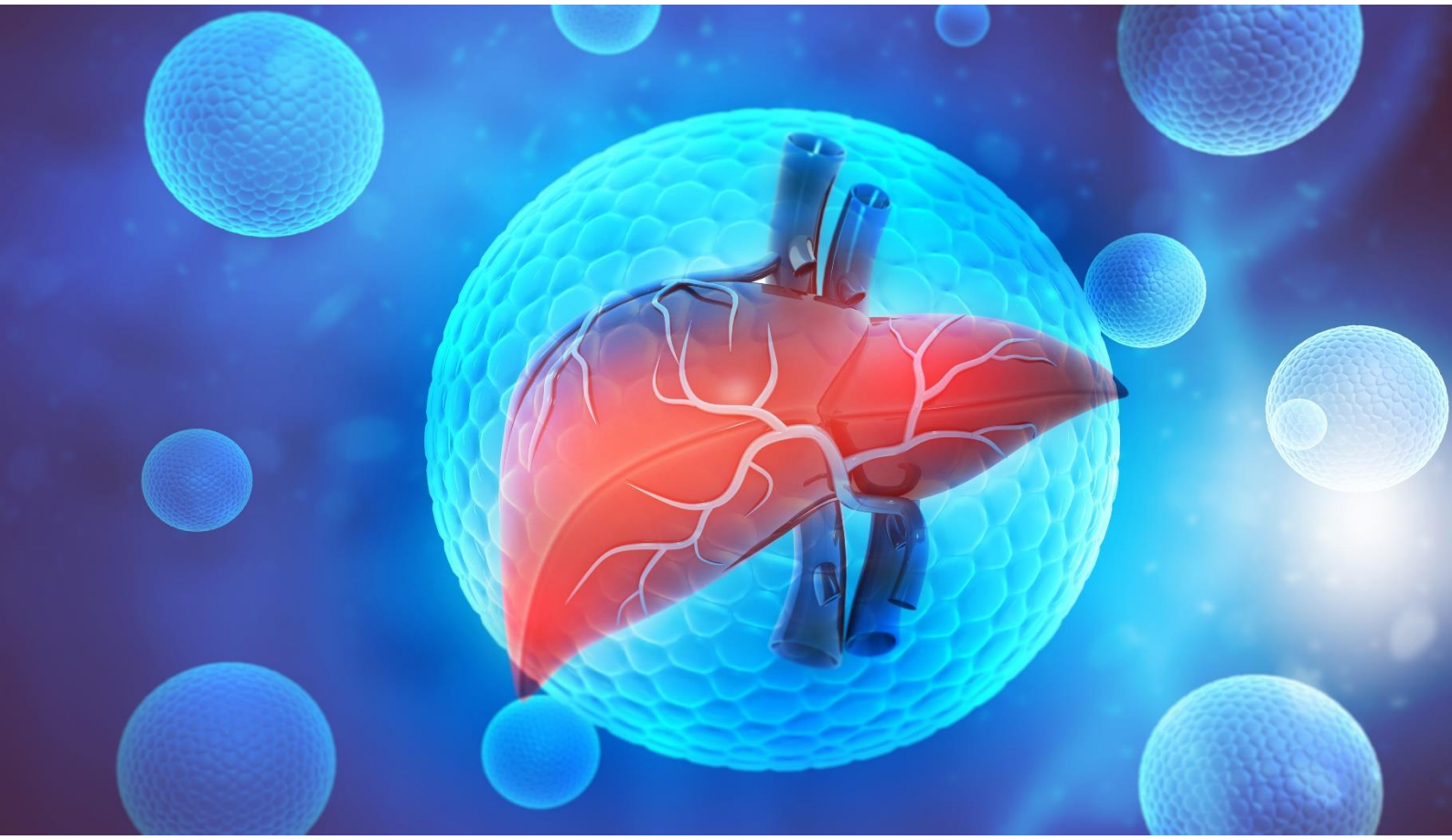

NASH – the next pharmaceutical block buster?

We are committed to bringing insight and high-quality solutions to our clients. In doing so we help them meet the many challenges of today's complex healthcare marketplace.

