This report focuses on Liver Disease therapies currently approved and in development. It highlights BPI news as well as predictive and competitive intelligence on potentially market-moving clinical events in the space. The report also provides analytics on global sales forecasts for individual drugs.
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Introduction

In this report BPI highlights some of the major recent developments, important catalysts and current trends occurring in the liver disease drug development field focusing on nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC) and hepatitis.

The American Cancer Society estimates over forty thousand new cases of HCC will be diagnosed in the US in 2017 and approximately twenty-nine thousand people will die. While 780k patients are estimated to be diagnosed with HCC this year, liver cancer prevalence is expected to increase in the coming years given the rise of hepatitis B (HBV) and hepatitis C (HCV) predictors; aside from the viral infections, a high number of HCC cases are attributed to alcoholic liver disease.

NASH is an emerging field, with no current FDA-approved treatment and the prevalence is generally accepted to be 3-5% of the US population. An extensive number of patients will progress to cirrhosis, liver cancer or liver failure. According to BioPharm Insight’s data, there have been 14 licensing deals involving a drug targeted to treat NASH in the past 5 years; the most notable companies include Merck (NYSE:MRK), Allergan (NYSE:AGN) and Novartis (VTX:NOVN). Some notable development players in the field include Intercept Pharmaceuticals (NASDAQ:ICPT) and Genfit (EPA:GNFT) both in Phase III and expected to reach peak sales over USD 6bn.

In recent years, a number of therapies had tried to challenge Bayer’s (ETR:BAYN) Nexavar (sorafenib) in HCC, but with no success. Notable trials that failed to hit their primary endpoint in head-to-head studies include Bristol-Myers Squibb’s (NYSE:BMY) brivanib, Genentech/Abbott’s linifanib and Pfizer’s (NYSE:PFE) sunitinib. But in April 2017, the FDA expanded the approval of Bayer’s Stivarga (regorafinib) to include treatment of patients with HCC who have been previously treated with Bayer’s Nexavar. This is the first treatment to be approved by the FDA in almost a decade. Following this, the FDA has accepted BMS’s Opdivo (nivolumab) under priority review for second-line HCC with a 24 September PDUFA date.

Gilead Sciences’ (NASDAQ:GILD) Phase II trial investigating GS-0976 for NASH has drawn cautious safety optimism from experts. Whilst the drug mechanism does not elicit safety concerns, available 10-subject data is too small to draw conclusions. However, because the mechanism is untested in NASH, there is a possibility for the drug to affect other biological pathways.

A source close to the study told this news service Gilead is working with CRO PRA Health Sciences (NASDAQ:PRAH) for its Phase II GS-0976 trial for NASH.

BioPharm Insight reported Galectin Therapeutics (NASDAQ:GALT) GR-MD-02 for NASH with cirrhosis draws hazy Phase IIb success predictions from experts since its mechanism is yet to be tested for this indication. The company failed a Phase Iia trial late last year in NASH, missing both its primary and secondary endpoints, but other experts noted this has no bearings in the ongoing trial’s success potential as it only ran for four months. The top-line data readout of this trial is on track for December 2017.

Although Bayer’s Stivarga was approved recently for HCC, experts told this news service it may see limited real world uptake relative to its positive Phase III performance. Some experts noted only 20-30% of patients are tolerant to Nexavar and discontinuation rates reaching 30-40%.

BMS’s Opdivo has evoked overall Phase III optimism from experts for first-line HCC due to an encouraging efficacy signal in Phase I/II second-line HCC, as well as success in other cancer indications. But some experts added overall response rate (ORR) success does not necessarily translate to an overall survival (OS) benefit, considering patients could still die from liver disease even if Opdivo is able to reduce the cancer.
BioPharm Insight data shows global sales for Opdivo in all approved conditions are expected to exceed USD 17bn in 2026. Opdivo is FDA approved in first-line melanoma, renal cell carcinoma, urothelial carcinoma, Hodgkin’s lymphoma, second-line head and neck, and second-line non-small cell lung cancers.

Top-line results from the Phase IIa ACHIEVE trial assessing Spring Bank Pharmaceuticals’ (NASDAQ:SBPH) SB 9200 for hepatitis B virus (HBV) infection was announced this in May. The results demonstrated an encouraging safety profile with no serious adverse events during the 12-week study.

BioPharm Insight reported if SB 9200 moves onto Phase III, it should use surface antigen (HBsAg) clearance or reduction as a primary endpoint to demonstrate clinical value. But before moving to Phase III, some experts noted there should be clearer evidence SB 9200 can knock down HBsAg levels for a long period of time to draw development success confidence.

An investigator for this trial told BPI there has been one reported case of gout, noting it is unclear if this is also seen in other locations. The trial CRO is Quintiles (NYSE:Q), which is responsible in facilitating communication, as well as monitoring trial progress.

Experts agreed AbbVie’s (NYSE:ABBV) ABT-493 (glecaprevir)/ABT-530 (pibrentasvir) (G/P) for HCV has a clear argument for FDA approval based on high response rates reported in several Phase III trials. One expert added the drug combination was able to show efficacy in treatment-naïve subjects, as well as in subjects with renal impairment.

BioPharm Insight further reported G/P has the potential to become the standard-of-care due to its eight-week treatment duration. Experts added G/P’s pangenotypic efficacy would also do away with genotyping, also speeding up treatment.

Finally Promethera Biosciences’ Phase IIa HepaStem for acute-on-chronic liver failure (ACLF) has foggy safety projections since disease symptoms are so severe it could be hard to identify what adverse events (AEs) are caused by the treatment. Experts said issues such as allergic reaction, toxic substance accumulation or tumour generation should be monitored. Some noted the Phase IIa trial design details are encouraging for success as the enrolment criteria and secondary efficacy endpoints may make it easier to see a treatment signal in a complicated disease.
Gilead employs PRA Health Sciences for Phase II GS-0976 trial for NASH – source

21 APR 2017

**Gilead Sciences** (NASDAQ:GILD) is working with **PRA Health Sciences** (NASDAQ:PRAH) for its Phase II GS-0976 trial for nonalcoholic steatohepatitis (NASH), a source close to the study said.

The CRO is responsible for routine trial monitoring, among other standard CRO responsibilities, he said on the sidelines of this year’s EASL International Liver Congress (ILC) in Amsterdam.

Both companies did not respond in time for publication.

The placebo-controlled, 127-subject Phase II trial (NCT02856555) has a primary endpoint investigating safety after 12 weeks and then 30 days later, ClinicalTrials.gov shows. The trial is still ongoing in 36 US locations, but no longer recruiting participants, with a primary completion date of June 2017, ClinicalTrials.gov shows.

Today at ILC, Gilead presented Phase I proof-of-concept data for GS-0976 showing use after 12 weeks led to de novo lipogenesis and reduction in liver fat and stiffness. Data collected from 10 treated subjects showed 20mg oral once daily led to statistically significant improvements in liver fat content and noninvasive markers of fibrosis, a media release shows.

GS-0976 is an Acetyl-CoA Carboxylase inhibitor, which could lead to prevention of new production of lipids, the company website shows. NASH is caused by fat that is stored in the liver due to a variety of causes other than excessive alcohol consumption. Fat storage can lead to inflammation, progressive fibrosis and cirrhosis.

Gilead has a market cap of 87.2bn, whilst PRA’s is USD 4.1bn.

by Reynald Castaneda in Amsterdam
Gilead’s Phase II NASH drug expected to prove safe but limited data draws caution, MOA rationale for early efficacy signals – experts

26 APR 2017

- Lipogenesis and lipid oxidation targeted
- Unclear if GS-0976 is dose dependent
- Biopsies may lead to dissimilar readings

Gilead Sciences’ (NASDAQ:GILD) Phase II trial investigating GS-0976 for nonalcoholic steatohepatitis (NASH) has drawn cautious safety optimism from experts. Whilst available 10 subject data is too small to draw conclusions, GS-0976 mechanism does not elicit safety concerns, they added. But one expert noted the drug’s downstream target could lead to side effects related to elimination of fat in the liver.

Some analysts view GS-0976 efficacy is derisked due to data from 10 NASH subjects showing improvements. While some experts said early data is encouraging, helping to validate GS-0976 inhibition of Acetyl-CoA carboxylase (ACC) to limit liver fat production (de novo lipogenesis), others noted more data is required to pull more efficacy confidence.

Although some experts argued the trial should have only enrolled subjects with their NASH validated via gold standard liver biopsy, others noted noninvasive magnetic resonance elastography (MRE) is still appropriate in this early phase of research. One expert noted MRE is actually a high standard of NASH diagnosis as it undercuts biopsy flaws.

The placebo-controlled, randomised 127 patient Phase II trial has a primary endpoint of safety after 12 weeks and then after 30 days (NCT02856555), ClinicalTrials.gov shows. The trial has a primary completion of June 2017.

Gilead did not respond to a request for comment.

NASH is a chronic liver disease, triggered by accumulation of liver fat, which then leads to inflammation, fibrosis and cirrhosis.

