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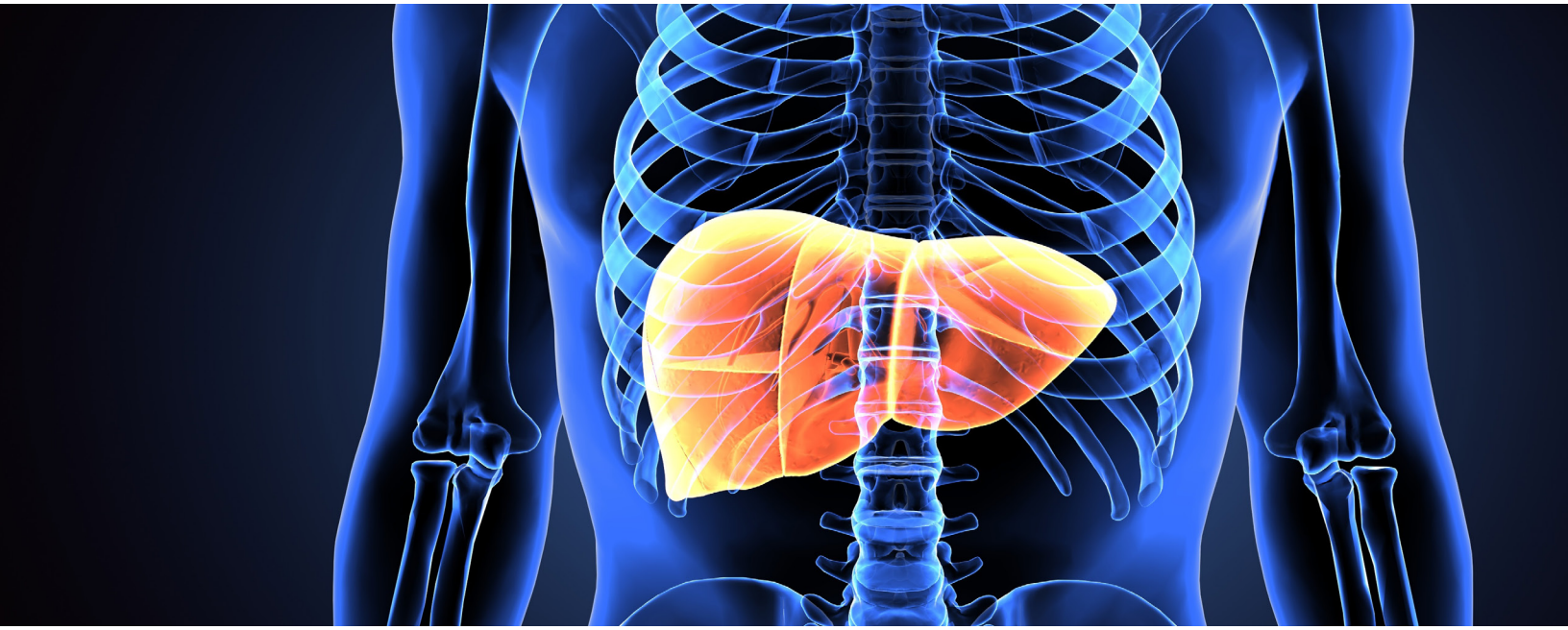
The NASH Dash:
Analysis Of The Non-Alcoholic Steatohepatitis (NASH) Drug Pipeline & Market



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Introduction

When Siddhartha Mukherjee crowned cancer as the "Emperor of All Maladies," he was aptly able to capture the sheer prowess of the disease in a few words. While no other illness beats cancer in the scale of destruction and suffering it can cause, there is one that has remained in the shadows, silently gnashing its teeth until Jurgen Ludwig brought it to the attention of the medical community by giving it a name in 1980: Non-alcoholic steatohepatitis (NASH).[1]

NASH is the advanced form of non-alcoholic fatty liver disease (NAFLD), a chronic disease marked by excessive fat accumulation in the liver. The growing global burden of NASH and NAFLD is indisputable, with the prevalence of NAFLD expected to grow to ~30% by 2030.[2]

For pharmaceutical companies, NASH has remained a relative graveyard of drug development over the past 40 years: no disease-specific approved therapies have made it to market. The NASH pipeline is littered with failures in late-stage trials—including the FDA's recent rejection of the much-anticipated Farnesoid X receptor (FXR) agonist, obeticholic acid (OCA, Intercept Pharmaceuticals)— which is likely to impact other companies developing NASH therapeutics. While some companies with programs that have demonstrated a positive risk-benefit profile may be unfazed by this, others will likely require a strategic re-positioning to maximize value for their assets in the near-term.

ANALYSIS OF THE NASH MARKET

Back Bay Life Science Advisors analyzed the first wave of drugs (at Phase 3) poised to change the NASH management paradigm and shape the ambiguous pricing and reimbursement landscape. We also looked at the most promising second wave of drugs (at Phase 2), many of which have already demonstrated improved safety and/or efficacy in topline data released to date.

In addition, we examined the historical transaction landscape for NASH, identifying key trends for companies looking to build their pipeline and address the multifaceted nature of the disease. Last, we analyzed the potential market access dynamics that will complicate pricing for a therapy in this space given the lack of marketed analogs and uncertainty over the clinical relevance of surrogate endpoints.

