Introduction

Despite the increasing number of pipeline agents advancing to late-phase clinical trials, the future of the non-alcoholic steatohepatitis (NASH) market is uncertain. There has been much debate over a suitable and sustainable pricing strategy for a NASH therapy that satisfies every party involved, including patients, payers, and manufacturers. The lack of a disease-specific approved therapy in NASH creates a degree of ambiguity over what the market will be able to bear. However, the strict prior authorization criteria and prohibitive co-payments introduced by payers in response to the high initial prices of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor class of lipid-lowering treatments should be a warning sign to manufacturers of what can happen if drugs are priced inappropriately high for their respective markets.

Poor initial uptake of PCSK9 inhibitors highlights risk of pursuing premium pricing in a highly prevalent indication

Following the approvals of Repatha (evolocumab; Amgen/Astellas) and Praluent (alirocumab; Sanofi/Regeneron) in 2015, the two therapies were predicted to achieve blockbuster status due to their robust ability to lower low-density lipoprotein cholesterol (LDL-C). However, with initial list prices set at over $14,000 per patient per year, the PCSK9 inhibitors struggled to compete with the inexpensive generic statins, priced at less than $50 per year, which monopolized the market. In addition, payers refused to reimburse costs due to the lack of cardiovascular outcomes trial (CVOT) data available at the time of launch, which meant that additional clinical benefit (reduction in major adverse cardiovascular events [MACE]) compared to statins had to be inferred from further LDL-C declines. Consequently, payers implemented strict reimbursement criteria to restrict use to the most high-risk dyslipidemia patients, which resulted in significantly lower than expected market adoption. Although future CVOTs subsequently highlighted the class's ability to reduce the risk of heart attacks, stroke, and death in Praluent's case, payer-induced restrictions remained in place.

In the face of continued disappointing prescription volumes, even after CVOTs had provided hard evidence of benefit on MACE, Amgen conceded to lowering the annual list price of Repatha by 60%, from $14,100 to $5,850, in October 2018. Despite Sanofi and Regeneron striking an exclusive deal for Praluent with Express Scripts, involving a large rebate in return for the preferred PCSK9 inhibitor position in their formulary earlier in 2018, elderly patients on Medicare Part D plans still faced high co-pay costs. Therefore, in February 2019, Praluent followed in the footsteps of Repatha with a new list price of $5,850. Ultimately, this cut out-of-pocket costs for elderly patients using the Medicare Part D plan to $25–$150 per month. A payer interviewed by Datamonitor Healthcare noted that NASH drug manufacturers should learn from the market access challenges experienced with Praluent and Repatha due to the initial pursuit of high list prices, as setting a lower list price in exchange for higher prescription volumes may be a more profitable strategy.
Lack of marketed analogs and uncertainty over clinical relevance of surrogate endpoints complicates NASH pricing

With no marketed analogs available to act as benchmarks for the price of future NASH therapies, manufacturers and payers may struggle to agree on a drug cost that is both affordable and cost-effective. In addition, there is uncertainty regarding how well the surrogate endpoints currently used in clinical trials correlate with real-world clinical benefits, which could increase payer resistance to premium prices.

“**PCSK9s were highly restricted when they came out, the prior authorization criteria were well beyond the label, and I think that is a challenge, that if you can avoid that it will be much better for the manufacturers, and the manufacturers of PCSK9 learned the hard way and reduced their prices, but I think it would be smart for the NASH manufacturers to start off lower, and use those lessons.”**

**US payer**

Furthermore, there are limited epidemiology data on the size of the addressable NASH market due to a lack of reliable diagnostic tools, which increases the challenge of determining an affordable price. Liver biopsy is the current gold-standard for diagnosing NASH, however, its high cost and invasive nature means that patients can be reluctant to undergo the procedure, and physicians reserve its use for patients with other evidence of suspected NASH. Moreover, patient warehousing, coupled with the anticipated rise in diagnosis and treatment rates once therapies enter the market, is expected to significantly increase the population size as compared to current estimates. As the price must correlate with the size of the population to ensure affordability, this is a significant problem that manufacturers and payers will need to address. There is also no formal report on the economic burden of NASH on healthcare systems, which ultimately leaves it to payer discretion to determine the value of a NASH therapy.

“We are going to have to understand what those surrogate endpoints mean, and how that affects outcomes. So, what is that going to mean for a downstream cost? What are we achieving by improving those surrogate markers?”