NO CONCERNING SAFETY SIGNALS YET

GS-0976’s safety profile is encouraging as the drug is yet to show severe side effect signals, said Dr Eric Lawitz, lead Phase II investigator and vice president of scientific and research development, Texas Liver Institute. According to data from an open-label, proof-of-concept trial with 10 NASH subjects, GS-0976 was well tolerated and all undisclosed adverse events were Grade 1 or 2 with no subjects prematurely discontinuing from the trial, a 21 April media release shows. Data from the Phase I trial (NCT02876796) with healthy subjects is also reassuring because high doses of 50mg and 200mg did not lead to significant safety signals, Lawitz said on the sidelines of last week’s EASL International Liver Congress in Amsterdam.

GS-0976’s safety profile is harder to predict in the larger 127-subject Phase II with limited data, said Dr Stephen Harrison, Phase II investigator and medical director of Pinnacle Clinical Research, San Antonio, Texas and Dr Salvatore Petta, gastroenterology lecturer, University of Palermo, Italy. But GS-0976’s mechanism does not inspire safety concerns, Petta said. The drug is metabolised quickly in the liver, which means the likelihood of systemic side effects is limited, Lawitz added.

However, because the mechanism of GS-0976 - ACC inhibition - is very untested in NASH, there is possibility for the drug to also affect other biological pathways and thus could trigger unexpected side effects, said Mattias Ekstedt, gastroenterology senior lecturer, Linkoping University, Sweden. Maintaining the right amount of fat in the liver is important in homeostasis with regards to insulin resistance, Ekstedt said. Therefore, if too much liver fat is eliminated, hormone rates could be affected and GS-0976 impact is currently unclear, he added.

The main cause of NASH death is cardiovascular disease, which means that any heart-related side effects should undergo extra scrutiny, Ekstedt said. If subjects stop storing fat in the liver, there could be the possibility of the body storing fat somewhere else, like in cardiac muscle tissue, which could be an additional risk factor, noted Ekstedt.

MECHANISM ENCOURAGING FOR EARLY EFFICACY SIGNALS

The aforementioned data media release shows use of 20mg GS-0976 for 12 weeks led to median decrease of 29% in hepatic de novo lipogenesis and a 43% median relative decrease in liver fat content, from 15.7% - 9% (p=0.006). This efficacy data demonstrates that GS-0976 and ACC inhibition is worth investigating further, Petta and Lawitz said. But...
Ekstedt said available data was too premature to give full confidence of efficacy potential.

Lawitz argued ACC is an ideal NASH target because ACC is involved in generation of complex fatty acids, where high rates lead to lipotoxicity and cell signalling that pave the way to inflammation and then fibrosis.

It is an advantage that GS-0976 targets both ACC isoforms 1 and 2, Harrison said. This is because ACC 1 works in the mitochondria, which is responsible for liver oxidation, and ACC 2 works in the cytoplasm, responsible for de novo lipogenesis, Lawitz said. Increasing liver oxidation burns fat in the liver and de novo lipogenesis limits liver fat production, Lawitz explained.

In the Phase II trial, 5mg and 20mg of GS-0976 is being investigated, ClinicalTrials.gov shows. Both doses are being tested to see if the drug is dose dependent, Lawitz said. According to earlier mouse trials the drug seems to be dose dependent but results are unconvincing as animal data may not apply to humans, Lawitz added. Petta said the lowest dose possible with a metabolic effect is ideal to reduce side effect risk.

**MRE APPROPRIATE FOR PHASE II**

The Phase II trial has an inclusion criteria of MRE with liver stiffness of more than or equal to 2.5 kPa or a historical liver biopsy consistent with NASH and non-cirrhotic fibrosis, ClinicalTrials.gov shows.

However, because the mechanism of GS-0976 - ACC inhibition - is very untested in NASH, there is possibility for the drug to also affect other biological pathways and thus could trigger unexpected side effects.

Harrison said it was premature to assume noninvasive imaging alone would be a reliable way to measure NASH. Change in MRE, assumed to relate to liver stiffness and thus liver fibrosis, has unclear clinical significance, Harrison said. The protocol should require all subjects to have liver biopsy since it is the current standard measure, Petta said. Biopsies zero in on fibrosis and it would demonstrate how much the liver has improved, Petta noted.

A significant number of potential subjects are turned off by invasive biopsy making MRE an ideal option during clinical trials to help enrolment, Lawitz said. Liver biopsies involve a small needle being inserted into the liver to collect a tissue sample. In contrast, MRE exposes low frequency mechanical waves to the tissue, allowing for an image to be generated.

But Ekstedt argued MRE is actually an appropriate inclusion criteria over biopsy. Two biopsy samples of the same patient could lead to a different reading and different clinician interpretation, whereas MRE imaging does not have this same issue, Ekstedt said.

Whilst MRE can measure fibrosis adequately, it is not able to measure inflammation or ballooning precisely since they are two notable elements in NASH, Ekstedt said. However, it is yet to be shown if inflammation or ballooning is prognostically important in NASH, Ekstedt said.

That said, since this is an early stage trial, where the purpose is to find an efficacy signal, enrolling subjects via MRE or biopsies is still acceptable, Harrison and Petta said. Ideally, subjects would have both MRE and liver biopsy to confirm MRE as a potential less invasive way to measure NASH but this could be applied in future trials, Harrison and Petta said.

Gilead has a market cap of USD 90.2bn.

*by Reynald Castaneda in London*
Galectin’s Phase IIb GR-MD-02 has hazy future in NASH with untested MOA; Phase IIa signals in advanced fibrosis inadequate to predict success

28 APR 2017

- Ongoing NASH-CX is a one-year trial, NASH-FX is 4 months
- 10-20% drop in hepatic venous pressure clinically relevant
- Phase III primary endpoint should be fibrosis improvement

Galectin Therapeutics (NASDAQ:GALT) GR-MD-02 for non-alcoholic steatohepatitis (NASH) with cirrhosis draws hazy Phase IIb success predictions since its mechanism is yet to be tested for this indication, experts said. The failed Phase IIa trial in NASH with advanced fibrosis has no bearing in the ongoing trial’s success potential since it only ran for four months and is too small at 30 subjects, others noted.

The Phase IIb’s primary endpoint - reduction in hepatic venous pressure gradient - is appropriate surrogate measure of cirrhosis reduction considering cirrhosis increases blood pressure in the portal veins, some experts noted. But this would have to be changed if the drug moves on to Phase III to mirror other NASH drugs ahead in the development pipeline, they added.

The placebo-controlled 162-subject Phase IIb trial is enrolling NASH subjects with cirrhosis (NCT02462967), ClinicalTrials.gov shows. The top-line data readout of the NASH-CX is on track for early December 2017, a March 28 media release shows.

Galectin directed BioPharm Insight’s questions to its 28 March conference call transcript. Galectin is preparing a publication for the NASH-FX trial, it states.

NASH is a liver disease due to excessive accumulation of fat in the liver, leading to inflammation and then fibrosis. Fibrosis is stage one of liver scarring and if such scar tissue builds up, it develops to liver cirrhosis.

MECHANISM LOGICAL FOR NASH

Although GR-MD-02 is yet to demonstrate efficacy in NASH, its mechanism as an inhibitor of the protein galectin-3 is logical for the liver disease, said Dr Eric Lawitz, Phase IIb investigator and vice president of scientific and research development, Texas Liver Institute and Dr Salvatore Petta, gastroenterology lecturer, University of Palermo, Italy.

Protein galectin-3 is present in immune cells at low rates during normal conditions but rises during chronic liver disease, Petta explained. Therefore, inhibiting galectin-3 could have an effect in limiting inflammation, which in turn would have a domino effect in limiting fibrosis and thus cirrhosis, Petta said, adding inflammation encourages cell-cell signalling that paves way to fibrogenesis.

An analyst report states genetic modification in mice where galectin-3 is eliminated prevents fibrosis in the liver, lung, kidney and heart. However, translating this to success in human trials is challenging as both have different physiologies, said Petta and Dr Stephen Harrison, lead Phase IIb investigator and medical director of Pinnacle Clinical Research, San Antonio, Texas.

It is, however, encouraging that GR-MD-02 has an effect on fibrogenesis in human dermatological conditions like psoriasis and atopic dermatitis, Harrison said. A 6 March Galectin media release shows a Phase IIa trial investigating GR-MD-02 for moderate-to-severe plaque psoriasis led to an average PASI (Psoriasis Area and Severity Index) reduction of over 50% in all patients in the 24-week trial.

Harrison noted the failed Phase IIa NASH-FX trial investigating GR-MD-02 in NASH subjects with advanced fibrosis does not apply to ongoing NASH-CX trial for NASH with cirrhosis, Harrison and Lawitz said. Results from the exploratory, single-site NASH-FX trial did not meet its primary and secondary efficacy endpoints, a September 2016 media release shows.

Although GR-MD-02 is yet to demonstrate efficacy in NASH, its mechanism as an inhibitor of the protein galectin-3 is logical for the liver disease.