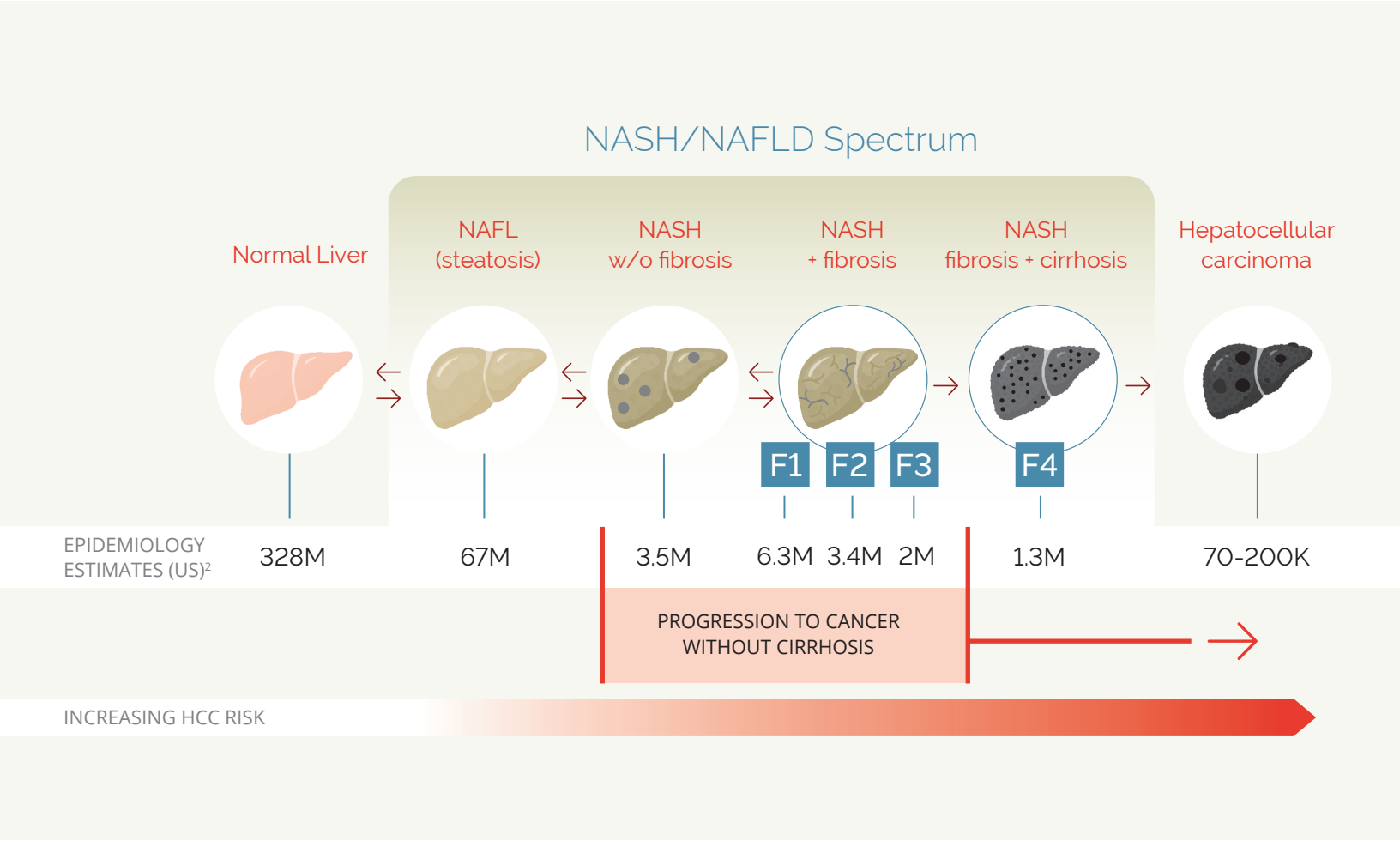
NAFLD/NASH: The Silent Epidemic

FROM HEALTHY LIVER TO NAFLD AND NASH-RELATED PATHOLOGIES

Nonalcoholic fatty liver disease (NAFLD) is a continuum of liver pathologies ranging from simple hepatic steatosis (>5% fat liver content, also known as nonalcoholic fatty liver (NAFL) to NASH. In contrast to NAFL, NASH is associated with varying degrees of hepatocyte inflammation, ballooning, and fibrosis (F1-F3) **[Figure 1: The Progression of a Healthy Liver to NAFLD and NASH-Related Pathologies].**

Approximately 20 to 25% of patients with NASH F1-F3 fibrosis can progress to cirrhosis (F4) within a decade, although the rate may vary depending on underlying comorbidities.[3,4] Subsequent hepatocellular carcinoma (HCC) development is reported in ~12.8% of patients with cirrhosis and fibrosis (<3 years), although HCC may also manifest in the absence of liver fibrosis

Figure 1:
The progression of healthy liver to NAFLD and NASH related pathologies



and cirrhosis.[5] Consequently, the extent of fibrosis is universally considered a strong predictive factor for correlating the progression of NAFLD with life-threating complications.

Several factors contribute to the progression to HCC; these include modifiers such as genetic (PNPLA^3, TM6SF2)[6,7] and environment (high caloric diet, sedentary lifestyle)[8–11] and comorbidities such as obesity (BMI > 30kg/m^2), insulin resistance and/or type 2 diabetes).[12–15] The underlying metabolic derangements are multi-factorial and include insulin resistance,[16–21] immune and inflammation dysregulation,[22–26] impaired free oxygen radical scavenging,[27,28] deficiencies in mitochondrial structure and function,[17,29] enhanced hepatic iron,[30,31] and hepatotoxic byproducts of gut bacteria.[32,33]

In the U.S., the reported prevalence of NAFLD is ~10-46%, with most biopsy-based studies reporting a NASH prevalence of ~3 - 5%, resulting in an adult prevalent NASH population of ~3.9 million-19.7 million.[34–36] The expected prevalence of NAFLD and NASH is expected to increase in the US and internationally for at least another decade,[2,37] with one panel of international experts dubbing NAFLD as the "silent epidemic."[38] Their concerns are substantiated by recent data, highlighting the burden of NAFLD in young adults (n=4201, 18-24 years) with obesity identified as the driving risk factor.

While the majority of NASH patients are diagnosed in their 40s to 50s, Abeysekera et al. used transient elastography to show that 20% of young adults had steatosis and ~2.7% had fibrosis (F2–F4) by 24 years of age.[39] Given that rates of obesity are gradually increasing over time,[40] morbidity and mortality due to progressive NAFLD will likely manifest at a younger age, leading to significant clinical and economic burden over the next decades.

DIAGNOSIS AND CURRENT TREATMENTS

As most patients with NAFLD remain asymptomatic, laboratory tests showing high liver aminotransferases or hepatic steatosis incidental to abdominal imaging is the more common path to diagnosis. Liver biopsy is the gold standard method for diagnosis of NASH, with biopsy confirmed endpoints required for FDA and European Medicines Agency (EMA) approval of NASH candidates. Despite being the gold standard, liver biopsy as a clinical inclusion criteria and outcome measure for NASH studies is far from being perfect. Recent data indicates suboptimal reliability between hepatopathologist's scoring of paired liver biopsy samples which may ultimately impact treatment effect in pivotal studies.[41,42]

The primary treatment for NASH now is lifestyle modification through diet and exercise, with the ultimate goal of reducing weight.[43,44] However, the degree of weight loss required for histologic improvement of NASH may be difficult to achieve and even harder to sustain for patients. In some cases, bariatric surgery remains the only effective weight-loss therapy[45-47] and has also demonstrated gains in cardiovascular outcomes,[48] the leading cause of premature mortality in patients with NAFLD.[49,50]

For patients with non-cirrhotic biopsy-proven NASH but without diabetes, vitamin E (800 international units per day) may be used, although evidence is

limited. In patients with NASH and diabetes, metformin and/or pioglitazone/liraglutide may be prescribed. For patients with advanced NASH (F4), liver transplant remains the only option. Given the lack of FDA approved NASH pharmacological interventions, and NASH becoming the leading indication in patients with HCC on liver transplant waitlists [51], there is a high clinical need for effective drugs.

Nash Drug Pipeline and Market: the First Wave

At peak, the global NASH market is expected to hit an average of $13 billion annually by 2030.[52] As of June 2020, the NASH pipeline of first wave drugs holds 54 clinical candidates in development by 47 companies that are evaluating 29 different mechanisms of action. Over the last two decades, the NASH pipeline has seen many late-stage programs fail to show clinical efficacy, despite targeting a broad range of mechanism of actions **[Figure 2/Table: Late-Stage NAFLD/NASH Programs].**

Competition to be the first marketed NASH drug remains high, with several late-stage candidates vying for the opportunity. However, lack of harmony between the FDA and the EMA complicates the development pathway for NASH.[53] While the FDA only requires the achievement of one NASH endpoint (improvement of ≥1 stage in fibrosis with no worsening of NASH or, improvement in NASH resolution with no worsening of fibrosis)[54], the EMA's draft guidance requires efficacy in both these endpoints.[55] This will likely limit or delay approvals of first movers in the major European markets.