**US payer**
**Label restrictions will prompt companies to pursue higher prices**

There are two possible pricing strategies that manufacturers could follow: a conservatively priced drug aimed at reaching the wider patient market, or an aggressively priced therapy with a restricted patient population, though it is becoming more apparent that companies will strive for the latter.

Although a low price would enable more lenient reimbursement criteria aimed at the wider NASH population, manufacturers will be restricted by regulatory bodies, which are expected to limit the approvals of the first generation of NASH agents to F2/F3 patients based on current clinical trial enrollment criteria. F2/F3 patients are the most popular focus of clinical trials for therapies currently in mid-late-phase development, reflecting the fact that these patients have sufficiently advanced disease to be able to detect a treatment benefit, but not so advanced that they are likely to be unresponsive to treatment. Despite patients with F4 or cirrhosis being the highest priority to treat, it is unlikely that a therapy will be approved for this difficult-to-treat population in the near future due to the plethora of failed clinical trials in this subgroup. Indeed, selonsertib (Gilead) and emricasan (Conatus/Novartis) have been investigated in F4 patients but have failed to meet their primary efficacy endpoints. While Ocaliva’s (obeticholic acid; Intercept Pharmaceuticals) Phase III REGENERATE trial has enrolled F4 patients, the drug’s modest efficacy in F2/F3 patients makes it unlikely that it will succeed in improving fibrosis in more advanced patients. As a result, NASH therapies are not expected to be indicated for F4 patients in the short term, and payers will likely limit the reimbursement criteria to patients with F2/F3 NASH until there is proof of efficacy in F4 patients. In addition, companies are reluctant to pursue clinical trials in F4 patients as cirrhosis has conventionally been viewed as irreversible, which will further delay the possibility of finding a therapy for these patients.

“*It is quite concerning that only a tiny fraction of clinical trials for NASH even look at F4 population, and I think that many are appropriately scared off by the fact that cirrhosis is viewed as irreversible, there are examples where the patient’s cirrhosis can reverse, but usually it takes five years or longer, at least in the hepatitis B and hepatitis C experience.*”

**US key opinion leader**

Although Ocaliva was studied in F1 patients in the Phase III REGENERATE trial, it was an exploratory analysis and it is unclear whether Intercept will apply for approval in this subgroup. Patients with F1 NASH are often asymptomatic, with multiple comorbidities, and therefore will likely be unwilling to pay for a premium-priced therapy to add to their regimen. Moreover, as these patients are at low risk of disease progression, physicians are expected to predominantly recommend lifestyle changes, such as diet and exercise.
Intercept will strive for a premium price for Ocaliva while it monopolizes the market

Ocaliva is expected to fulfill a major unmet need, being the first therapy approved for the treatment of NASH. This gives Intercept a unique opportunity to price Ocaliva at a premium, while it monopolizes the NASH market. Intercept will likely have to lower the price of Ocaliva once the market becomes more saturated in order to retain market share while competing with lower-priced therapies, but the short-term high price will nevertheless contribute to Ocaliva's dominating position in the market, with it expected to achieve global revenues of $6,527m in 2027 (Figure 1).

The current list price for Ocaliva is $79,000 per patient per year for the orphan indication, primary biliary cholangitis (PBC). However, as NASH has a significantly larger patient population, this will inevitably be cut once it is approved as a treatment for NASH. Datamonitor Healthcare expects Ocaliva to have an initial price between $15,000–$20,000 in the US and €5,000–€9,000 in the EU, where national health technology assessment bodies have a lower tolerance of high prices. Therapies that enter the market later will likely have a lower cost ranging between $10,000–$15,000 in the US, which will force Ocaliva to adopt a lower price. These assumptions are based on data collected from a pulse survey of 60 gastroenterologists in the US and five major EU countries (France, Germany, Italy, Spain, and the UK), and three key opinion leader interviews conducted in the US and France.

“It is an asymptomatic condition, and we know that patients that are taking inexpensive generic drugs for asymptomatic chronic conditions do not take their medications, so for somebody to be taking a drug that is going to be expensive for them in an ongoing fashion, and they are not really having any symptoms, I do not think that that is going to be successful.”

US payer

Manufacturer pricing strategies

“For a first drug, in the context of no competition, I think that the price range over $20,000 per year I think would be easily justified, I think in the context of 3–5 years I am quite uncertain about whether that will also hold true.”