This is because the failed NASH-FX trial only ran for four months, which is a trial design flaw as NASH takes at least a year to demonstrate fibrosis reduction, the trial’s primary and secondary endpoints, Harrison and Lawitz added. This means that the ongoing NASH-CX trial has a better shot at demonstrating cirrhosis reduction as the trial runs for a year, Harrison added.

However, a longer trial means it is a higher success bar due to expectations that there should be reduction of cirrhosis after a year, Harrison said. Phase III trials usually run for one to four years where an effect in NASH is able to be seen via histological analysis after a year, emphasising the need for year-long trials to demonstrate efficacy, Petta added.
The NASH-FX trial only had 30 subjects which makes it challenging to assess if the failed results would apply in the ongoing 162-subject trial, Lawitz said. NASH-FX data shows GR-MD-02 was found to be safe with no serious adverse events, the 6 March media release shows. Harrison added GR-MD-02’s advantage is that it is well tolerated even on this site injection despite a fortnightly IV administration.

**CHOICE OF ENDPOINT VS LIKELY PHASE III REQUIREMENT**

Whilst liver biopsy is the gold standard in NASH, hepatic venous pressure gradient is an acceptable FDA primary endpoint, Harrison said. This means that the trial is equipped to demonstrate efficacy at Phase IIa and speak to potential performance on a liver biopsy endpoint for a potential Phase III, he said.

If GR-MD-02 moves on to Phase III, it is likely to follow the design elements of Intercept Pharmaceuticals (NASDAQ:ICPT) Ocaliva (obeticholic acid) (NCT02548351) and Genfit’s (EPA:GNFT) elafibranor (NCT02704403), said Harrison, Lawitz and Mattias Ekstedt, gastroenterology senior lecturer, Linkoping University, Sweden. This means that hepatic venous pressure gradient would have to be abandoned for fibrosis improvement without worsening of steatosis as a primary endpoint, Lawitz and Ekstedt said.

Harrison noted the Phase Ib trial also has liver biopsy as a secondary endpoint to help reaffirm results from hepatic venous pressure gradient.

“A direct measure of the liver via biopsy would have been a superior compared to depending on blood pressure decrease to estimate fibrosis reduction.”

Petta noted hepatic venous pressure gradient is a logical endpoint because fibrosis blocks the blood flow that goes through the liver. If GR-MD-02 is able to reduce fibrosis, blood pressure in the portal vein would ease, Petta and Lawitz explained.

A 10-20% reduction in hepatic venous pressure gradient would be clinically relevant, Petta said. It would be ideal to see subjects go below 11mg of mercury if their baseline is above this measure, Lawitz said. The transcript shows the trial have enrolled subjects with 12-15mm of mercury. However, it is hard to predict if GR-MD-02 is able to achieve this due to the multifactorial nature of NASH, Petta said. A direct measure of the liver via biopsy would have been a superior compared to depending on blood pressure decrease to estimate fibrosis reduction, Petta explained. The success of this surrogate endpoint depends on the trial’s success in enrolling cirrhotic subjects, added Ekstedt.

Once GR-MD-02 is successful in establishing efficacy in NASH, perhaps it could be worth investigating in patients with NASH and psoriasis, Harrison said. The link between these two indications is currently unclear, but systemic inflammation is the driver for both diseases, Harrison said.

Galectin has a market cap of USD 104.7m.
NASH Drug Trends

Biopharm Insight data shows the numerous upcoming events for some notable NASH drugs. Intercept Pharmaceuticals’ obeticholic acid in Phase III and Gilead’s GS-9674 in Phase II -- both targeting the farnesoid X receptor expressed in the liver and intestines -- are expecting results in 2019, and 1Q18, respectively. A noteworthy catalyst is the Phase III RESOLVE-IT initial results for Genfit’s (EPA:GNFT) elafibranor expected in early 2019 and believed to be the first to market. Though delays may be a reality as the company announced in April 2017 that trial enrolment was delayed by up to 6 months. (Table 1, p. 10)

Table 1. NASH - Currently Under Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Stage of Development</th>
<th>Next Expected Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obeticholic acid</td>
<td>Intercept Pharmaceuticals</td>
<td>FXR Agonist</td>
<td>Phase III</td>
<td>Phase III REGENERATE Trial topline data expected in 2019</td>
</tr>
<tr>
<td>Elafibronor</td>
<td>Genfit</td>
<td>PPAR Alpha and Delta Agonists</td>
<td>Phase III</td>
<td>Phase III RESOLVE-IT Initial results expected early 2019</td>
</tr>
<tr>
<td>Cinicriviroc</td>
<td>Allergan</td>
<td>CCR2/CCR5 Inhibitors</td>
<td>Phase III</td>
<td>Phase III AURORA has an estimated primary completion date in 2019</td>
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<tr>
<td>Selonsertib</td>
<td>Gilead Sciences</td>
<td>ASK1 Inhibitor</td>
<td>Phase III</td>
<td>Phase II results for selonsertib and prednisone expected in 2Q18. Phase III STELLAR 3&amp;4 results expected in 2020</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Novo Nordisk</td>
<td>Synthetic GLP-1 analog</td>
<td>Phase II</td>
<td>Phase II results expected in 2H19</td>
</tr>
<tr>
<td>GS-9674</td>
<td>Gilead Sciences</td>
<td>FXR Agonist</td>
<td>Phase II</td>
<td>Phase II results expected 1Q18</td>
</tr>
<tr>
<td>GR-MD-02</td>
<td>Galectin Therapeutics</td>
<td>Galectin-3 Inhibitor</td>
<td>Phase II</td>
<td>Phase II NASH-CX trial expected end of 2017</td>
</tr>
<tr>
<td>Aramchol</td>
<td>Galmed</td>
<td>Synthetic Fatty Acid/Bile Acid Conjugate</td>
<td>Phase II</td>
<td>Phase II interim analyst expected in 1H17. Topline results from the full study are expected in 2018</td>
</tr>
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All data comes from the BioPharm Insight database and BioPharm Insight’s proprietary intelligence. The report reflects as of 20 May 2017. Figures may vary from day to day as the database is continually being updated.
BioPharm Insight licensing deal data shows the largest NASH drug licensing deal in the last five years to be Gilead Sciences' USD 1.2bn deal with the Massachusetts-based Nimbus Therapeutics' subsidiary Nimbus Apollo. The deal was for its Acetyl-CoA Carboxylase inhibitor program, which includes GS-0976 (previously named NDI-010976). This was followed by Gilead's deal with Germany-based Phenex Pharmaceuticals for PX-104 (now known as GS-9674) in 2015. (Table 2, p. 11)

Table 2. NASH Licensing Deals in the Past 5 Years

<table>
<thead>
<tr>
<th>Licensor</th>
<th>Licensee</th>
<th>Drug Name(s)</th>
<th>Total Deal Value (USDm)</th>
<th>Date Announced</th>
<th>Most Advanced Phase</th>
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<tbody>
<tr>
<td>Nimbus Therapeutics</td>
<td>Gilead Sciences</td>
<td>GS-0976</td>
<td>1,200</td>
<td>4 April 2016</td>
<td>Phase I</td>
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<tr>
<td>Phenex Pharmaceuticals</td>
<td>Gilead Sciences</td>
<td>PX-102</td>
<td>470</td>
<td>6 January 2015</td>
<td>Phase I</td>
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<tr>
<td>Ngm Biopharmaceuticals</td>
<td>Merck</td>
<td>NP201</td>
<td>450</td>
<td>24 February 2015</td>
<td>Pre-Clinical</td>
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<tr>
<td>Pharmaxis</td>
<td>Boehringer Ingelheim</td>
<td>PXS-4728A</td>
<td>222.5</td>
<td>18 May 2015</td>
<td>Phase I</td>
</tr>
<tr>
<td>Bhv Pharma</td>
<td>Islet Sciences</td>
<td>Remogliflozin</td>
<td>116.85</td>
<td>3 March 2015</td>
<td>Phase II</td>
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<td>Conatus Pharmaceuticals</td>
<td>Novartis</td>
<td>Emricasan</td>
<td>50</td>
<td>20 December 2016</td>
<td>Phase II</td>
</tr>
<tr>
<td>Galmed Pharmaceuticals</td>
<td>Samil Pharmaceutical</td>
<td>Aramchol</td>
<td>8</td>
<td>28 July 2016</td>
<td>Phase II/III</td>
</tr>
</tbody>
</table>

All data comes from the BioPharm Insight database and BioPharm Insight’s proprietary intelligence. The report reflects as of 20 May 2017. Figures may vary from day to day as the database is continually being updated.
Bayer’s Stivarga for second-line HCC likely to see limited use for Nexavar-tolerant patients, side effects may overshadow efficacy – experts

4 MAY 2017

- Nexavar, Stivarga has same mechanism
- Poor uptake in CRC due to side effects
- Side effects may dwarf 3-month benefit

Bayer’s (ETR:BAYN) Stivarga (regorafenib) for second-line hepatocellular carcinoma (HCC) may see limited real world uptake relative to its positive Phase III performance, experts agreed. They noted a Phase III trial enrolment criteria focusing on subjects tolerant to Bayer’s first-line Nexavar (sorafenib), yet only around 20-30% of patients are tolerant to Nexavar, with discontinuations reaching around 30-40%, some noted.