The first wave of NASH candidates includes:

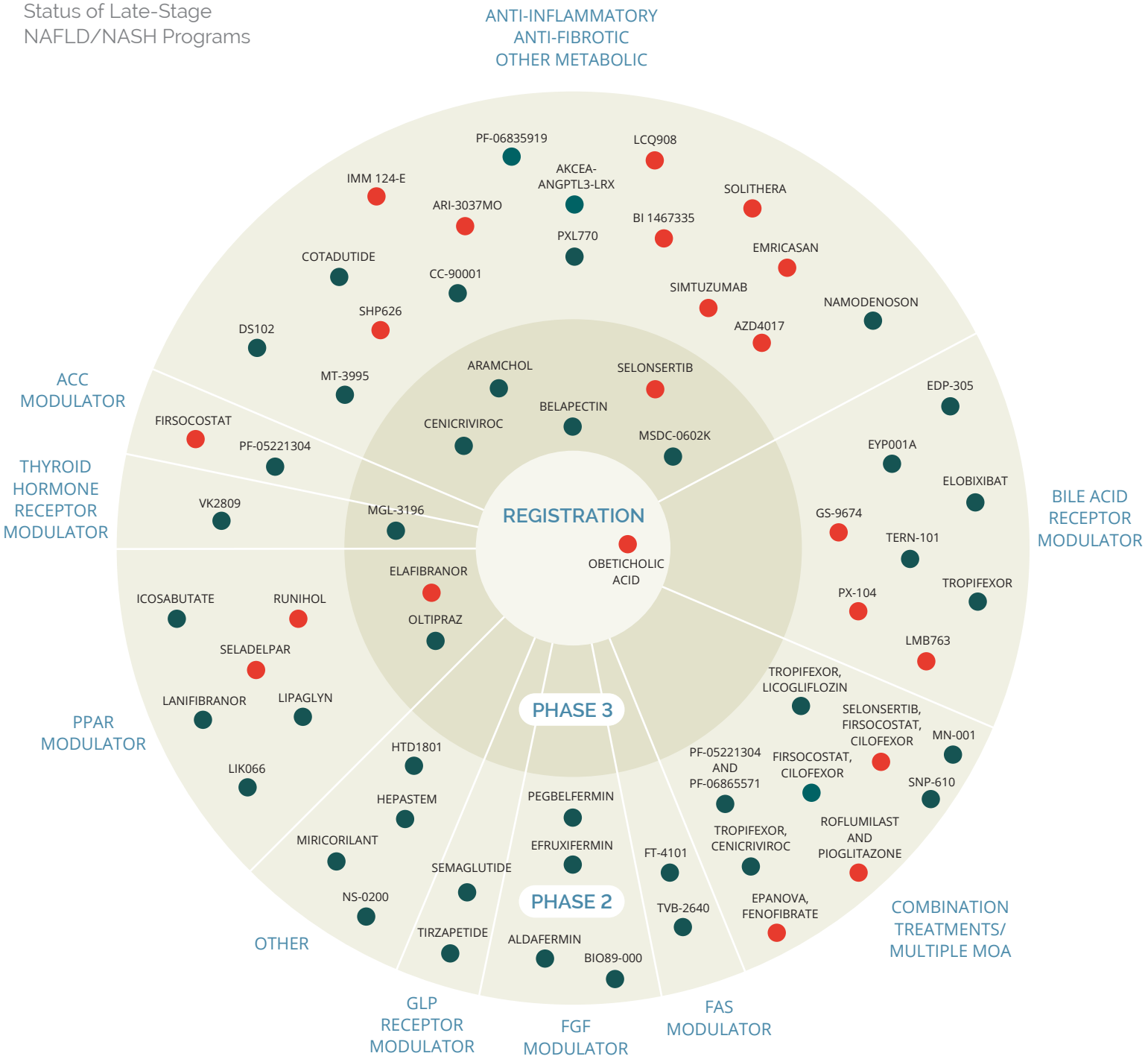
1. Obeticholic acid - Intercept Pharmaceuticals

Intercept's application for accelerated approval for obeticholic acid (OCA) was denied by the FDA on June 29, 2020, contrary to expectations.[56] OCA is approved for primary biliary cholangitis (PBC) under the name Ocaliva, providing Intercept with an opportunity to familiarize physicians with the drug prior to launch in NASH. In the pivotal study (REGENERATE) OCA demonstrated improvement in liver fibrosis (>1 stage) without worsening of NASH at 18 months in the treatment vs placebo group (23% vs 12%)[57] **[Figure 3: Comparison of Efficacy Data (Fibrosis Improvement NASH Resolution)]**

However, concerns remained about OCA's side effects: 51% of patients experienced pruritis (with 9% terminating treatment), and 20% of patients required statins due to elevations in low-density lipoprotein cholesterol (LDL-C). After reviewing the data submitted for accelerated approval, the FDA deemed the demonstrated efficacy to be "modest" and not strong enough to warrant safety risks. Intercept has a year to respond to the agency's concerns and is scheduled to present additional data at liver conferences over the next months. However, the company recently cut the workforce by an estimated 25%.[58]

Figure 2:

Status of Late-Stage NAFLD/NASH Programs



Given the multifactorial pathophysiology of NASH, there is a diverse range of therapies in the pipeline, despite numerous failed programs in the past.

Active

Failed

Sources: Industry sponsored programs for NASH were downloaded from clinicaltrials.gov (July 2015-July 2020), company websites, press releases.

Placement of dots within a phase does not correlate to the relative status of one program to another.

Figure 2 / Table 1:
Late-Stage NAFLD/NASH Programs

PHASE	STATUS	MECHANISM OF ACTION	DRUG NAME	COMPANY NAME
Registration, now in Phase 3	Failed	Bile acid receptor agonist	Obeticholic acid	Intercept Pharmaceuticals
Phase 3	Active	SCD1 regulator	Aramchol	Galmed Pharmaceuticals
Phase 3	Active	Galectin-3 inhibitor	Belapectin	Galectin Therapeutics
Phase 3	Active	CCR2 antagonist; CCR5 antagonist	Cenicriviroc	Takeda, Abbvie
Phase 3	Active	mTOT regulator	MSDC-0602K	Cirius Therapeutics, Inc.
Phase 3	Failed	ASK1 inhibitor	Selonsertib	Gilead Sciences
Phase 3	Failed	PPAR-alpha agonist; PPAR-delta agonist	Elafibranor	Genfit
Phase 3	Active	Thyroid hormone receptor beta agonist	MGL-3196	Madrigal Pharmaceuticals, Inc.
Phase 3	Active	TGF beta inhibitor	Oltipraz	PharmaKing
Phase 2	Failed	ACC Inhibitor	Firsocostat	Gilead Sciences
Phase 2	Active	ACC Inhibitor	PF-05221304	Pfizer
Phase 2	Active	ANGPTL3 antisense	AKCEA-ANGPTL3-LRx	Akcea Therapeutics
Phase 2	Failed	Niacin receptor agonist	ARI-3037MO	Arisaph Pharmaceuticals
Phase 2	Failed	HSD1 inhibitor	AZD4017	AstraZeneca
Phase 2	Failed	VAP-1 inhibitor	BI 1467335	Boehringer Ingelheim
Phase 2	Active	c-JNK1 Inhibitor	CC-90001	Bristol-Myers Squibb
Phase 2	Active	GCGR & GLP-1 receptor agonist	Cotadutide	AstraZeneca
Phase 2	Active	5-lipoxygenase inhibitors	DS102	Afimmune
Phase 2	Failed	Caspase inhibitor	Emricasan	Conatus Pharmaceuticals Inc.
Phase 2	Failed	LPS antibody	IMM 124-E	Immuron Ltd.
Phase 2	Failed	DGAT1 inhibitor	LCQ908	Novartis
Phase 2	Active	Mineralocorticoid receptor antagonist	MT-3995	Mitsubishi Tanabe Pharma Corporation
Phase 2	Active	Adenosine A3 receptor agonist	Namodenoson	Can-Fite BioPharma
Phase 2	Active	KHK inhibitor	PF-06835919	Pfizer
Phase 2	Active	5'AMPK stimulant	PXL770	Poxel SA
Phase 2	Failed	ASBT inhibitor	SHP626	Shire
Phase 2	Failed	LOX2 antibody	Simtuzumab	Gilead Sciences
Phase 2	Failed	Bacterial 23S ribosomal RNA inhibitor	Solithera	Melinta Therapeutics
Phase 2	Active	Bile acid receptor agonist	EDP-305	Enanta Pharmaceuticals
Phase 2	Active	IBAT inhibitor	Elobixibat	Albireo
Phase 2	Active	Bile acid receptor agonist	EYP001a	ENYO Pharma
Phase 2	Failed	Bile acid receptor agonist	GS-9674	Gilead
Phase 2	Failed	Bile acid receptor agonist	LMB763	Novartis
Phase 2	Failed	Bile acid receptor regulator	Px-104	PheneX Pharmaceuticals, Gilead

Figure 2 / Table 1:

Late-Stage NAFLD/NASH Programs Continued ...