The valuation outputs we generate can be easily integrated with any in-house existing financial systems, presentation styles or platforms that may be currently operational. This ensures a faster uptake within the business, enabling resources to be re-directed towards implementing the outputs and leveraging new information.

NASH – the next pharmaceutical block buster?

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NASH – the next pharmaceutical block buster?

Hailed as the next “blockbuster” in the market, NASH (non-alcoholic steatohepatitis, ICD-10-CM K75.81) is a liver condition that arises due to other diseases, namely it is associated with diabetes, metabolic syndrome and obesity.

NASH is part of a wider spectrum of fatty liver disorders known as NAFLD (non-alcoholic fatty liver disease). NASH represents a specific sub-set of NAFLD identified as patients at high risk of developing progressive liver disease including fibrosis and cirrhosis.

The internet is full of speculative forecast estimates that this market represents a $35Bn untapped potential, with 27 million patients expected in the USA by 2030.

Let’s look at the NASH market in a little more detail and explore the main contributing factors to developing the market, what the actual potential is for products entering this market and why it may not be the $35Bn market that the analysts expect.

NASH – who are the patients?

And more importantly, how many are there of them?

If we consider the main conditions that are associated with the development of NAFLD (before we get to the sub-set that are NASH), these include some very large, highly prevalence indications such as type 2 diabetes, metabolic syndrome and obesity. However, there is significant overlap between these three conditions since obesity is one of the dimensions of metabolic syndrome, and metabolic syndrome is considered a risk factor for type 2 diabetes or that type 2 diabetes could be viewed as a subset of metabolic syndrome.

In very broad terms, diagnosed NAFLD probably represents an overall patient population of around 48 million patients in the USA alone in 2020 (Lazo et al 2013, based on NHANES analysis coupled with UN demographic data for the USA, exact estimates vary according to diagnostic and screening criteria used). There are estimates however that report nearly 80-100 million Americans affected by NAFLD (according to a paper published by Perumpail et al in 2017). The higher estimates of NAFLD since they are based on prospective population surveys reflect the true overall prevalence of NAFLD (the clinically ascertainable – i.e. these are patients that would meet the criteria for a diagnosis of NAFLD, however not all patients that would meet the criteria are diagnosed).

Diagnosis of NAFLD

The current rate of diagnosis within NAFLD is unknown, although from an analysis of NHANES (which estimates the total prevalence of NAFLD regardless of diagnostic status) coupled with registry data, an estimate of the actual diagnosis rate can be made. In order to forecast the

NASH market, diagnosis of NAFLD would naturally affect the clinically available NASH population. In addition, a study conducted by Polanco-Briceno in 2015 found that only around 50% of primary care physicians routinely screen for NAFLD or NASH in their daily practice.

It is unclear as to whether the diagnosis rate of NAFLD will increase in the next 10 years. For our analysis, we have maintained the current estimated diagnosed population with NAFLD, meaning that any increases in detection would represent an upside to the forecast.

This represents a wide spectrum of liver disease, with NASH representing a relatively modest sub-set within NAFLD.