Some experts added, in this niche population, clinicians may not be interested in switching from first-line Nexavar to second-line Stivarga because both drugs have the same kinase inhibitor mechanism, while others argued Stivarga has the advantage of a more potent and wider effect.

While some analysts view the 573-subject Phase III RESOURCE trial (NCT01774344) as showing no deviation from Stivarga’s known safety profile, experts noted Stivarga is anticipated to have poor real world side effects, which is likely to be its ultimate uptake barrier. Stivarga - approved for colorectal cancer (CRC) in September 2012 - has seen poor uptake due to severe real world side effects not reflected in clinical trials, and could also be the case in HCC, some noted.

Stivarga was approved for HCC in patients previously treated with Nexavar on 27 April. Analysts predict Stivarga could lead to EUR 500m worldwide sales in second-line HCC. Nexavar worldwide sales are anticipated at EUR 940m in 2018 in all indications.

INVESTIGATION LIMITED TO NEXAVAR-TOLERANT SUBJECTS

Real world numbers show Nexavar-tolerant patients are a niche population, thus shrinking the pool of potential Stivarga patients.

But Sangro and the spokesperson noted Stivarga covers a different variety of tyrosine kinases to Nexavar, which targets RAF/MEK/ERK pathway in tumour cells and tyrosine kinases VEGFR/PDGFR in tumour vasculature, public information shows. On the other hand, Stivarga inhibits multiple membrane-bound and intracellular kinases including RET, VEGFR 1,2,3, c-Kit, PDGFR-alpha, -beta, among others.

Real world numbers show Nexavar-tolerant patients are a niche population, thus shrinking the pool of potential Stivarga patients.

INVESTIGATION LIMITED TO NEXAVAR-TOLERANT SUBJECTS

Real world numbers show Nexavar-tolerant patients are a niche population, thus shrinking the pool of potential Stivarga patients, said Dr Tim Greten, chief, gastrointestinal malignancies section, National Cancer Institute, Bethesda, Maryland. A Bayer spokesperson said there are approximately 780k patients diagnosed annually worldwide. In all HCC patients, only about 20-30% may be Nexavar-tolerant based on real world experience, said Dr Alejandro Forner, hepatologist, Hospital Clinic Barcelona, Spain. Nexavar is the only proven active substance in systemic HCC therapy for first-line treatment. Patients halt Nexavar treatment due to a variety of reasons, including the cancer not being receptive or excessive toxicities, explained Dr David Pinato, National Institute of Health Research clinical lecturer, London.

Pinato added Nexavar discontinuation rate in trials and real world does not match, supporting the fact Nexavar-tolerant patients are in a minority. Bayer started a Phase IV trial to see variation of discontinuation worldwide and data shows cessation rates going as high 30-40% in some territories, Pinato said on the sidelines of last month’s EASL International Liver Congress in Amsterdam.

Nonetheless, this doesn’t mean there is no need for Stivarga because Nexavar-tolerant patients still need a second-line option, said Dr Bruno Sangro Gomez-Acebo, Phase III investigator and head of Hepatology Unit, Clinica Universidad de Navarra, Spain. The Bayer spokesperson said Stivarga is the first and only available treatment directly after Nexavar.

Uptake within this small pool of patients may be limited because both drugs are kinase inhibitors, which may not inspire clinicians to move from first-line Nexavar to second-line Stivarga, said Greten and Dr Joachim Mertens, gastroenterologist, University Hospital Zurich, Switzerland. It is unusual to see the same mechanism in first and second-line, Greten said, adding the only indication which has that is gastrointestinal stromal tumours, where tyrosine kinase inhibitors are increased in dose from first to second-line.
The justification in switching from Nexavar to Stivarga is a Nexavar dose increase is uncommon due to the side effect risk, said Greten. Stivarga has a wider and more potent effect on its target without having to increase the dose, Sangro and Forner added. But Pinato noted a head-to-head trial between Stivarga and Nexavar is unlikely to transpire as both are Bayer drugs.

**SIDE EFFECTS ULTIMATE BARRIER**

Stivarga’s expected poor real world side effect profile is likely to be its ultimate uptake barrier, Greten and Forner said. The most common Phase III grade 3 or higher treatment-related side effects include hypertension, hand-foot skin reaction, fatigue and diarrhea, a June 2016 media release shows. But real world side effects are anticipated to be at higher rates or more severe because Phase III subjects are asymptomatic, have better liver function or have less comorbidity compared with real world patients, Pinato said.

Stivarga also has more severe real world side effects than Nexavar, which could diminish enthusiasm to switch amongst hepatologists, Mertens said. In a 2013 Nexavar study in real world HCC patients, dose reductions were triggered by hand-foot syndrome, diarrhea, increased liver biochemistry, weight loss and constitutional symptoms (Shingina, A et. al. Can J Gastroenterol. 2013 Jul; 27(7): 393- 396). In contrast, in CRC, Stivarga is associated with hand-foot skin reaction, rash or desquamation, stomatitis, diarrhea, hypertension, liver abnormalities, and fatigue (de Wit, M. et. al. Support Care Cancer. 2014; 22(3): 837- 846).

“Stivarga’s expected poor real world side effect profile is likely to be its ultimate uptake barrier.”

Patients may not be open to Stivarga if they already had a poor experience with Nexavar in first-line, Pinato said. But Sangro and the spokesperson said, because clinicians/patients know what side effects to anticipate from experiences with Nexavar, there may be some open mindedness in using Stivarga. Stivarga’s side effect profile is based on 100k subjects so far, and they are all well-known and manageable, the spokesperson said. For example, hypertension concerns are manageable via standard hypertension medication, Greten said, with Sangro noting this is a more common issue with Nexavar. Timing as to when Stivarga’s use begins could also contribute in reducing side effect risk, the spokesperson said.

However, Mertens noted Stivarga’s OS benefit over placebo is only three months, thus the risk/benefit and quality of life queries may not justify use. The Phase III data release shows Stivarga subjects had a median OS of 10.6 months vs 7.8 months for placebo with best supportive care (pless than 0.001).

A potential uptake gauge could be Stivarga in CRC, where oncologists are averse to prescribing it due to its side effects, Greten said. Bayer reported 2016 US sales of EUR 275, dropping from EUR 313 in 2015, with the report stating this decrease is due to strong undisclosed competition in the US. But Forner and Sangro noted experience in CRC may not be an appropriate gauge for Nexavar success in HCC because it is a third or fourth-line option in CRC and thus clinicians have relatively poor experience. In CRC, many oncologists and gastroenterologists are not open to putting their patients to Stivarga with its severe side effects due to fears of cumulative toxicities, limiting uptake in CRC, Sangro added. In second-line HCC, there are no other available second-line options thus clinicians may be more open to use, Sangro said.

Bayer has a market cap of EUR 99.2bn.

*by Reynald Castaneda in London*
BMS’ Phase III Opdivo liver cancer trial inspires expert efficacy optimism but liver cirrhosis, active comparator are potential spoilers

28 APR 2017

- Limited data in first-line HCC efficacy
- No successful HCC drug since 2008
- Side effects unclear if caused by drug

Bristol-Myers Squibb’s (NYSE:BMS) Opdivo (nivolumab) has evoked overall Phase III optimism from experts for first-line hepatocellular carcinoma (HCC) due to an encouraging efficacy signal in Phase I/II second-line HCC, as well as success in other cancer indications.

However, some noted second-line results may be inappropriate to gauge Phase III success due to different types of patients. The same experts were, however, optimistic Opdivo could show a clinically relevant 20% Overall Response Rate (ORR) in Phase III, based on results in other cancer indications.

But some experts noted ORR success does not necessarily translate to overall survival (OS) benefit, considering subjects could still die from liver disease even if Opdivo is able to reduce the cancer. An investigator noted, however, the trial enrolled subjects with good liver function.

Another hurdle is Bayer’s (ETR:BAYN) Nexavar (sorafenib) being a challenging comparator to beat since no other HCC therapies have been successful in showing superiority, some experts said.

Analyst reports have not commented on potential success prospects for the ongoing trial, though one report noted interim results in the Phase I/II in treatment-naïve subjects were encouraging.

The Phase III CHECKMATE-459 trial (NCT02576509) is comparing Opdivo to Nexavar for 33 months in 700 subjects, with co-primary endpoints of ORR and OS, ClinicalTrials.gov shows. Results are anticipated in 3Q17.

BMS did not respond to a request for comment.

Analysts estimate Opdivo to have worldwide sales of USD 4.09bn in 2017 rising to USD 13.43bn in 2021 in all indications, Opdivo is FDA approved in first-line melanoma, renal cell carcinoma, urothelial carcinoma, Hodgkin’s lymphoma, second-line head and neck, and second-line non-small cell lung cancers.

PREVIOUS DATA SHOW EFFICACY SIGNAL IN HCC

Results from the Phase I/II trial (NCT01658878) in second-line HCC is encouraging for first-line usage as it shows Opdivo has an efficacy signal, said Dr Alejandro Forner, hepatologist, Hospital Clinic Barcelona, Spain and Dr Bruno Sangro Gomez-Acebo, Phase III investigator and head of Hepatology Unit, Clinica Universidad de Navarra, Spain. Results demonstrated 62% of subjects were still alive after 12 months, with eight patients (19%) achieving a complete or partial response, a 29 May 2015 press release shows.