PHASE	STATUS	MECHANISM OF ACTION	DRUG NAME	COMPANY NAME
Phase 2	Active	Bile acid receptor agonist	Tern-101	Terns Inc/Eli Lilly
Phase 2	Active	Bile acid receptor agonist	Tropifexor	Novartis
Phase 2	Failed	DGAT2 inhibitor; Lipoprotein lipase stimulant; PPAR-gamma agonist; PLA2 inhibitor; PPAR-alpha agonist	Epanova, Fenofibrate	AstraZeneca
Phase 2	Active	LT receptor antagonist; 5-LO inhibitor; PDE3/4 inhibitor	MN-001	MediciNova
Phase 2	Active	ACC Inhibitor and DGAT2 Inhibitor	PF-05221304 And PF-06865571	Pfizer
Phase 2	Failed	PDE4 inhibitor; PPAR-gamma agonist	Roflumilast and Pioglitazone	AstraZeneca
Phase 2	Active	ASK1 inhibitor; ACC inhibitor; Bile acid receptor agonist	Selonsertib, Firsocostat, Cilofexor	Gilead Sciences, Novo Nordisk
Phase 2	Active	CYP 2E1 inhibitor; DGAT1 inhibitor	SNP-610	Sinew Pharma
Phase 2	Active	Bile acid receptor agonist; CCR2 antagonist; CCR5 antagonist	Tropifexor, Cenicriviroc	Novartis, Allergan (Abbvie)
Phase 2	Active	Bile acid receptor agonist; SGLT1/2 inhibitor	Tropifexor, Licogliflozin	Novartis
Phase 2	Active	FAS inhibitor	FT-4101	Forma Therapeutics
Phase 2	Active	FAS inhibitor	TVB-2640	Sagimet Biosciences
Phase 2	Active	FGF19 regulator	Aldafermin	NGM Biopharmaceuticals
Phase 2	Active	FGF21 stimulant	BIO89-000	89bio Ltd
Phase 2	Active	FGF21 stimulant	Efruxifermin	Akero Therapeutics
Phase 2	Active	FGF21 stimulant	Pegbelfermin	Bristol-Myers Squibb, Ambrx
Phase 2	Active	GLP-1 receptor agonist	Semaglutide	Novo Nordisk
Phase 2	Active	GIP & GLP-1 receptor agonist	Tirzapetide	Eli Lilly
Phase 2	Active	Mesenchymal stem cell therapy	HepaStem	Promethera Biosciences
Phase 2	Active	Unclassified	HTD1801	HighTide Therapeutics
Phase 2	Active	GCR II antagonist	Miricorilant	Corcept Therapeutics
Phase 2	Active	Unclassified	NS-0200	NuSirt Biopharma
Phase 2	Active	PPAR regulator	Icosabutate	NorthSea Therapeutics, BASF
Phase 2	Active	PPAR regulator	Lanifibranor	Inventiva Pharma
Phase 2	Active	SGLT1/2 inhibitor	LIK066	Novartis
Phase 2	Active	PPAR-alpha partial agonist; PPAR-gamma partial agonist	Lipaglyn	Zydus Discovery DMCC
Phase 2	Failed	Succinate receptor 1 agonist	Runihol	POLYSAN Scientific & Technological Pharmaceutical Company
Phase 2	Failed	PPAR-delta agonist	Seladelpar	CymaBay Therapeutics
Phase 2	Active	Thyroid hormone receptor beta agonist	VK2809	Viking Therapeutics

Although Intercept's first mover advantage with OCA as a monotherapy for NASH is now at risk, the drug may still be part of the first wave of therapies to hit the market. The company presented additional data from the REGENERATE study post-FDA rejection at the International Liver Congress 2020. Sustained improvement in non-invasive biomarkers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), serum markers of fibrosis (FIB-4, AST to platelet ratio index [APRI]), and liver stiffness (FibroScan vibration-controlled transient elastography [VCTE]) were associated with changes in histologic fibrosis.[59]

Moreover, combinatorial studies may be on the horizon, although likely delayed given the FDA setback. In 2019, Intercept entered into an undisclosed licensing deal with Aralez Pharmaceuticals for the pan-PPAR agonist, bezafibrate.[60] The company is currently planning to investigate the efficacy of OCA and bezafibrate in patients with PBC and the future expansion to NASH would not be out of the question given the complexity of the disease. Even with Elafibranor's (PPAR-alpha and PPAR-delta agonist, Genfit) recent failure in Phase 3[61] Intercept may consider pursuing development of bezafibrate in NASH post-PBC given the promising results from the pan-PPAR agonist Lanifibranor (Inventiva) released in June 2020.[62]

Last, data from the REVERSE trial evaluating OCA in compensated NASH patients (F4) has yet to be released with trial enrollment completed in January 2020. Although NASH patients with cirrhosis represent a smaller subset of the NASH addressable market (~1 million),[2] morbidity and mortality is highest, with approximately twice the annual inpatient ($61,000 vs. $34,000) and out-patient charges ($12,000 vs. $8,800) compared to patients without cirrhosis.[63]

2. MGL-3196, Resmetirom - Madrigal Pharmaceuticals

Currently in Phase 3 trials with target enrollment exceeded as of September 2020, Resmetirom has demonstrated the strongest clinical efficacy to date (29% vs 12% ≥1 stage fibrosis improvement, treatment versus placebo) in Phase 2 studies of NASH **[Figure 3]**.[64]

The (THR) β-selective agonist's strong ability to reduce hepatic fat and multiple atherogenic lipids (LDL cholesterol, apolipoprotein B, triglycerides, lipoprotein) suggests a possible cardiovascular benefit, which is highly desirable in the NASH population.[65] Data presented at the summit of The European Association for the Study of the Liver (EASL) 2020 showed that once daily oral 80 mg and 100 mg dose of Resmetirom led to ≥50% and ≥60% reductions in liver fat, respectively, and were associated with a statistically significant 64% NASH resolution.[66]

Resmetirom led to a statistically significant reduction in markers of net collagen deposition in the liver supporting the anti-fibrotic action of Resmetirom. Despite the strong correlation observed between patients experiencing high-fat reductions measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF), and histological biopsy data, the FDA would require biopsy data to make approval decisions. Familiarizing liver specialists with MRI-PDFF and pursuing incorporation of the procedure into US and European clinical guidelines will likely drive broad clinical adoption.