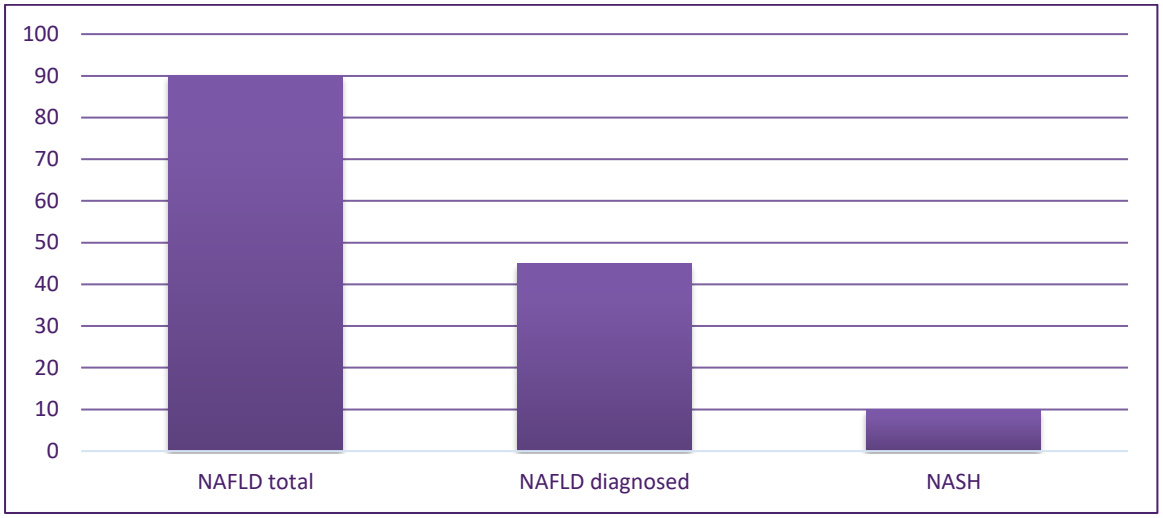

Figure 1. Patient waterfall chart of NASH in the context of NAFLD

Overall estimates of the proportion of NAFLD with NASH mostly estimate around 20-25% of NAFLD that will develop NASH. This has also been estimated at around 3% of the overall US population (Younossi et al, 2016), which correlates to around 11 million patients with NASH in the USA by 2020.

Let's proceed with a working hypothesis of ~ 11 million NASH patients. Let's now look at how those patients are diagnosed and managed currently and why.

Contributing causes of NASH according to the paper by Younossi et al in 2016 estimated that NASH patients had the following comorbid conditions:

- Obesity – 82%
- Type 2 diabetes – 48%
- Hyperlipidaemia – 82%
- Metabolic syndrome* – 76%
- Hypertension – 70%

**There are 5 components of metabolic syndrome which include: obesity, high blood pressure, reduced HDL levels or increased triglycerides, elevated fasting plasma glucose – a risk factor for developing diabetes, patients meet 3 or more of criteria to classify as having metabolic syndrome, hence there is significant overlap between all of the conditions that give rise to NASH.*

NASH staging

To further differentiate the NASH population, assets in development are targeted at specific grades or stages of NASH. A rough breakdown of NASH by stage in the USA according to the Batts & Ludwig staging system is as follows:

Fibrosis Stage	Description	% NASH
Stage 0	No fibrosis	29%
Stage 1	Portal fibrosis	36%
Stage 2	Periportal fibrosis	12%
Stage 3	Septal fibrosis; no obvious cirrhosis	8%
Stage 4	Cirrhosis	15%

Table 1. Batts & Ludwig staging for NASH

Current management of patients

As with NAFLD, not all patients with NASH are likely to be diagnosed. While it is unclear as to the proportion that would be diagnosed, we have made the assumption that based on likely symptoms, patients at more advanced stages of NASH are more likely to be diagnosed than those in earlier stages who may be largely asymptomatic.

Considering this combination of stage of NASH and likely diagnosis, we would consider that a reasonable working hypothesis for the clinically identifiable patient caseload with NASH that has been diagnosed and is under physician care could be around 6.5 million patients in the USA (of a total of ~11 million patients).

Since many NASH patients have an underling condition such as type 2 diabetes or associated conditions, the mainstay of treatment recommended as first line is diet and exercise (which is the main treatment option recommended for T2DM patients before starting treatment with oral anti-diabetic medications).

According to a survey by Rinella et al (2016) of 482 gastroenterologists and hepatologists, the main drug treatments recommended for patients with NAFLD & NASH were metformin and pioglitazone. Overwhelmingly, diet and exercise were recommended to > 90% of patients by both physician types.

The main takeaway message here is that these patients tend to be advised to lose weight and exercise in order to address the obesity and diabetes issues. Exercise and weight

management will also help manage hypertension and dyslipidaemia. This trend in patient management will remain, with a small percentage managed with drug treatment.