US key opinion leader
Overlapping doses with PBC and NASH will complicate Ocaliva’s pricing

Phase III REGENERATE data demonstrated Ocaliva’s ability to improve fibrosis in 23% of patients treated with the 25mg dose, compared to 12% in the placebo group (Biomedtracker, 2019). Although these results appear modest, they are favorable compared to other therapies that target fibrosis, such as cenicriviroc (Allergan/Takeda). As Ocaliva was associated with a high incidence rate of pruritis, Intercept has hinted toward a dose-titration technique to improve tolerability, similar to the dosing approach in the PBC indication. However, this strategy would mean incorporating the 10mg dose into the NASH treatment, which overlaps with the dosing in PBC. This is problematic as pricing is dose-based rather than indication-based, and thus to ensure that a starting 10mg dose was affordable for NASH patients, Intercept would have to significantly lower the 10mg price, thus severely reducing PBC revenues. Payers have suggested that the manufacturer will have to create a titration pack, with a different National Drug Code, to protect the orphan pricing in the PBC indication.
Prevention of negative hepatic outcomes will help to justify the economic burden of novel NASH therapies on healthcare systems

Although Intercept has not revealed plans on pricing, it is likely that the company will strive for a premium list price by arguing that patients with advanced NASH fibrosis are at high risk for disease progression with higher near-term therapeutic costs, thus prevention of further disease progression could offer long-term cost savings (analogous to arguments used to support use of novel direct-acting antivirals in the hepatitis C setting). NASH therapies targeting more advanced NASH patients have the potential to prevent serious hepatic outcomes including liver decompensation, hepatocellular carcinoma, liver transplant, and death, though this is yet to be proven, with outcome trial results for Ocaliva expected in October 2022. Prevention of these outcomes would have significant cost-saving benefits to healthcare systems. The cost of the disease increases significantly as the patient progresses to more advanced stages of NASH. Indeed, a study using Markov models for NASH predicted the lifetime cost of all NASH patients in the US in 2017 to be $222.6bn, with the cost of the advanced patients, a significantly smaller NASH population, comprising 43% of costs.

The timeframe of disease progression for NASH patients is unclear, which casts doubts over cost-saving benefits from preventing hepatic outcomes

Reducing the risk of hepatic outcomes is still hypothetical, as no trials have yet obtained data on this endpoint, and payers will likely have to wait three to five years for this; therefore decisions on reimbursement must be based on surrogate endpoints. In addition, there is no reliable way of predicting which NASH patients are at risk of disease progression or estimating the timeframe until adverse outcomes occur. This is problematic for non-Medicare payers as there is the risk that they face the upfront costs of NASH treatment, but due to the ability of patients to switch plans over time, the patient might not be a member of the plan when hepatic outcomes become apparent, and no savings are therefore realized.

Medicare plans for patients that are aged ≥65 years have a longer forecast and are more inclined to have higher upfront costs, to capture downstream savings as members are still likely to be part of the same plan. However, with commercial plans in younger patients, the average member turnover is approximately 2.5 years, therefore if a patient condition was going to worsen over the next 5–10 years, the plan may not want to pay a premium upfront.

“We do not know that these patients that have NASH, that have an F3 fibrosis, are all going to end up as high-cost patients, maybe it will take 10 years for them to get to that stage.”

US payer

It is not a good story from the manufacturer, telling the story of cost-savings due to prevention of hepatic outcomes, to payers, because we do not know that every patient progresses, and they all progress at different rates, and the high resource utilization may not be occurring for years to come.”

US payer

Payers’ response to prohibitively high costs

Market growth would be severely limited if payers refuse to reimburse therapies at premium prices

There is a high risk that manufacturers will initially set prohibitively high prices. This will likely result in payer refusal to reimburse costs for all but the highest-risk patients, severely stunting the commercial potential of the NASH market, similar to what was observed with the PCSK9 class. Payers are expected to respond to premium prices with strict reimbursement criteria requiring prior authorization forms and possibly pay-per-performance plans.

“The first therapy will have the advantage of filling an unmet need because it will be the first one to market, but what will happen is, as we have subsequent drugs, and again, depending on which order they come in, if they are targeting the same population, then we can decide whether or not we need all of them.”

US payer
Strict reimbursement criteria will limit patient access to the therapies

Prices that exceed $670 per month in Medicare or commercial plans will likely get placed on the specialty tier, which increases the financial burden for patients by increasing co-payments, and therefore restricts accessibility. If all manufacturers targeting the same patient population strive for specialty-tier pricing, payers will likely play companies off against each other and preferentially reimburse one agent in exchange for steeper discounts, with the remaining drugs omitted from the formulary.