Figure 3:

Comparison of efficacy (fibrosis improvement, NASH resolution) data as of September 2020

	RESULTS BY PHASE (CURRENT STATUS)															
	PHASE 3 RESULTS (PHASE 3)		PHASE 2 RESULTS (PHASE 3)						PHASE 2 RESULTS (PHASE 2)							
DRUG	Placebo	Obeticholic acid, 25mg	Placebo	Resmetirom dose titrated	Placebo	Cenicriviroc 150mg	Placebo	Aramchol 600mg	Placebo	EFX 28mg, 50mg, 70mg	Placebo	Aldafermin 1 mg	Placebo	Semaglutide 0.4 mg	Placebo	Lanifibranor 1200mg
ROA, DOSING REGIMEN	Oral, QD		Oral, QD		Oral, QD		Oral, 300 mg BID		SQ, QW		SQ, QD		SQ, QD		Oral, QD	
# SUBJECTS	407	404	41	84	145	144	40	78	2	40	22	50	58	56	81	83
TIME FRAME	18 month		~9 month		~13 month		~13 month		~4 month		6 month		18 month		6 month	
FIBROSIS IMPROVEMENT (≥1 STAGE) WITH NO WORSENING OF NASH	10.6%	21%*	23%	29%*	10%	20%*	17.5%	29.5%	0%	48%	18%	38%	NR	NR	24%	42%*
NASH RESOLUTION WITH NO WORSENING OF LIVER FIBROSIS STAGE	7.9%	14.9%*	6%	27%*	16%	19%	7.5%	16.7%	50%	48%	9%	24%	17.2%	58.9%*	19%	45%*

*p<0.05, ROA: route of administration, SQ: subcutaneous injection, QD: once daily, BID: twice daily, QW: once weekly, NR: not reported

Sources: company press release, websites (provided within the text in the paper)

While results of Phase 2 (n=125) have yet to be repeated in the much larger Phase 3 study (n=2000), the company is well positioned in the NASH space given the strong risk-benefit profile. Compared to most other manufacturers in the space, Madrigal has not announced any trials for F4 patients, which may restrict use to F2–F3 patients. Pursuing a strategic partnership with a large pharma company for further clinical development within this population should be prioritized to de-risk value for the program.

3. Cenicriviroc - Allergan

After acquiring Tobira Therapeutics in 2016 for ~$1.7 billion, Allergan entered the NASH race by adding Cenicriviroc (CVC) to its developmental pipeline.[67] Even though CVC has a differentiated mechanism of action compared to OCA and Resmetirom, weaker efficacy data compared to both those candidates have reduced confidence in the drug's efficacy as a monotherapy **[Figure 3]**.[68] Not surprisingly, Allergan has teamed up with Novartis to test CVC in tandem with the latter's FXR agonist Tropifexor in a Phase 2b study that could combine CVC's anti-inflammatory effects with Tropifexor's anti-lipogenesis profile.[69] Furthermore, Allergan acquired multiple FXR agonists after its 2016 buyout of Akarna Therapeutics for $50 million upfront,[70] and the potential to run late-stage clinical trials in the F4 population provides a potential favorable developmental path forward for CVC.

4. Aramchol – Galmed Pharmaceuticals

Aramchol is a novel, first in class SCD1 modulator, aiming to reduce liver fat and collagen production. While the Phase 3 ARMOR study is currently recruiting patients, the Phase 2b ARREST study data demonstrated significant reductions in liver enzymes (aspartate transaminase and aspartate aminotransferase), and hemoglobin A1c compared to placebo.[68] Although the biochemical improvement and glycemic control is a desirable trait, the drug failed to demonstrate statistically significant improvement in either of the FDA required endpoints **[Figure 3].**[71]

The primary endpoint of reduction in mean liver fat in the Phase 2b study, was higher in the lower dose group (400mg vs placebo) compared to the higher dose (600mg vs placebo), with the higher dose not reaching statistical significance. Like Resmetirom's Phase 2 study (n = 247), the sample sizes are relatively small and conclusive evidence will be dependent on results from the larger Phase 3 studies (n = 2000).

To further strengthen the program, Galmed announced a licensing and share purchase agreement with One Way Liver Genomics for the development of a non-invasive, blood-based companion diagnostic tool for Aramchol.[72]

5. Belapectin - Galectin Therapeutics

Galectin's lead NASH agent is uniquely positioned in pursuing a label for the management of cirrhotic NASH patients without esophageal varices. While the Phase 2b study failed to show a reduction in portal hypertension (hepatic venous

pressure gradient [HVPG] ≥ 6 mm Hg) or improvement in fibrosis, a subgroup analysis of patients without esophageal varices did show statistically significant decrease in HVPG and development of varices.*

Galectin decided to pursue further development in this subgroup and after receiving the FDA's nod on an adaptive trial design, started enrollment in June 2020. The adaptively designed Phase 2b/3 trial aims to confirm the efficacy seen in the subgroup analysis with interim results expected in Q22023. Given that NASH patients with cirrhosis (F4) represent a subset (~1 million) of the larger NASH F1-F3 population.[2]

Nash Drug Pipeline: the Second-Wave Candidates

1. FGF21 Stimulants

a. BIO89-100 - 89bio

b. Efruxifermin (EFX) - Akero Therapeutics

c. Pegbelfermin - Bristol Myers Squibb/Ambrx Inc

Fibroblast growth factor 21 (FGF21) is a starvation induced pleiotropic hormone with numerous beneficial metabolic effects, including enhancement of insulin sensitivity and reduction of triglycerides and cholesterol in mouse models of diabetes and obesity.[73,74] Similar outcomes have also been observed in obese nonhuman primates and humans with Type 2 diabetes.[75,76] While the exact mechanism of action in NAFLD has not been fully elucidated, emerging mouse data suggests that FGF21 may directly act on hepatocyte cells to modulate liver metabolism, which could be beneficial to patients with NASH.[77]

With the release of topline data from 89bio and Akero in the second half of 2020, the competition within the FGF21 stimulant pipeline has intensified. While both programs provide a compelling package, additional data will be needed to robustly compare across trials. So far:

- At comparable doses, 89bio's agent demonstrated a 70% reduction in liver fat in treatment versus placebo arms[78] compared to 63% for Akero's Efruxfermin (EFX).[79]
- Unlike 89bio, Akero has released fibrosis data from a small number of patients, with around half the subjects in the treatment group experiencing at least one stage improvement in fibrosis, albeit not statistically significant **[Figure 3]**.
- 89bio also tested a once fortnightly dosing regimen which led to a 60% reduction in liver fat. While 89bio's fortnightly dosing schedule may constitute a more attractive option, EFX did demonstrate higher efficacy at 70mg.

* Chalasani, N. et al. Effects of Belapectin, an Inhibitor of Galectin-3, in Patients With Nonalcoholic Steatohepatitis With Cirrhosis and Portal Hypertension. *Gastroenterology* (2020) doi:10.1053/j.gastro.2019.11.296.

- The frequency of GI events in treatment groups was less for BIO89-100 than EFX (pooled doses): diarrhea (BIO89-100 9.5% vs. EFX 36%), nausea (BIO89-100 4.8% vs. EFX 33%), vomiting (BIO89-100 0.0% vs. EFX 16%) and increased appetite (BIO89-100 15.9% vs. EFX 22%). Considering the FDA's decision in June 2020 to not approve obeticholic acid (OCA), a superior safety profile (such as decreased rate of nausea, diarrhea, vomiting) may provide 89bio a leading edge if fibrosis improvement is demonstrated and safety data is replicated in later stage trials.

In contrast, proof-of-concept studies for BMS/Ambrx pegylated FGF21 stimulant have shown statistically significant improvements in liver fat reductions in treatment versus controls groups (-6.8%) after 16 weeks but the magnitude is considerably small compared to Akero and 89bio's agent.[80] Eyes are on the two Phase 2 trials (Falcon 1 and Falcon 2) evaluating FDA approved NASH specific endpoints to provide persuasive efficacy data for this program.

