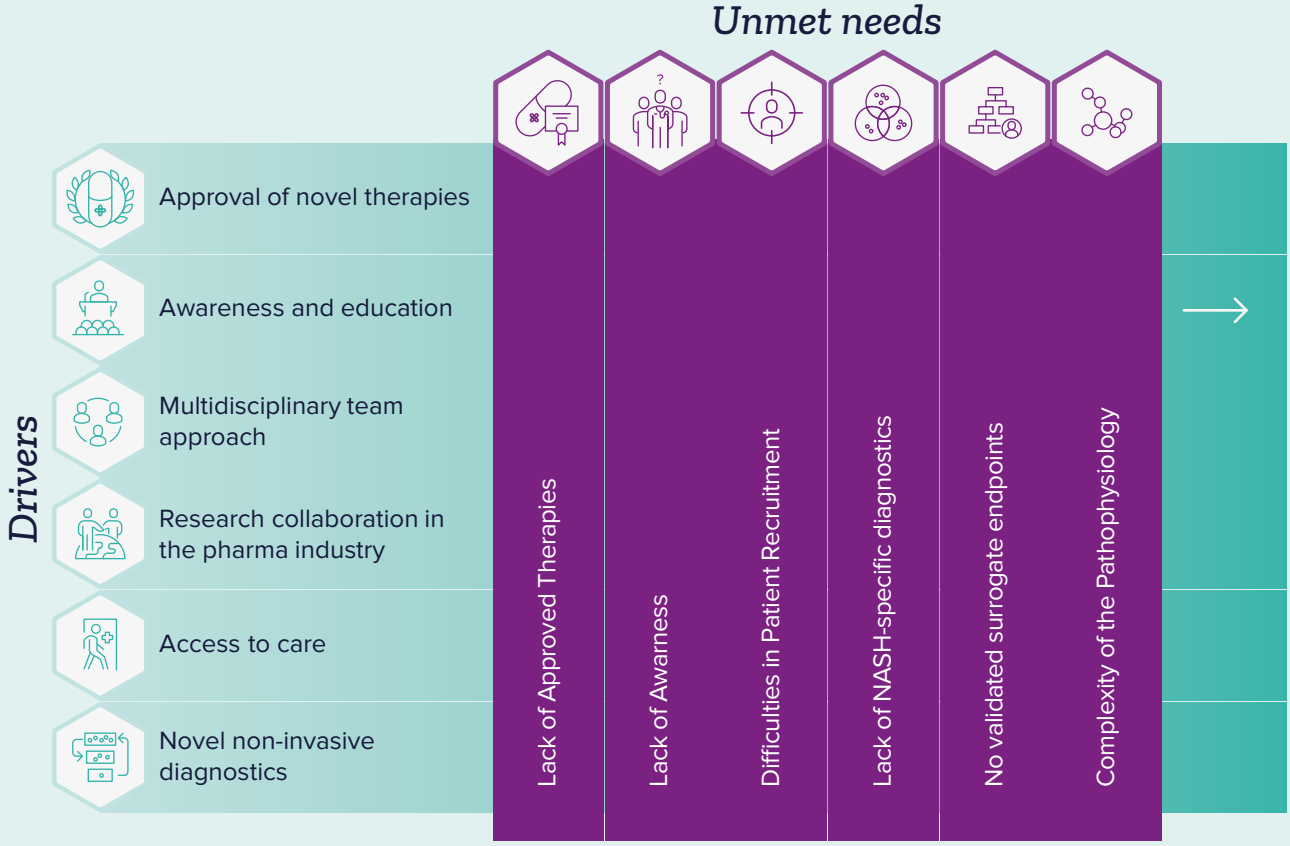
With multiple drugs in development, the pharma industry needs to understand which mode of action is going to be the game changer and become the backbone for NASH treatment.