A payer interviewed by Datamonitor Healthcare expected that prior authorization criteria will be implemented at costs over $400–$500 per month, with drugs priced ≤$500 per month expected to have prior authorization criteria in line with the approved labels. However, pricing >$500 per month could result in more restrictive prior authorization criteria that go beyond the label. Payers will most likely want to restrict use to F2/F3 patients, as this subgroup has shown efficacy in clinical trials and is a high priority to treat compared to F1 patients. Moreover, the lack of efficacy of pipeline agents in F4 NASH patients creates a significant unmet need, which could encourage physicians to prescribe off-label drugs to these high-priority patients. To prevent this, payers will not include F4 patients in the reimbursement criteria until proof of efficacy is demonstrated.

“We do not want somebody with F4 because we do not know if maybe that is too far gone, and they are not going to have value from it, but yet providers may try because there is nothing else, so we might limit it in that respect.”

US payer

Payers will also likely require biopsy-proven NASH with documented medical proof rather than physician attestation, which will further limit patient accessibility.

“We will say the patient has to have a liver biopsy to prove their fibrosis score in order to be eligible, because we know that somebody who is asymptomatic and maybe does not really need to be on the drug at this point in time, the provider is not going to put them through a liver biopsy just to give them the drug.”

US payer
Although a pay-per-performance plan is optimal in theory, such contracts are particularly difficult to implement in practice due to the large number of patients and issues surrounding tracking liver biopsies for individuals, therefore it is unlikely that they will be used.

“So in an integrated delivery network where they have all the data easily retrievable, they have the access to medical records, that is a place where that might be very reasonable, but for larger plans where providers are part of many plans, to capture that data may be difficult, and then how often are we going to mandate liver biopsies, or are we going to allow surrogate markers for fibrosis to be accurate in terms of a contract that is based on outcome? That is the question. So, I think it makes sense in a way that the drug performs in the way the manufacturer promises, but I think it is hard to operationalize, so I am not sure how realistic that will be.”

US payer

**Combination treatments might be the best approach to treat NASH, but will the cost make these unaffordable for patients?**

Given the mediocre efficacy of NASH monotherapy approaches to date, and the complex pathophysiology of the disease, several companies are investigating combinations of NASH therapies in a bid to tackle underlying metabolic causes of the disease and improve anti-fibrotic/anti-inflammatory efficacy. Indeed, Novartis and Gilead recently announced plans to combine semaglutide with firsocostat and cilofexor, while Genfit has launched a clinical program to include combinations of elafibranor with a sodium-glucose cotransporter-2 inhibitor and glucagon-like peptide-1 analog. Novartis and Allergan have also entered into an agreement to combine cenicriviroc with tropifexor, and Novartis and Pfizer have initiated a combination trial with early-phase therapies. While such combinations may be more clinically promising than monotherapies, they pose a substantial problem for payers and patients because a regimen comprising multiple premium-priced drugs would be prohibitively expensive. Thus, manufacturers will have to be mindful of the total regimen cost for payers and patients (who may have to pay separate co-payments for individual components of the regimen), and will have to price the regimen based on the clinical benefit it provides, rather than the number of components it includes. This strategy may be simpler to implement for regimens comprised entirely of novel NASH therapies, but for regimens comprising new NASH agents and therapies that are already on the market and priced for different primary indications (eg semaglutide for type 2 diabetes), manufacturers will need to be careful to avoid pricing patients out of the market and/or disrupting established pricing for other indications (as with Ocaliva in its existing PBC indication).
Conclusion

Although Ocaliva will have the advantage of fulfilling a significant unmet need, as it is expected to be the first approved treatment for NASH, a prohibitively high price risks severely hampering its commercial prospects. It would be unwise for competitors to replicate Intercept's pricing strategy as this could cause the market to break down before it evolves. Therefore, late-entry therapies will likely be priced lower, which will force Intercept to drop the price of Ocaliva in order to maintain its dominant position in the market. Payers will respond to premium costs with strict reimbursement criteria to restrict patient accessibility, including prior authorization forms, or keep therapies off formularies altogether. As NASH is an unknown space for payers, with no marketed drugs, poor epidemiological data, and no formal economic reports to better understand the impact of the disease on the economy, payers will be left to determine the worth of a NASH therapy alone.

About the Author

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Analyst Hannah Cohen provides in-depth insights focusing on cardiovascular and metabolic disease markets. She liaises with key opinion leaders, analyzes treatment landscapes and tracks market moving events to build robust forecasts. Since joining Datamonitor Healthcare in 2018, Hannah has produced content on cardiovascular and metabolic diseases specializing in chronic heart failure and non-alcoholic steatohepatitis. Prior to Informa, Hannah graduated from the university of Nottingham with a Neuroscience degree.
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