New treatments in development

The closest product to launching in NASH in the USA is Ocaliva (obeticholic acid) from Intercept. Ocaliva is already licenced for the treatment of Primary Biliary Cirrhosis, a rarer liver disease affecting around 140,000 patients in the USA in 2019.

The REGENERATE study, the pivotal phase 3 trial for NASH enrolled patients with stage 2 and 3 NASH. Preliminary results have been received well by the FDA with an expected launch date in 2020. A further study in patients with stage 4 NASH has a primary complete date of June 2021, with an expected launch in stage 4 patients in 2022.

The initial market for Ocaliva in 2021 will be limited to ~ 20% of the overall NASH population (if we take the likely diagnosed population of 6.5 million, this is a total eligible population of some 1.3 million patients, or 2.2 million if we include the total NASH population regardless of likely diagnosed status).

Of course, not all patients will receive treatment, so an estimate of product uptake needs to be factored into the overall number of patients expected to receive Ocaliva. If we assume the current rate of drug treatment of ~ 10-15% of the market, we end up with an overall estimate of between 100-200k patients (if we base this on 1.3 million NASH stage 2-3) or 200-300k (based on 2.2 million NASH stage 2-3).

	Conservative Forecast	Higher Estimate Forecast
Likely Diagnosed	60%	100%
Stage 2-3 @ 20%	1.3	2.2
Treatment @ 10-15%	100-200k	200-300k

Table 2. Estimated ranges of diagnosed and treatment eligible patients for NASH stages 2-3

Possible barriers to Market access

According to a study conducted by Polanco-Briceno et al (2016), awareness of NAFLD and NASH was generally low in primary care physicians in the USA (~18% considered themselves as relatively well informed vs. 88% of specialists), so while hepatologists are familiar with treating NASH and using obeticholic acid, they are not the usual physicians that manage patients with diabetes, hypertension or dyslipidaemia. Specialists treating these patients are less familiar with NASH, liver complications and suitable treatment options which has been

reflected in the reports providing information on how patients with NASH are currently managed. Of course, some of this may be linked with a lack of effective or licenced treatments and may change in the future, but currently this may provide a barrier to uptake of NASH-specific treatments since patients are not seeing the most appropriate physicians to manage their NASH symptoms or that their usual care physician are not educated regarding liver complications, disease progression and suitable treatment options.

Pricing and reimbursement

Ocaliva is already licenced for use in patients with PBC. The current average cost per day of treatment in the USA ranges from $150-$200 (depending in health care provider, based on list price obtained from Rx Price Index database for Big4, FSS and NADAC price information).

There are two dose versions currently available, 5mg and 10mg. From the clinical trials, the dose most likely to be used in NASH patients is from 10-25mg. While there is flat price currently between the 5 and 10 mg forms, it would likely follow that the 25mg would be priced at parity with the lower dosed formulations.

However, it is most likely that the PBC price would not be reimbursed for a population as large as NASH. Although if the addressable population truly sits around the 100-200k mark, this is not too dissimilar to the overall patient caseload with PBC (although Ocaliva is not used in 100% of PBC patients).

As a potential upside, Ocaliva might maintain price parity across the two indications, however it is more likely that the price for NASH will have to be considerably lower. It is not clear at the present time how much lower the price may need to be, thus two scenarios have been run within the potential market valuation – one at PBC price, but with a reduced uptake into the patient population, and one with a reduced price and no reduction in patient volume.

	Conservative Forecast	Higher Estimate Forecast
Total estimated treatment pool	100-200k	200-300k
Estimated days of treatment (DoT) in 2021 (assuming 6 months on market, 80% compliance)	220k	365k
Estimated cost per DoT	$80	$160
Reduction in use due to price	0%	60%
Rough revenue estimate for 2021*	$1.7 Bn	$2.3 Bn

Table 3. Estimated forecast ranges for new NASH assets in first year of launch, 2021

**Please note, this assumes all patients treated for 6 months with a launch date of July 1st, 2021. It is more likely that only a proportion of the patients will be put on to treatment across the 6 months of the year when Ocaliva is licenced and approved for use in NASH. This also assumes no delay between marketing authorisation for NASH and reimbursement since the product is already in market for PBC.*

The addition of stage 4 fibrosis to the indication set expands the market potential to include another **15%** of patients, so may effectively double the clinically relevant treatment population, taking revenues to between $3.5 Bn to $4.7 Bn.