2. FGF19 Analog

a. Aldafermin - NGM Biopharmaceuticals

Another agonist of the endocrine FGF family under investigation as a NASH therapeutic is FGF19. Similar to FGF21, the pleiotropic effects of FGF19, such as inhibition of insulin-induced hepatic lipogenesis and inhibition of bile acid synthesis from cholesterol via cytochrome P450 7A1, provide a rationale for clinical investigation in NASH patients.[81,82]

NGM Biopharmaceuticals' engineered FGF19 demonstrated positive efficacy data in Phase 2b studies of NASH patients with F2-F3 fibrosis, although statistical significance was not achieved for either endpoints **[Figure 3]**.[83]

- Approximately 38% of patients in the treatment arm showed fibrosis improvement of ≥1 stage with no worsening of NASH, compared to 18% in the placebo arm.
- Additionally, 24% of patients in the treatment arm achieved resolution of NASH with no worsening of liver fibrosis as compared to 9% in placebo.
- Statistically significant improvement of liver fat content reduction using the non-invasive MRI-PDFF was demonstrated (39% in treatment vs. 8% in placebo).

NGM also initiated a Phase 2b study, designed to evaluate Aldafermin in NASH patients with F4 liver fibrosis and well-compensated cirrhosis. Overall, the outlook for NGM's pipeline lead is promising with a Phase 2b/3 study underway to test efficacy in a larger cohort before moving on to ~2,000 patient pivotal trials.

NGM was backed by Merck after signing a $450 million research and development deal in 2015.[84] While Aldafermin is wholly owned by NGM, Merck collaborated with NGM to develop a differentiated pre-clinical asset (NGM313)

for obese, insulin resistant NAFLD patients. After positive Phase 1b data read-out, Merck paid $20 million to NGM and acquired the global rights to NGM313/MK-3655, a fibroblast growth factor receptor 1c-beta-klotho (FGFR1c/KLB) agonistic antibody with once a month dosing.[85] While phase 2b/3 studies have yet to be initiated, Merck plans to develop the drug for both NASH and patients with type 2 diabetes. Although Merck is behind other big players in the NASH space, the differentiated mechanism of action and once monthly dosing regimen may bolster value for the program as it nears pivotal trials.

3. FXR Agonists

a. Tropifexor - Novartis

b. EDP-305 - Enata Pharmaceuticals

c. PXL007/EYP001- Poxel/Enyo Pharma

Farnesoid X receptor (FXR) has demonstrated a crucial role in modulating inflammation in NASH, since the seminal description of FXR knock-out (KO) mice exhibiting increased bile acid levels, steatosis, fibrosis and inflammation.[86] Recent data points to FXR-mediated inhibition of key factors in the inflammatory pathway (such as NF-κB[87], Mcp-1[88]) and induction of lipocalins[89] to ultimately inhibit the pro-inflammatory cascade leading to NASH.

Although this data is promising, the pharmacological effects of FXR agonists (OCA, Intercept Pharmaceuticals) in NASH patients studied to date are accompanied with dermatological side effects,[57] with some researchers attributing this to the steroidal nature of the candidate.[90] Despite this, there are several additional FXR agonist candidates in Phase 2.

With a similar mechanism of action as OCA, Tropifexor and EDP-305 are vying to stand out against the lead NASH agent. While Tropifexor has already demonstrated a superior tolerability profile in NASH patients, recent data from Enata in patients with primary biliary cholangitis (PBC) raise concerns for the program.[91] Approximately 3% of patients dropped out in the lower dose arm and ~18% in the higher dose arm, leading Enata to axe the program and refocus on NASH.

As the industry awaits NASH-specific results, Enata may still face an uphill battle considering the FDA's rejection of OCA. Even if efficacy is comparable to Tropifexor, the latter's cleaner safety and tolerability profile could allow it to emerge as the preferred FXR agonist. In collaboration with Pfizer, Novartis is in Phase 1 trials evaluating combining Tropifexor with one or more of Pfizer's ACC inhibitor (PF-05221304), DGAT2 inhibitor (PF-06865571), and a KHK inhibitor (PF-06835919).[92] The Swiss giant is focusing its efforts on the FXR-agonist program, and recently made headlines by offloading its FGF21 simulator (LLF580) to Boston Pharmaceuticals in an undisclosed deal.[93]

Despite Tropifexor's potential as a safe anti-inflammatory and anti-steatotic NASH drug candidate it is important to note that published data have not demonstrated statistical significance, making cross-trial comparisons

inconclusive. Furthermore, Poxel and Enyo's PXL007/EYP001 recently entered Phase 2 studies after demonstrating significant improvements in NASH parameters (e.g., fibrosis, steatosis, ballooning, inflammation, and NAS score) in a murine model (Phase 1 safety study was conducted in hepatitis B).[94] While neither Poxel/Enyo or Enata can match Novartis's resources, additional efficacy/safety data will be key for all programs to establish their mark as a frontrunner with this mechanism of action, given the volatility of the NASH pipeline.

4. Glucagon-like Peptide-1 (GLP-1) Agonist

a. Semaglutide - Novo Nordisk

Glucagon-like peptide-1 (GLP-1) agonists are currently used for diabetic patients and work by improving insulin sensitivity and promoting weight loss.[95] They have also shown direct effect on the lipid metabolism of hepatocytes and reducing hepatic steatosis.[96,97]

Experts in diabetes care, Novo Nordisk is yet another big pharma company hoping for a NASH win. After announcing promising Phase 2 results in H1 2020, Novo's CSO stated "Semaglutide looks to become a standalone and maybe an anchor drug in the future for NASH."[98]

The study met the NASH resolution endpoint but failed to hit the key secondary endpoint of at least one stage of liver fibrosis improvement with no worsening of NASH. In addition, rates of adverse events, such as GI complications, were similar to prior studies of semaglutide.[95] With an already strong metabolic disease franchise, Novo is well-positioned to make a name in NASH if efficacy data from Phase 3 studies pans out favorably.

5. Peroxisome Proliferator-Activated Receptor (PPAR) Regulators

a. Lanifibranor - Inventiva

Peroxisome proliferator-activated receptor (PPAR) regulators are nuclear receptors consisting of three isotypes (PPAR-α, PPAR-β, PPAR-δ) primarily involved in lipid metabolism and inflammation. Synthetic PPAR-δ agonists (thiazolidinediones)[99] and PPAR-α agonists (fenofibrates)[100] are indicated as a treatment for Type 2 diabetes.

Dysregulation of PPAR isoforms has been observed in limited NASH specific studies. One study using 125 human liver samples demonstrated that PPAR-α gene expression negatively correlates with NASH severity, and insulin resistance and positively with adiponectin.[101] Another study using liver biopsies also showed negative correlation between severity of hepatic and reduction in PPAR-β/δ mRNA.[102]

In clinic, the PPAR-isoform selective agonist mechanism of action for NASH has experienced more disappointments than success in the last two years, with only Inventiva's Lanifibranor still in development. The failure of Elafibranor (Genfit, Phase 3)[58] and Seladelpar (CymaBay, Phase 2)[103] have raised skepticism for this class of agents in NASH as a monotherapy. Lanifibranor is a pan-PPAR

agonist, while Elafibranor targets PPAR alpha and delta, and Seladelpar is only delta subtype selective. Recently published positive data from Inventiva demonstrated statistically significant efficacy in both FDA preferred NASH endpoints **[Figure 3]**.[62]

Regardless, mean weight gain of 2.7kg was observed at the highest dose of 1200mg, and 2.4kg at 800mg, along with 14 patients experiencing oedema (12 of those received Lanifibranor). While there were no dropouts, Lanifibranor's tolerability profile will be under scrutiny as data from Phase 3 matures.