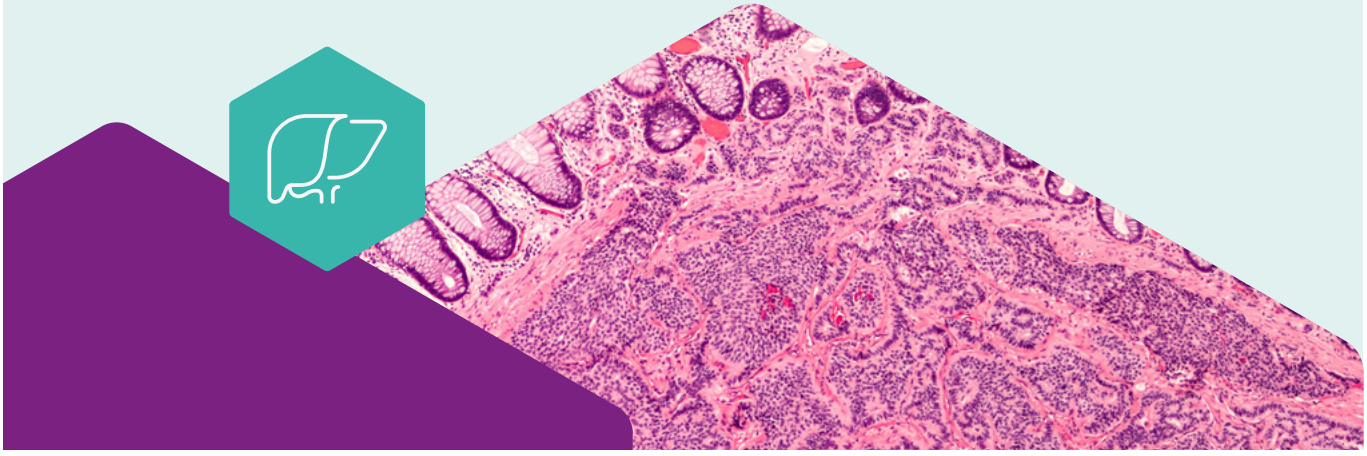
UNMET NEED 6: No validated surrogate endpoints
Surrogate endpoints specific to NASH may facilitate the therapy approval pathway. This could help accelerate approval which would be most beneficial to patients with an advanced stage such as patients with cirrhosis.

> "Currently there is insufficient evidence to support the use of histological improvements as a surrogate endpoint that is reasonably likely to predict clinical benefit to support accelerated approval, in general, the FDA expects to evaluate drugs for the treatment of compensated NASH cirrhosis under the traditional approval pathway."[16]

DRIVER : Research collaboration in the pharma Industry
Pharma companies need to focus efforts on establishing more validated surrogate endpoints and ensuring these are incorporated into guidelines and policies.

Drivers and unmet needs within NASH





What's in the NASH pipeline?