Future landscape snapshot for NASH

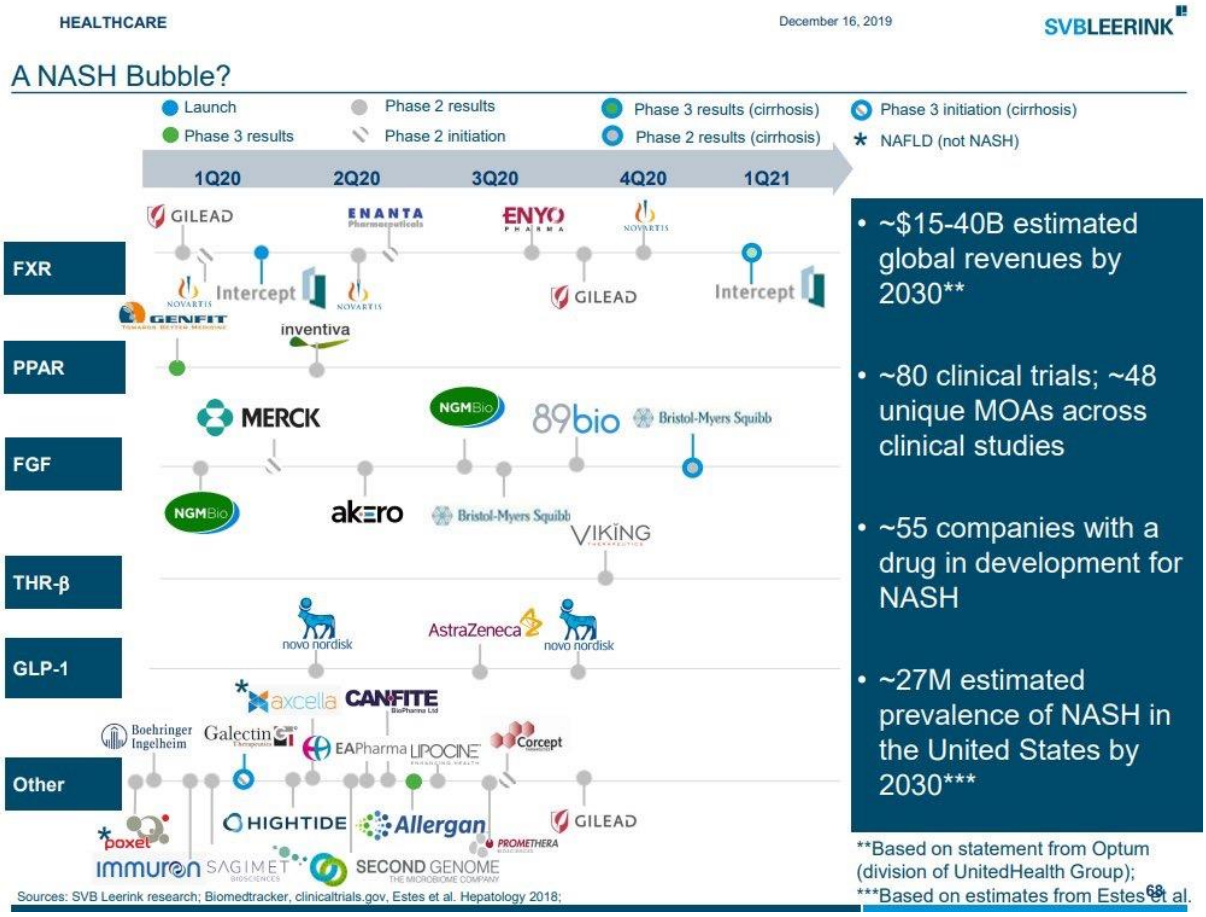

Figure 2. Clinical development landscape for NASH

The development landscape for NASH is relatively crowded with some big names in the mix as well as many smaller boutique biotech companies.