6. THR- β Agonist

a. VK2809 - Viking Therapeutics

Currently in Phase 2b trials, the selective thyroid hormone receptor beta agonist, VK2809 under developing by Viking Therapeutics has fallen behind completing target enrollment by the end of 2020 due to the COVID-19 pandemic.[104]

Data presented in August 2020 showed meaningful reductions in median liver fat content in VK2809-treated patients versus placebo (45.4% versus 18.7%) at 16 weeks.[105] Given that Resmetirom leads the pack with a similar mechanism of action, and comparable dosing/safety data, VK2809 will likely need to win on efficacy to gain market share if Madrigal secures a NASH win.

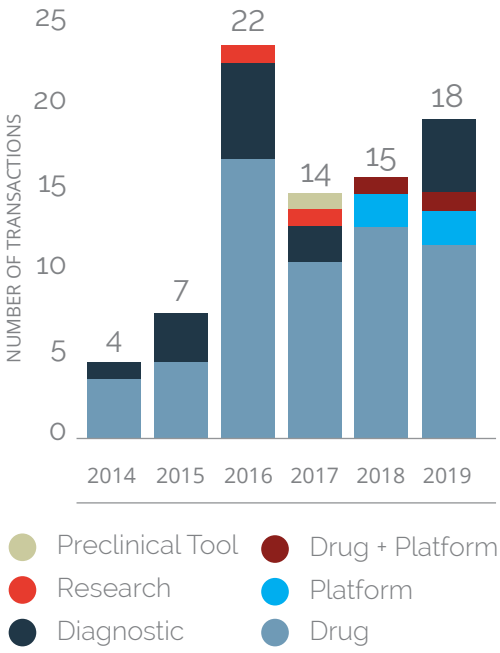
Nash Drugs: the Third Wave?

In addition to the first and second wave drugs included in our analysis, the following programs are under consideration to target the disease:

- *Long acting antidiabetics:* Korea based Hanmi Pharmaceuticals is developing a long-acting glucagon, GIP, and GLP-1 triple agonist (HM15211) with once weekly administration for NASH patients (Phase 2 ready). Hanmi also entered into a $860 million deal with Merck for a different dual agonist (Efinopegdutide; a GLP-1/glucagon receptor dual agonist).[106] Hanmi is studying the dual approach for type 2 diabetes and Merck is developing the candidate in NASH. This collaboration indicates Merck is building a diversified portfolio for NASH and likely waiting for the initial rollout of NASH drugs to address remaining regulatory and pricing questions.
- *Stem cell modulators:* After raising $44.9 million in series D financing, the Belgium based cell therapy company Promethera is advancing HepaStem, an intravenously administered mesenchymal stem cell therapy for F3-F4 NASH patients.[107] While mouse data have shown anti-fibrotic and anti-inflammatory signals, feasibility and efficacy in NASH remain to be demonstrated,[108] as data from the 24-patient Phase 2 study initiated in May 2019 has yet to read-out.

Figure 4:

NASH Transactions by Year and Technology, 2014-2019



Number of NASH centered transactions (including M&A deals, collaborations, licensing deals, research deals, and spinouts) from 2014 to 2019, further broken out by technology type.

Source: Cortellis Clarivate database. www.Cortellis.com

- *Mitochondria:* CohBar, a California-based, clinical-stage biotechnology company is developing mitochondrial based therapies for diseases linked to aging and metabolic dysfunction, including NASH and obesity. The lead candidate CB4211, is a novel-optimized analog of a naturally occurring mitochondrial peptide (MDP) in Phase 1 trials, with the first patient recently dosed in August 2020.[109] Given the uncertain and resource-intensive development pathway for NASH, CohBar will likely leverage the differentiated mechanism of action to identify a strategic partner to de-risk clinical development.

Nash Deals and Transactions

Big Pharma, including Gilead, Novartis, and Allergan, have turned their business development attention to NASH in recent years, with a flurry of activity in 2016 (with 22 deals in 2016, up from seven in 2015) **[Figure 4: NASH Transactions by Year and Technology, 2014-2019]**.[110] At publication, the most significant deal in this space is Allergan's acquisition of Tobira Therapeutics and its two assets for NASH, for a total deal value of $1.7 billion (19x Tobira's valuation, 2016).

Several other deals in the same year were driven by the need for companies to adapt as they encountered obstacles in development.

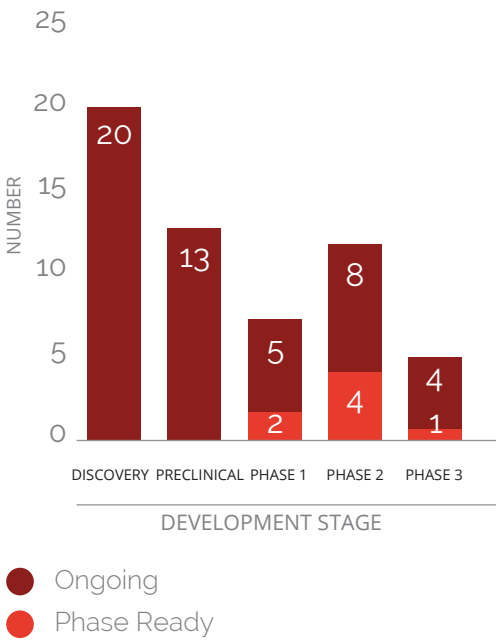
- There has been an increase in using diagnostics to identify the appropriate patient population that may be amenable for a therapy. This has become increasingly important as therapies fail in broader NASH populations. Additionally, clinical trials are currently using liver biopsy-based tests, which are invasive, expensive, and potentially risky for patients (e.g., bleeding, perforation, infection) and are a challenge for trial recruitment.[111]

- There is an increasing trend in collaborations between pharmaceutical companies to develop combination therapies, as a monotherapy is likely to post modest or equivocal data, and therefore will not be an effective therapy. This is due to NASH's complex pathophysiology (oxidant stress, inflammation activation, fibrogenesis, microbiome, increased intestinal permeability, immune cell mechanisms, etc.) that results in heterogeneity of phenotypes.

- Novartis' Global Development Unit Head (Immunology, Hepatology and Dermatology) Eric Hughes has stated that they "want to collaborate with multiple partners" to "target different pathways in NASH with a broad array of therapies as an essential strategy to bring the best treatments to patients."[92] For example, in Phase 2 trials, Allergan's Cenicriviroc did not demonstrate a resolution of NASH, but did demonstrate improvement in fibrosis. While it is continuing to be studied as a monotherapy in Phase 3, there is an ongoing Phase 2 trial assessing it in combination with Novartis' FXR agonist Tropifexor.

Figure 5:

NASH Transactions by Phase, 2014-2019



Number of NASH centered transactions (including M&A deals, collaborations, licensing deals, research deals, and spinouts) from 2014 to 2019 by stage of leading NASH asset at the time of deal, with "phase ready" indicating the asset has not begun the indicated phase.

Source: Cortellis Clarivate database. www.Cortellis.com

Moving forward, there are factors that will impact M&A activity volume in both directions. There could be a slowdown of deal activity in the near term, as many of the larger players have placed their bets on the most promising early stages assets (over half of the transactions in the past five years were for discovery/preclinical assets) and are waiting for their initial bets to "play out" **[Figure 5: NASH Transactions by Phase 2014-2019]**. However, approval and success of OCA could reinvigorate deal activity as commercial entities look for a fast follower advantage, and clear Phase 3 data will further enable M&A deals.