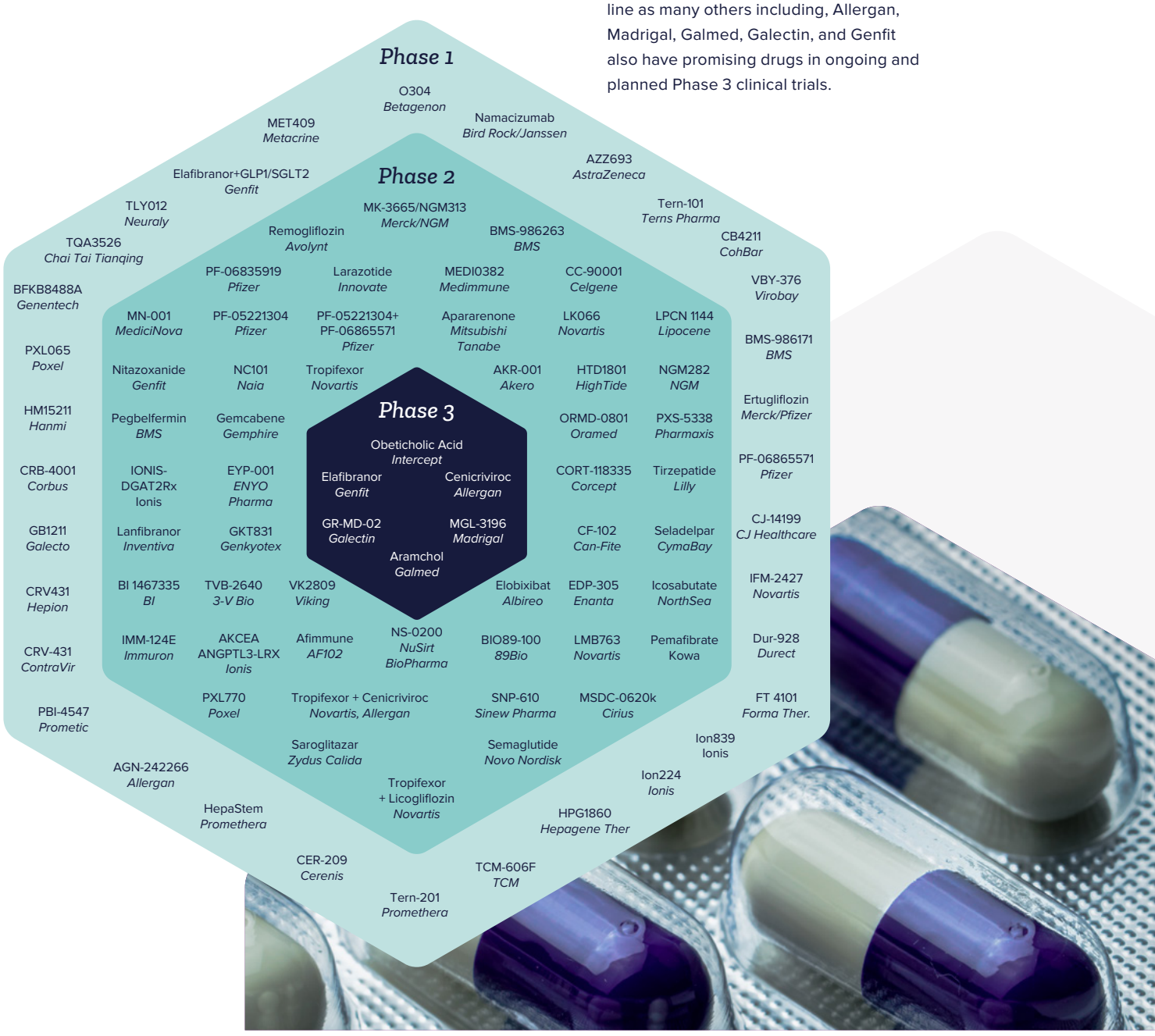
Currently over 80 potential unique novel therapies are under development

81 ongoing clinical trials and 69 new trials are planned. The trials mostly evaluate monotherapy regimes, however four combination therapies are also under investigation.[17,18]

Assets in development

Data correct as of 09.11.19

The current front-runner, based on positive Phase 3 data announced in February 2019, is obeticholic acid, developed by Intercept Pharmaceuticals. Obeticholic acid is already approved by the FDA to treat an orphan indication, primary biliary cholangitis (PBC), another form of liver disease, and it is now competing to become the first treatment approved by the FDA specific to NASH patients with liver fibrosis (F2 or F3). However, it will be a tight race to the finish line as many others including, Allergan, Madrigal, Galmed, Galectin, and Genfit also have promising drugs in ongoing and planned Phase 3 clinical trials.



Anti-diabetic drugs

In addition to testing novel MOAs developed specifically for NASH, the pharma industry is also investigating anti-diabetic drugs as a potential avenue of treatment.

Type 2 diabetes and insulin resistance are risk factors that can predispose a patient to NAFLD, and subsequentially to NASH. Thus the use of anti-diabetic drugs, alone or in combination with additional treatments, may have a therapeutic benefit.[19]

Due to the high rate of co-morbidity of diabetes and obestity in NASH patients a treatment with the potential to target two indications is very appealing to both physicians and payers offering dual health and cost benefits.

Drugs with an anti-diabetic mechanism of action which are currently under clinical investigation in NASH include Glucagon-like peptide 1 receptor (GLP-1R) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium/glucose cotransporter 2 (SGLT2) inhibitors.