A more comprehensive report of the NASH market from a patient and /or forecast perspective for G7 markets can be found on our website (https://blackswan-analysis.co.uk/resources/).

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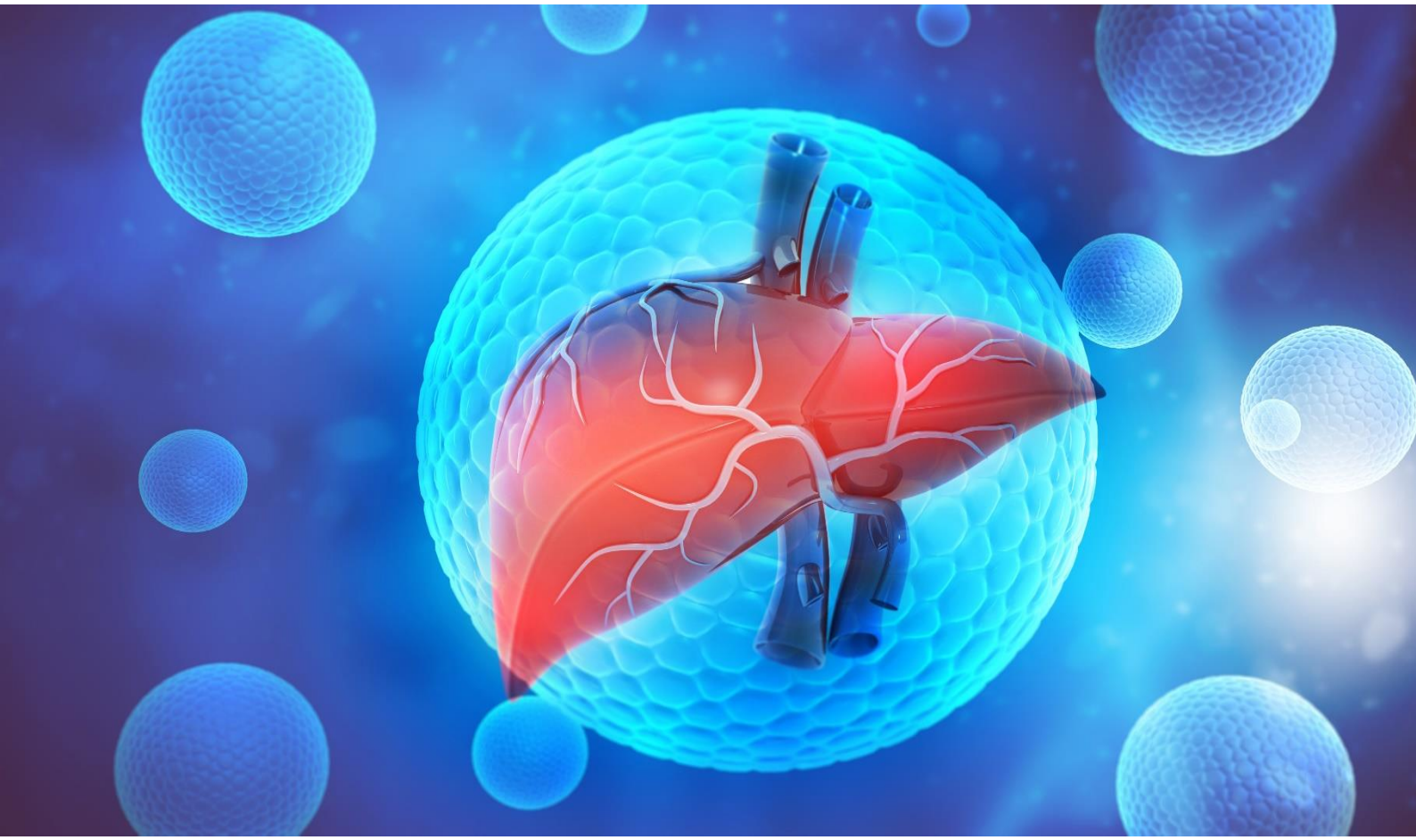

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