Market Access

The challenges of successfully developing and launching a NASH drug does not end in the clinic; questions remain on the optimal commercial strategy for these novel assets, especially around pricing and market access.

- *Large patient population:* Given a large patient population, including the potential of a substantial undiagnosed patient population, payers will likely ensure novel branded medications are being used in appropriate patient populations via prior authorizations that require appropriate diagnostic and staging criteria have been considered.
- *Lack of analogs:* There are currently no approved products for NASH, and, therefore, no pricing benchmarks for pipeline assets exist.
- *Likelihood of combination therapies:* Due to the complexity of NASH, an effective treatment regimen is likely to be a combination approach, which will make it difficult for any single therapy to be priced at a significant premium.
- *Uncertainty of real-world clinical benefits:* It is unclear how surrogate endpoints utilized in clinical trials will translate to real-world clinical impact, which may drive payers to implement stricter restrictions (as demonstrated by some of the pricing challenges PCSK9s encountered when launched in CV disease, further explained below).

Balancing the tradeoff between price and volume will determine the success of future NASH therapies. Developers are asking whether the best strategy is to lower price in order to gain access to a broader patient population, or to price higher and only have access to restricted sub-populations.

The commercial risk of a faulty pricing strategy has been demonstrated by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in cardiovascular disease. When Repatha (evolocumab; Amgen/Astellas) and Praluent (alirocumab; Sanofi/Regeneron) launched in 2015, they were priced at $14,000 annually per patient, which was a significant premium compared to the standard of care generic statins (<$50 annual cost). The pricing reflected the products' robust data in lowering low-density lipoprotein cholesterol (LDL-C). However, due to the absence of cardiovascular outcomes trial (CVOT)

and direct data of additional clinical benefit, payers restricted utilization to the most high-risk dyslipidemia patients. This resulted in significantly lower uptake than projected, and even with new CVOT data demonstrating reduction of risk in heart attacks, stroke, and death, restrictions remained. Considering this, Amgen reduced the price of Repatha by 60% to a $5,850 annual list price in 2018. While Sanofi and Regeneron were able to negotiate a contract with Express Scripts to be placed on its formulary's preferred tier, Medicare Part D patients still struggled to pay the high out-of-pocket co-pay costs. Eventually, they reduced Praluent's list price to match Repatha's list price.[112]

As Intercept prepared for what would be a 2020 launch of OCA, much attention was paid to its pricing and market access strategy. Beyond the clinical questions regarding the safety/efficacy profile, Intercept will have to navigate pricing strategically, given OCA is marketed for treatment of primary biliary cholangitis (PBC) under the trade name Ocaliva. As an orphan disease with an estimated prevalence in the range of 100,000 to 150,000,[113] Ocaliva commands a premium price with an annual wholesale acquisition cost (WAC) of $80,000 in the United States.

Given the disparity between the size of the two patient populations—NASH is estimated at ~260 times the size of the PBC population—it is unlikely payers would agree to that price point for NASH even with restricted access for biopsy-confirmed patients. Indeed, Wall Street analysts project a range of potential pricing bands for OCA from ~$10,000 to $30,000, much closer in line with therapies marketed for highly prevalent cardiovascular diseases.

While it is common to look to analog markets and products when determining price, value-based pricing considerations are increasingly common. These analyses consider the potential price of a drug in the context of clinical benefit and impact on life span and quality of life, relative to current alternatives. These analyses are benchmarked to the value of the drug relative to one incremental quality of life year (QALY) gained (e.g., a cost threshold in which the drug extends one year of life in good health). In light of the REGENERATE trial data, the Institute for Clinical and Economic Review (ICER) developed a perspective on an acceptable price point for an asset in NASH.[114] Based on a QALY threshold of 100K (e.g., an appropriate price if one year of life in good health is valued at $100,000), ICER arrived at a cost effectiveness threshold of $17,150. Interestingly, if only used in F3 patients this rises to $19,780, highlighting the the higher clinical need and greater price potential in more severe patients. Not surprisingly, if priced at the current price, in PBC a QALY would have to be valued over $1 million for OCA to be cost-effective.

Given the stark disparity in market dynamics between NASH and PBC, it is no surprise that Intercept has been considering a careful market access approach to commercialize the same molecule at different prices for two diseases. The company has communicated to the street that it is considering a dual brand strategy for OCA in PBC and NASH. Pharma has used this approach in the past to sell the same active pharmaceutical ingredient at two separate price points in two different indications. However, due to the recent focus on drug

pricing from the public, it is becoming increasingly difficult for companies to successfully pursue a dual brand strategy, with very limited examples in the last 10 years.

The most well-known example of this approach is Pfizer's sildenafil, marketed as Viagra, a treatment for erectile dysfunction requiring a ~50 mg tablet per dose, and Revatio, a sildenafil oral suspension for pulmonary arterial hypertension requiring 5 to 20 mg three times per day. However, with the same formulation launched for NASH and PBC, Intercept will need to ensure dosing, pill size, and packaging are sufficiently differentiated that the likely lower-priced NASH drug is not substituted for the higher-priced Ocaliva brand in PBC.

Given the size of the NASH market, payers have prospectively communicated they may establish significant utilization/approval criteria prior to reimbursing OCA.[115] To alleviate payer concerns, Intercept is going to great lengths to communicate it is focusing marketing efforts on liver and GI specialists which will allow them to target a circumscribed NASH population and prevent widespread utilization. In multiple quarterly updates, the company has communicated it will ensure the drug is not inappropriately prescribed and its commercial strategy will be to target the ~15k hepatologists and gastroenterologists that have a large NASH patient load in order to treat the 1.5 million (out of 19 million NASH patients) with fibrosis.116 In addition, Intercept also released market research that shows many physicians would be comfortable identifying patients with early fibrosis with non-invasive testing and imaging—the implication being that biopsy could be a requirement by payers to allow access.[116]

Summary

- The economic and health burden of the growing NASH population in the U.S. is a matter of immense concern, given that NASH is expected to become the leading indication for liver transplants in the U.S. in the next few years for patients with and without HCC
- Currently there are no disease-specific approved drugs for NASH, with multiple historical failures creating a substantial unmet need for the patient population
- Given the complex and poorly understood nature of NASH, there are a variety of mechanisms of actions under investigation by biopharma
- The first wave of NASH drugs are all expected to be monotherapy treatments with the FDA's current refusal to grant obeticholic acid accelerated approval intensifying the race to the finish line for several late-stage agents
- Based on current clinical trial guidelines, the FDA requires biopsy confirmed success in at least one of the following endpoints to grant accelerated approval: 1) improvement of ≥1 stage in fibrosis with no worsening of NASH; 2) improvement in NASH resolution with no worsening of fibrosis. In contrast to the FDA, the EMA draft guidance requires efficacy in both endpoints in a co-primary fashion, which may complicate timely approvals in the five major European markets (Germany, France, Spain, Italy, UK)
- On top of the regulatory challenges, the first wave of NASH therapies will face unchartered reimbursement territory; and any novel therapy may encounter strict prior authorization from payers tied to the enrollment criteria of pivotal trials
- With a flurry of deal activity in NASH during the 2016-2017 timeframe, recent clinical setbacks may have a cooling effect on the deal making. However, approval and success of OCA could reinvigorate the deal space as commercial entities look for a fast follower advantage
- Key remaining areas of unmet need and future development include successful development of non-invasive diagnostics to monitor NASH progress and evaluate response to treatment, combination regimens to manage NASH and the associated comorbidities, and more clinical trials focusing on the severe F4 patients

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