Monotherapy examples: Semaglutide, Tirzepadine, Licogliflozin (LIK066), MEDI0382

Combination examples: Tropifexor + Licogliflozin (LIK066), Elafibranor + GLP-1 and SGLT2[20]

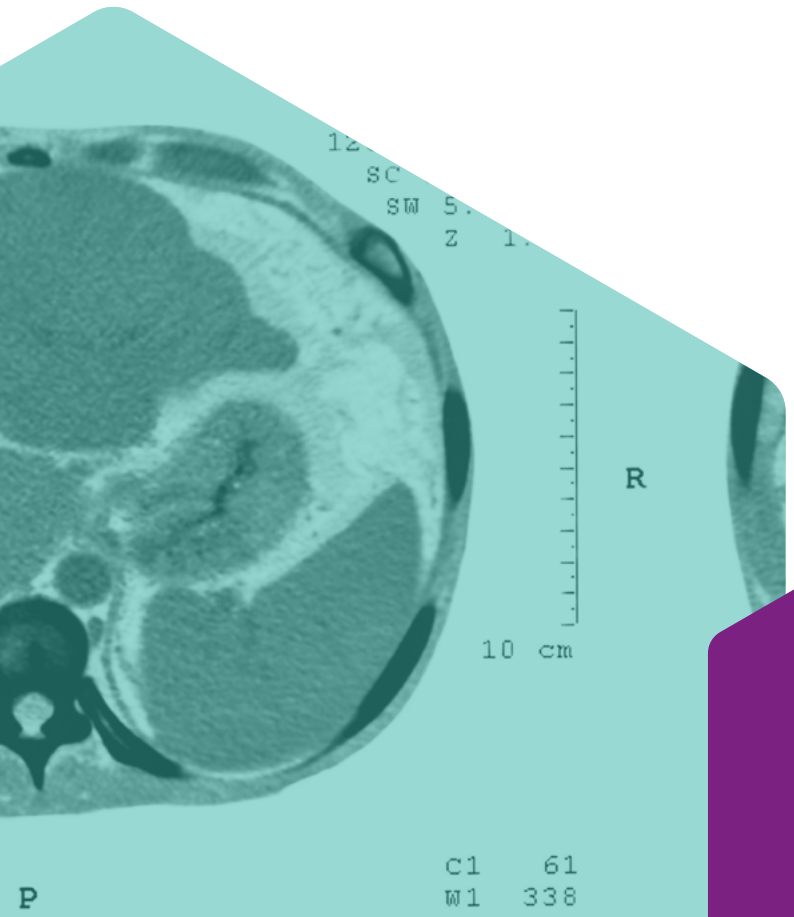
Combination therapy

NASH is a multifactorial and multifaceted disease consisting of a complex myriad of pathogenic pathways.

Novel drugs currently under development only target one aspect of the multiple factors that can lead to NASH and this may be insufficient for the best clinical outcome.

Like the nature of the disease, the treatment of NASH will require a multifaceted approach of drugs with a combination of anti-inflammatory, anti-fibrotic and metabolic modes of action to effectively target the disease.

Initiating more combination studies are an essential first step to validate a mode of action that can used as backbone of these future combination regimes.



Conclusion

NASH is becoming a public health burden with significant impact on all-cause morbidity and mortality. With multiple drugs in development, the pharma industry needs to understand which mode of action is going to be the game changer and become the backbone for NASH treatment.

Greater clinical collaborations will allow pharma to overcome challenges while driving innovation, with the ultimate goal of improving patient care.

Initially, the price of NASH medication is likely to be high - financial analysts report a conservative price tag estimate of at least $10K/year but potentially much more.[21]

The NASH community foresee only patients with the greatest liver scarring being likely to get coverage and reimbursement. However, as more new treatments come to market, genuine competition in the industry will likely drive prices down offering patients more cost-effective treatment options in the future.

So, as the race to cross the finish line first picks up pace, the significant opportunities and unmet need within the NASH market, will mean even those who follow later will be winners.

About the Author

Thomas Geninatti is a Consultant at Deallus based in the Los Angeles office. He has significant experience across a variety of therapeutic areas including oncology, immune-oncology, hematology, liver diseases, and autoimmune diseases. He offers a unique understanding and appreciation of product management throughout the lifecycle thus delivering clients with valuable impact analyses.

Thomas holds a BS and MS in Biomedical Engineering from the Politecnico di Torino, Turin, Italy and a Ph.D. in Biomaterials Engineering from a unique program between the Houston Methodist Research Institute, Houston, Texas and the Chinese Academy of Sciences, Beijing, China where his interdisciplinary research concentrated on implantable drug delivery devices for ad hoc release of therapeutics.

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About Deallus

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***Deallus** / di æ lus / (adj): intelligent, bright, astute, insightful, perceptive*

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