Sangro added reduction of tumour burden in Opdivo subjects was observed over an extended period, approximately 16 months, where typically HCC patients live for only 2.5-8.5 months. This is a stellar result since there are no second-line therapies in HCC and majority of patients die at the 12-month mark, added Dr Joachim Mertens, gastroenterologist, University Hospital Zurich, Switzerland.

However, available Phase I/II data - second-line HCC and interim first-line HCC - shows Opdivo is ideal for second-line patients who have already failed Nexavar, which is a different subpopulation from the ongoing first-line Phase III, said Dr David Pinato, National Institute of Health Research clinical lecturer, London. Forner said second-line data may not be an appropriate gauge to predict first-line success because second-line patients may still be experiencing OS improvements from first-line therapy.

Opdivo is ideal for second-line patients who have already failed Nexavar, which is a different subpopulation from the ongoing first-line Phase III.

Interim Phase I/II analysis shows 54 subjects who did not have Hepatitis C and HIV infection and were treatment-naive showed an ORR of 20% whilst the 9-month overall survival rate was 79.8%, according to an ASCO 2016 presentation (LBA101). However, complete results are yet to be reported and are required to comment on first-line efficacy, said Merten and Dr Tim Greten, chief, gastrointestinal malignancies section, National Cancer Institute, Bethesda, Maryland.
It is encouraging that Opdivo has already been approved for other indications, where the ORR is similarly around 20%, said Pinato, adding that a similar result should be expected in the ongoing Phase III. A 20% ORR would be an unprecedented rate for HCC since first-line gold standard Nexavar only leads to a 2% ORR, Pinato and Greten said. If results in other tumour types are an indication, 20% of Opdivo subjects would see HCC reduction and another 30% could see some degree of modulating effect where the cancer stops progressing, Pinato said.

Sangro said, whilst a 15-20% ORR would be ideal in Phase III, durability of effect is a more important marker of Phase III success as it spells out how long the subjects live. The Phase III trial has potential to be stopped early should Opdivo subjects have survival rates remarkably longer than in the comparator arm, which is possible given Opdivo’s ORR, Pinato said.

**OS INFLUENCED BY LIVER DISEASE**

Pinato and Forner said there have been drugs that succeeded in other indications but failed in HCC due to the challenges in balancing liver complications in HCC. It is unclear if a high ORR would translate to OS success in HCC, Greten and Forner said.

Greten explained there are two components in OS in HCC - the first is the cancer (which has been demonstrated to be receptive to Opdivo) but the other is liver cirrhosis. This means that even if Opdivo reduces the cancer, subjects could die from liver disease complications affecting OS, Mertens and Pinato said. But Sangro said Phase III subjects need to have good liver function to be enrolled. This ensures that deaths are more likely due to cancer progression than liver disease complications, Sangro said.

In melanoma and NSCLC, OS was investigated without a success bar in mind and Phase their III data shows 20% of subjects were still alive with metastatic disease two to three years post diagnosis, Pinato said.

**NEXAVAR A POTENTIALLY HIGH BAR**

Another potential Phase III success hurdle is Nexavar being perceived as being a high efficacy bar, said Greten, Forner and Sangro. All drugs that have gone head-to-head with Nexavar in HCC have failed, they explained.

But Mertens argued Nexavar is actually a low success bar with a very small three month OS benefit. Most failed HCC drugs were either not active enough or were extremely toxic, so Nexavar may not be a high success bar, Forner said. However, Nexavar has had very good real world results, which could be reflected in the ongoing trial, Forner added.

In Opdivo’s Phase III, theoretical side effects that could surface include autoimmune reaction, drug induced liver injury, hepatitis reactivation, liver failure due to virus flare-up, said Pinato. However, he played down the potential for these side effects, pointing to a lack of evidence for these occurring. In second-line HCC, Opdivo was well tolerated, with mild immune related side effects being the main concern, Sangro said, adding there is no reason this shouldn't be expected in first-line.

Phase I/II data shows majority of side effects include abnormal liver enzymes, rash, and elevation of amylase and lipase. With HCC it’s hard to identify which side effects are drug related, Pinato said. For example, there could be transient elevation of amylase or lipase but the cause is unclear and it is unclear if it is a good or bad signal, Pinato said.

BMS has a market cap of USD 95bn.

by Reynald Castaneda in London
Hepatocellular Carcinoma Drug Trends

According to BioPharm Insight data two drugs have been approved by the FDA for HCC, Bayer’s Nexavar (sorafenib) for first line HCC and Stivarga for second line. Two more approvals are expected this year, Eisai’s (TYO:4523) Lenvima (lenvatinib) for first line in 2017 and Bristol-Myers Squibb’s Opdivo (nivolumab) for second line on 24 September 2017. (Table 3, p. 16)

Table 3. Hepatocellular Carcinoma - Approved and Under Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism of Action</th>
<th>Stage of Development</th>
<th>Expected Approval Year</th>
<th>Next Expected Catalyst</th>
<th>Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexavar (sorafenib)</td>
<td>Amgen/Bayer</td>
<td>VEGFR, PDGFR and the Raf kinase inhibitor</td>
<td>Approved</td>
<td>Approved in 2007</td>
<td>-</td>
<td>1st Line</td>
</tr>
<tr>
<td>Lenvima (lenvatinib)</td>
<td>Eisai</td>
<td>VEGFR1-3, FGFR1-4, PDGF-alpha, RET and KIT inhibitor</td>
<td>Regulatory</td>
<td>2017</td>
<td>FDA Decision expected</td>
<td>1st Line</td>
</tr>
<tr>
<td>Stivarga (regorafenib)</td>
<td>Bayer</td>
<td>VEGFR1-3, TIE2, KIT, PDGFR-alpha, FGFR1 kinase inhibitors</td>
<td>Approved</td>
<td>Approved in 2017</td>
<td>-</td>
<td>2nd Line</td>
</tr>
<tr>
<td>Cometriq (cabozantinib)</td>
<td>Exelisis</td>
<td>VEGFR2 kinase inhibitor with picomolar activity and low nanomolar activity toward c-Met, RET, Kit, and Tie-2 kinases</td>
<td>Phase III</td>
<td>2018</td>
<td>Phase III CELESTIAL results expected in 2H17</td>
<td>2nd Line</td>
</tr>
<tr>
<td>Opdivo (nivolumab)</td>
<td>Bristol-Myers Squibb</td>
<td>Anti-PD-1 monoclonal antibody</td>
<td>Phase III</td>
<td>2L - 2017</td>
<td>Phase III CheckMate-459 for 1L HCC is expected in 2H17. PDUFA date for 2L HCC is on 24 September 2017</td>
<td>1st and 2nd Line</td>
</tr>
<tr>
<td>Keytruda (pembrolizumab)</td>
<td>Merck</td>
<td>Anti-PD-1 monoclonal antibody</td>
<td>Phase III</td>
<td>-</td>
<td>Phase III Keynote-240 trial update is expected at ASCO 2017</td>
<td>2nd Line</td>
</tr>
<tr>
<td>Livatag (doxorubicin)</td>
<td>Onxeo</td>
<td>Doxorubicin nanoparticle</td>
<td>Phase III</td>
<td>2018</td>
<td>Phase III results expected in mid-2017</td>
<td>1st Line</td>
</tr>
</tbody>
</table>

All data comes from the BioPharm Insight database and BioPharm Insight’s proprietary intelligence. The report reflects as of 20 May 2017. Figures may vary from day to day as the database is continually being updated.
BioPharm Insight data shows the global combined sales of Bayer’s Stivarga (regorafenib) and Nexavar (sorefenib), Eisai’s Lenvima and Exelisix’s (NASDAQ:EXEL) Cometriq (cabozantinib) are expected to tip over USD 3bn in 2022 in all indications. Cometriq’s sales display the largest growth over time from approximately USD 400m in 2017 to USD 1.4bn in 2022. Stivarga was approved last month; experts told this news service the drug was anticipated to have poor real world side effects, which is likely to be its ultimate uptake barrier. Stivarga’s sales were USD 295m in 2016 and are expected to reach USD 500m in 2022. (Graph 1, p. 17)

**Graph 1. Global Hepatocellular Carcinoma Sales Forecasts From 2015 - 2022**

All data comes from the BioPharm Insight database and BioPharm Insight’s proprietary intelligence. The report reflects as of 20 May 2017. Figures may vary from day to day as the database is continually being updated.

Forecast sales figures for the above drugs are calculated as the median of the analyst report forecasts for each specific drug. Extreme outliers are excluded. All forecasts are converted to USD based on the conversion rate of the report’s publication date.
Spring Bank’s Phase IIa HBV trial reports one gout case in one site, uric acid should be considered; Quintiles is CRO – investigator

13 MAR 2017

Spring Bank Pharmaceuticals’ (NASDAQ:SBPH) 300-patient Phase IIa ACHIEVE trial investigating SB 9200 for hepatitis B (HBV) has reported one case of gout in one site, a trial investigator said, noting it is unclear if this is also seen in other locations.

A rise in uric acid - which causes gout, a debilitating inflammatory arthritis - should be investigated, the investigator said. Whilst not a life-threatening disease, gout could potentially limit the use of SB 9200, the investigator added.

An analyst report states a 25% probability of success of an SB 9200-containing curing regime, with a nominal USD 1bn in peak sales.

The trial (NCT02751996) is so far on schedule, the investigator said, but one of the challenges is that treatment-naive subjects are more difficult to find. The relatively frequent follow-up visits may also discourage some young subjects at working age to participate, the investigator said.

Chronic HBV is also more prevalent in Hong Kong than in Korea, with Canadian sites usually recruiting Asian-Canadian or immigrants, the investigator noted.

Spring Bank did not respond to a request for comment.

The open-label, double-blind, randomised Phase IIa trial has a total of 12 sites in Canada, Hong Kong and Korea, ClinicalTrials.gov shows. The trial, focusing on noncirrhotic HBV subjects, will have two parts: subjects would first receive SB 9200 as a monotherapy for 12 weeks, which is then followed by 12 weeks of Gilead's (NASDAQ:GILD) Viread (tenofovir disoproxil fumarate), SEC filings show.

The primary endpoint for the trial is adverse events and HBV DNA decline, ClinicalTrials.gov shows. Interim analysis on efficacy/safety data on the first batch of subjects has yet to be performed, the investigator said.

The trial CRO is Quintiles (NYSE:Q), which is responsible in facilitating communication between sites and Spring Bank, as well as monitoring trial progress, the investigator said. Investigators are updated via email newsletters and meet regularly at international conferences, the investigator added.

Quintiles declined to comment.

The four doses being investigated are 25mg, 50mg, 100mg and 200mg, ClinicalTrials.gov shows. Since the trial is being done in batches, there may be no need to test the highest 200mg dose if efficacy is found in a lower dose, the investigator said. The dose likely to move forward is 50mg or 100mg as 200mg could lead to yet-to-be determined safety issues, the investigator noted.

SEC filings show top-line results from the first dose is anticipated in 1H17, and top-line results in all subjects in 1H18.

Whilst SEC filings show the trial initiated on June 2016, the investigator said the first batch of 20 subjects, receiving 25mg of SB 9200, started enrolling on October 2016. This batch of subjects finished dosing on February 2017, with a second batch of 20 subjects receiving 50mg likely to start enrolling in May.

SB 900 is designed to be a functional cure for HBV by increasing clearance of HBV surface antigen (SBsAg), the company website shows. The oral drug works by inhibiting viral replication and cause induction of intracellular interferon signaling pathways for antiviral defence, SEC filings show.

Spring Bank has a market cap of USD 90.7m.

by Reynald Castaneda in London
Spring Bank’s potential Phase III HBV trial should exhibit HBsAg reduction for clinical relevance, combo approach could supplement efficacy – experts

21 MAR 2017

• HBV DNA reduction not an impressive feature
• 700-1,000-subject, Phase III placebo-controlled
• Interferon combo could lead to longer results

If Spring Bank Pharmaceuticals’ (NASDAQ: SBPH) SB 9200 for chronic hepatitis B (HBV) moves on to Phase III, it should use surface antigen (HBsAg) clearance or reduction as a primary endpoint to demonstrate clinical value, experts said. Simply demonstrating HBV DNA reduction would not set it apart from already available therapies which are able to do so to very low levels, some noted.

Analysts have yet to detail Phase III design expectations. But experts agreed Phase III should also show SB 9200 efficacy in carriers and noncarriers of HBV e antigen (HBeAg) viral protein, a marker of HBV’s different stages of development. Cirrhotics and patients not appropriate for interferon therapy should also be enrolled to paint a bigger picture of SB 9200’s safety profile, some noted.

Whilst an analyst report states SB 9200 could become a component of a future HBV regimen with USD 1bn peak sales, it only gives the oral therapy a 25% probability of success for it becoming a part of a curing regimen. Consecutive use of SB 9200 and then Gilead Sciences’ (NASDAQ: GILD) Viread (tenofovir) could lead to longer-lasting HBsAg decrease, and therefore SB 9200 could be worthy of a regimen inclusion, some said. Perhaps SB 9200 could also be matched with interferon-based therapies for better treatment durability, one expert added.

Spring Bank did not respond to a request for comment.

This news service reported 16 March that SB 9200’s mechanism gaps and expert scepticism on animal data makes it hard to estimate Phase IIa success prospects. SB 9200 works by triggering the host immune system to induce interferon within hepatic cells and inhibiting viral nucleic acid synthesis (Korolowicz, KE, et. al. PLoS One. 2016 Aug 23;11(8)e0161313). Chronic HBV patients are defined as having detectable HBsAg during six-monthly tests, said Dr Mark Kane, an independent immunisation policy consultant in Seattle, Washington.

**HBsAg CLEARANCE KEY FOR SUCCESS**

Before moving on to Phase III, there should be clearer evidence SB 9200 can knock down HBsAg levels for a long period of time to draw development/commercial success confidence, Kane said. Because patients are lifetime HBV carriers, having clearance for only a few months would be clinically insignificant, Kane and a Phase IIa investigator noted. The ongoing Phase IIa trial does not have HBsAg clearance/reduction as a primary or secondary endpoint, but has HBV DNA decline as an efficacy primary endpoint (NCT02751996), ClinicalTrials.gov shows.

During Phase III, SB 9200 should show HBsAg clearance or a significant HBsAg reduction of around 2 log10, a Phase IIa investigator said. But HBsAg clearance would be better than a log10 reduction because a decline could still lead to some HBV patients being able to infect healthy people, Kane said.

The investigator noted relapse rates should be considered as a secondary endpoint.

Demonstrating efficacy in HBsAg is key for future SB 9200 commercial success because Viread and Bristol-Myers Squibb’s (NYSE:BMY) Baraclude (entecavir) already reduce HBV DNA, said Kane and Dr Nikolai Petrovsky, director of endocrinology, Flinders Medical Centre, Adelaide, Australia. Viread and Baraclude require lifetime use, Dr Stephen Ryder, consultant hepatologist, Queen’s Medical Centre in Nottingham, England. Viread and Baraclude are able to knock down HBV DNA levels to less than 1 log10 or less, but HBsAg levels are still an issue with patients, both Kane and Petrovsky said. Viread and Baraclude show HBsAg clearance in only 10% of all patients, the investigator said.

**Before moving on to Phase III, there should be clearer evidence SB 9200 can knock down HBsAg levels for a long period of time to draw development/commercial success confidence.**

Whilst reducing HBV DNA levels is still important as it prevents progression to cancer, liver cirrhosis, and makes HBV noninfectious, DNA is easier to clear than surface antigen, Kane and the investigator said.

**ASIA-PACIFIC IDEAL TRIAL LOCATION**

Phase III should have around 700-1,000 subjects as with other HBV trials, the investigator said. It could be easier to find subjects in Taiwan, Korea, Hong Kong, Australia and New Zealand, as observed in other HBV trials, the investigator added.
To be considered for the trial, patients should have elevated alanine transaminase levels, an indicator of chronic HBV, the investigator said. HBV DNA should be 2000 IU/ml as this is an indicator that the patient requires treatment, the investigator added. A lower DNA level indicates the disease is inactive or is an unusual HBV case, the investigator explained.

Future trials should also separate subjects who are HBeAg carriers and noncarriers, as this could affect SB 9200’s efficacy profile, the investigator said. Expression of HBeAg does not eliminate HBV replication, which could be an indication it is essential to this process, public information shows.

It is important to separate these groups because HBeAg carriers may be harder to treat since their HBV loads are higher at 7-8 log10, which means clearance may be harder to achieve, the investigator said. Kane explains knocking down as much as 4 log10 may lack clinical significance because the patient could still have a high HBV load. Ryder said HBeAg noncarriers are challenging to treat as they may require longer treatment periods to see clinical benefit, based on real-world experience.

Future trials should also separate subjects who are HBeAg carriers and noncarriers, as this could affect SB 9200's efficacy profile.

Since Phase II trials focused on noncirrhotic subjects, future trials could investigate SB 9200 in subjects with cirrhosis to add more detail on the therapy’s safety profile, the investigator said. Subjects who are not appropriate for interferon-based therapy or have renal disease should also be considered, the investigator added. Petrovksy said it is key SB 9200 does not lead to liver damage, considering its mechanism is related to liver cells.

SB 9200 IS COMBO WORTHY

Part B of the Phase II trial will investigate SB 9200 as a 12-week monotherapy or followed by Viread, ClinicalTrials.gov shows. A combination approach is logical since two points of attack could lead to better efficacy, Ryder said. This should be further investigated in Phase III, which should have three arms: a placebo arm, monotherapy, and combination with Viread, the investigator and Ryder said.

Preclinical data shows the order in which SB 9200 is used with Viread is significant, Kane noted. If SB 9200 is used first before Viread, there could be much higher HBsAg and longer-lasting effect, rather than the reverse, he noted. But Petrovksy said there needs to be more detail on how these two drugs work together.

The investigator said future trials could investigate SB 9200 with interferon-based treatments. SB 9200 could decrease the viral load and then interferon could strengthen immunomodulation, which would then extend the efficacy durability, the investigator explained. Interferon only is efficacious in 10% of all patients, but having a higher viral load clearance before interferon use could increase these rates, the investigator noted.

Spring Bank has a market cap of USD 104.7m.

by Reynald Castaneda in London
AbbVie’s G/P FDA approval for HCV supported by efficacy data, genotype 3 a potential blind spot – experts

1 FEB 2017

- High SVR12 rates regardless of genotype and cirrhosis
- Complete genotype 3 data needed to quell reservations
- Drug-drug interaction AEs possible with more patients

AbbVie’s (NYSE:ABBV) ABT-493 (glecaprevir)/ABT-530 (pibrentasvir) (G/P) for hepatitis C virus (HCV) has a clear argument for FDA approval based on high response rates reported in several Phase III trials, experts agreed. The drug combination was able to show efficacy in treatment-naive subjects, as well as in subjects with renal impairment, one expert added.

Whilst some experts had some reservations about G/P efficacy in genotype 3 - as full data has yet to be released and it is the hardest-to-treat genotype - one expert said available early results should ease concerns. Also, whilst Phase III trials only enrolled a few HCV subjects with cirrhosis, this shouldn’t be an approval barrier because real-world numbers of these types of patients are decreasing, some noted.

G/P is unlikely to be used in decompensated cirrhotic patients like other protease inhibitor therapies, some experts added. Whilst G/P so far has a positive safety profile, an adverse event registry may be needed to keep track of real-world side effects like drug-drug interactions, some added.

G/P’s application has been submitted to the FDA for approval but a PDUFA date has yet to be announced. An analyst report states G/P has a high likelihood for regulatory approval with AbbVie’s whole HCV portfolio growing to USD 2.6bn in 2020.

Glecaprevir is an HCV NS3/4A inhibitor and pibrentasvir is an NS5A inhibitor, the company website states. NS3/4A supports viral polyprotein maturation and evasion of the host’s innate antiviral immunity, while NS5A helps in RNA replication.

**RESPONSE RATES UNDERSCORE APPROVAL PROSPECTS**

All four experts agreed approval is primarily supported by G/P’s exceedingly high response rates during Phase III trials. In the ENDURANCE-1 trial (NCT02604017), 99% (348/351) of treatment-naive genotype 1 subjects without cirrhosis had sustained viral response for 12 weeks (SVR12) after eight weeks of therapy, a November 2016 media release states. In the SURVEYOR-2 trial (NCT02243293), 97% (196/203) of treatment-naive genotypes 2, 4, 5 and 6 subjects without cirrhosis had SVR12 after eight weeks, it shows.

G/P also hit these high SVR12 rates without interferon and ribavirin, traditionally used to help boost HCV therapy efficacy, noted Dr Antonio Craxi, gastroenterology professor, University of Palermo, Italy. G/P was also able to show Phase III efficacy in patients with renal impairment, with SVR not achieved by available therapies, said Craxi on the sidelines at this week’s Paris Hepatology Conference. In the EXPEDITION-4 trial (NCT02651194), 104 subjects with genotypes 1-6 with renal impairment had an SVR12 of 98%, he noted.

However, some reservations regarding G/P efficacy on genotype 3 still persist as full data has yet to be revealed with this hardest to treat population, said a Phase III investigator. A second Phase III investigator added full ENDURANCE-3 data should be released at this year’s EASL International Liver Congress in Amsterdam. However, initial Phase III data is reassuring, Craxi said. In the Phase III ENDURANCE-3 trial (NCT02640157), 95% (196/203) of treatment-naive noncirrhotic genotype 3 subjects had SVR12 after eight weeks, the aforementioned media release said.

The first investigator noted SVR12 rates 90% and above are welcome since the other 10% is usually due to poor patient adherence.

**EFFICACY IN CIRRHOTIC SUBJECTS DRAWS OPTIMISM**

Another feature supporting approval is G/P’s efficacy in patients with cirrhosis, Craxi said. For example, in the SURVEYOR-2 trial, genotype 3 patients, 40 treatment-naive compensated cirrhotic patients had SVR12 of 98% (39/40) after 12 weeks of treatment, whilst 47 nonresponsive cirrhotic patients had 96% (45/47) after 16 weeks of treatment, he noted.
Although these cohort sizes of cirrhotic subjects in the Phase III trials is small, cirrhotic subjects are unlikely to be an approval issue as real-world numbers are decreasing, explained Dr Angelos Hatzakis, head of the National Retrovirus Reference Center, Athens, Greece. For example, in the UK, cirrhotic patients have dripped from 70-30% since the advent of HCV therapies as they are the type of patients that were treated first, the first investigator said.

However, it is still important to demonstrate efficacy in cirrhotic patients, such as a postapproval trial, as there could still be some patients yet to be found via HCV screenings, Hatzakis said.

An AbbVie spokeswoman said its filings feature data from eight studies which evaluated 2,300 subjects across major HCV genotypes and in patients with specific treatment challenges.

**NOT RECOMMENDED FOR DECOMPENSATED CIRRHOTIC PATIENTS**

Because G/P is a protease inhibitor, it is unlikely to be approved in patients with decompensated cirrhosis, Craxi noted. This is because protease inhibitors as a class have unpredictable pharmacokinetic (PK) profiles in such patients, Craxi and the first investigator explained. The second investigator added protease inhibitors need to be heavily metabolised for efficacy and if the liver is decompensated, G/P is not metabolised enough to reach efficacious levels. Hatzakis said G/P was not tested in this niche group.

This is unlikely to prevent an FDA approval, however, considering the number of decompensated cirrhotic patients is also dwindling as they have either been cured or are beyond treatment, Craxi said. These patients are usually prescribed with Gilead Sciences’ (NASDAQ:GILD) Epclusa (sofosbuvir/velpatasvir) or Gilead’s Sovaldi (sofosbuvir) plus Bristol-Myers Squibb’s (NYSE:BMY) Daclizum (daclatasvir) if there are no renal issues, Craxi said. But if renal issues present, there are no available options, he noted.

All experts noted G/P’s positive safety profile also bolsters its approval chances. In the ENDURANCE-1, ENDURANCE-3 and SURVEYOR-2 trials, the most common side effects were headache and fatigue (no more than 20% of subjects), with no discontinuations reported. In contrast, Gilead’s voxilaprevir can cause diarrhoea and nausea in one in every four subjects, Craxi noted. Voxilaprevir is a part of Gilead’s three-component Phase III HCV drug which also contains sofosbuvir and velpatasvir.

The second investigator noted postapproval registries are nonetheless important as some side effects could appear with more patients using the drug. For example, for example, generic drug antiarrhythmic amiodarone with Sovaldi has been reported to lead to tachycardia with one reported death, the second investigator said. The first investigator said second-generation protease inhibitors could have drug-drug interactions which should be monitored postapproval.

The spokeswoman said it is premature to speculate G/P’s real-world side effects. But, if approved, the company will monitor and evaluate safety data just like its other approved therapies, she said.

AbbVie has a market cap of USD 99.5bn.

by Reynald Castaneda in London
AbbVie’s G/P could have SOC slot in HCV due to short eight-week therapy, triple combo competition an unlikely success spoiler – experts

2 FEB 2017

- Marketed therapy needs 12-16 weeks to work
- Very large trials needed to separate high SVRs
- Triple-ingredient is high risk for drug-drug AE

AbbVie’s (NYSE:ABBV) ABT-493 (glecaprevir)/ABT-530 (pibrentasvir) (G/P) for hepatitis C virus (HCV) has potential to become standard of care (SOC) due to its short eight-week treatment duration, experts agreed. G/P’s pangenotypic efficacy would also do away with genotyping, also speeding up treatment, they added.

Head-to-head trials would be ideal to spell out G/P’s efficacy compared with competition, one expert said. However, they could be hard to perform due to the high price of already available therapies and the need for very large trials to tease differences between high sustained viral responses (SVRs), some added.

Triple-ingredient HCV therapies under investigation could be potential spoilers for G/P success, some experts said. However, this is unlikely since G/P is able to reach high efficacy levels even with just two ingredients, some noted. Two-ingredient drugs also reduce risk of resistance and side effects, some added.

G/P has been submitted for FDA approval but a PDUFA date has yet to be announced. G/P has a high likelihood for approval with AbbVie’s whole HCV portfolio growing to USD 2.6bn in 2020, an analyst report shows.

This news service reported 1 February G/P’s argument for FDA approval is supported by SVR for 12 weeks (SVR12) of 95-99% in all genotypes. However, efficacy in genotype 3 is a blind spot since complete data will be unveiled in April at the EASL International Liver Congress in Amsterdam, some experts said.

Glecaprevir inhibits NS3/4A, a protease which supports viral polyprotein maturation and evasion of the host’s innate antiviral immunity, the company website states. Pibrentasvir inhibits NS5A, another protease which helps in RNA replication.

SHORTER THERAPY DURATION A DISTINCT EDGE

All experts agreed an eight-week treatment period versus the standard 12-week period is G/P’s distinct advantage. A shorter duration could mean less expensive overall treatment costs per patient, said a Phase III investigator and Dr Angelos Hatzakis, head, National Retrovirus Reference Center, Athens, Greece. Also, treatment failure due to nonadherence could be overcome by a shorter therapy period, said Dr Antonio Craxi, gastroenterology professor, University of Palermo, Italy.

The three most commonly used HCV therapies are Gilead Sciences’ (NASDAQ:GILD) Harvoni (sofosbuvir/ledipasvir) and Epclusa (sofosbuvir/velpatasvir), as well as Merck’s (NYSE:MRK) Zepatier (elbasvir/grazoprevir), said Craxi on the sidelines at this week’s Paris Hepatology Conference. Harvoni is used in patients with genotypes 1, 4, 5, 6 as a 12-week therapy for most patients, whilst Epclusa is used in genotypes 2 and 3 for 12 weeks, he added. Harvoni can be used for eight weeks but only for genotype 1b patients and ones with low viral counts, the first investigator and Craxi said. On the other hand, Zepatier is only used in genotypes 1 and 4, requiring 12 or 16 weeks of therapy, Craxi added.

Another G/P advantage is that it can be used in genotypes 1 to 6, all experts agreed. Whilst Epclusa is also pangenotypic, Epclusa’s real-world efficacy is weak in genotype 3, and thus could be an opportunity for G/P, the first investigator said. Despite Epclusa’s pangenotypic label, Harvoni is preferred in noncirrhotic genotypes 4-6 patients as it requires a shorter therapy period, Craxi noted. G/P’s pangenotypic nature is an advantage since genotyping adds treatment cost and could also delay therapy for a couple of weeks, Hatzakis and a second Phase III investigator.

G/P also doesn’t need ribavirin to boost efficacy, is easy to take as a daily oral therapy and has a positive efficacy profile, boosting market success potential, an AbbVie spokeswoman and a third Phase III investigator noted. G/P is a welcome addition to the HCV therapy arsenal as increasing competition could lead to lower prices, the first and third investigator said. The spokeswoman said it is premature to speculate about pricing.

HEAD-TO-HEAD TRIALS IDEAL BUT CHALLENGING

It would have been ideal to see a head-to-head comparison between G/P and all potential competition to emphasise
its superiority, the second investigator said. But trial comparisons are problematic because individual studies could be run in different regions and have different inclusion/exclusion criteria (like fibrosis stage or pretreatment requirements) that could favour one therapy over another, he explained.

However, such trials could be expensive due to the price of already available therapies, the second investigator said. For example, the Phase III ENDURANCE-3 trial (NCT02640157) investigating G/P efficacy in genotype 3 patients only has a comparator arm featuring the combo of Gilead’s Sovaldi (sofosbuvir) plus Bristol-Myers Squibb’s (NYSE:BMY) Daklinza (daclatasvir), he said. Adding another arm with Epclusa would have raised cost, he explained. Per course of treatment, Sovaldi costs USD 84,000, Daklinza costs USD 63,000 and Epclusa costs USD 74,760, public information shows.

The third investigator added head-to-head trials would need very large cohort sizes to truly differentiate efficacy because these therapies have very high SVRs. The spokeswoman said its filings feature data from eight studies which evaluated 2,300 subjects across major HCV genotypes and in patients with specific treatment challenges.

A potential spoiler for G/P market success is many patients are treated by already available HCV therapies, Hatzakis said. Craxi said postapproval trials investigating G/P efficacy in delaying reinfection could be an ideal next step to gain a market foothold. About 20-25% of patients could get reinfected within a year, he noted.

But trial comparisons are problematic because individual studies could be run in different regions and have different inclusion/exclusion criteria (like fibrosis stage or pretreatment requirements) that could favour one therapy over another.

Clinicians are already familiar with available therapies and could be hesitant to switch, the third investigator added.

**G/P COULD EDGE TRIPLE COMBO THERAPIES**

A potential G/P competition in future is the arrival of triple combo HCV therapy, said the first investigator. G/P, which features two protease inhibitor elements, doesn’t have a nucleotide inhibitor element, said Raymond Schinazi, director, Viral Eradication Scientific Working Group, Emory University, Atlanta, Georgia. Gilead’s triple combo sofosbuvir/velpatasvir/voxilaprevir has been submitted for FDA marketing application and is anticipated to launch this year, public information shows.

However, G/P should still be competitive since it is still very potent even with two compounds, which could actually reduce the risk of HCV resistance, the first investigator said. Three-molecule therapies could also increase the risk of drug-drug interaction, which is critical because HCV patients also take other medications to manage hypertension, diabetes and other conditions, the first investigator said. For example, Johnson & Johnson (NYSE:JNJ) Janssen’s Olysio (simeprevir) may have positive efficacy but uptake is low due to drug-drug interaction concerns, Schinazi said.

The three-molecule approach is likely to be reserved as a rescue therapy which is very niche, the first and second investigator said. At present, salvage therapy is extending available therapy for 16 weeks, Craxi said.

AbbVie has a market cap of USD 98.4bn.

by Reynald Castaneda in London
Hepatitis Drug Trends

According to BioPharm Insight data the combined sales of HCV drugs were over USD 16bn in 2016 but will fall to under USD 8bn in 2021. Gilead’s Harvoni (ledipasvir/sofosbuvir) would display the largest fall from USD 9.1bn in 2016 to USD 2bn in 2021. (Graph 2, p. 25)

Graph 1. Global Hepatitis C Virus Sales Forecasts From 2016 - 2021

All data comes from the BioPharm Insight database and BioPharm Insight’s proprietary intelligence. The report reflects as of 20 May 2017. Figures may vary from day to day as the database is continually being updated.

Forecast sales figures for the above drugs are calculated as the median of the analyst report forecasts for each specific drug. Extreme outliers are excluded. All forecasts are converted to USD based on the conversion rate of the report’s publication date.
Promethera’s Phase IIa HepaStem side effects for ACLF may be hard to distinguish due to severe disease, unmet need driving efficacy hope – experts

5 MAY 2017

- Mild ACLF ideal for safety/efficacy endpoints
- Senescence death may stop tumour generation
- HepaStem may be worthy as bridging therapy

Promethera Biosciences’ Phase IIa HepaStem for acute-on-chronic liver failure (ACLF) has foggy safety projections since disease symptoms are so severe it could be hard to identify what adverse events (AEs) are caused by the treatment, experts agreed. However, whilst an autoimmune attack may be unlikely, issues such as allergic reaction, toxic substance accumulation or tumour generation should be monitored, some noted.

HepaStem’s efficacy signal is also hard to predict due to no previous drug data in ACLF patients, experts said. Still, the Phase IIa trial design details are encouraging for success as the enrolment criteria and secondary efficacy endpoints may make it easier to see a treatment signal in a complicated disease, some noted.

The 12-subject, open-label Phase IIa trial is investigating two doses of HepaStem in 28 days (NCT02946554), with the primary endpoint looking for AE signals and secondary endpoints focusing on efficacy. ClinicalTrials.gov shows. The trial has a primary completion date in October. The trial has yet to enrol subjects, it shows, but an investigator said enrolment is imminent with the trial aiming to treat three subjects at a time.

A Promethera spokesperson said it will communicate aspects of its developmental candidates once clinical data is available.

HepaStem is an orphan stem cell therapy which administers 50 million human adult liver-derived cells to the subject’s liver, the company website shows.

HEPASTEM SIDE EFFECTS MAY BE HARD TO DISTINGUISH

ACLF is a combination of liver decompensation with organ failure, said Dr Vicente Arroyo, professor of medicine, University of Barcelona Medical School, Spain. Dr Didier Samuel, Phase IIa investigator and professor of gastroenterology, Université Paris-Sud, Villejuif, France, added ACLF is a multifactorial disease, which starts off with a decompensated, cirrhotic liver, then infection and bleeding followed by one or more organ failures, with some patients experiencing gastrointestinal bleeding and sepsis. Decompensation could be caused by alcoholic steatohepatitis or a hepatitis infection, Samuel said.

ACLF’s complexity indicates the condition perpetuates body failure and thus HepaStem AEs would be hard to predict, said Dr Anil Dhawan, director, Paediatric Liver, Gastrointestinal and Nutrition Centre, King’s College Hospital, London. The trial’s enrolment of mild subjects with ACLF grade 1 or ACLF grade 2 patients without circulatory or respiratory failure is thus a positive enrolment criteria, Samuel said. Enrolling more severe patients could mean AEs related to HepaStem would be more difficult to determine, he said.

Likely AEs that could surface may relate to the stem cell injection, Samuel said. However, if a subject dies, it could still be hard to distinguish if it was caused by the disease, as patients already have high morbidity/mortality rates, or injection complications, Samuel said on the sidelines of last month’s EASL International Liver Congress in Amsterdam.

Dr William Bernal, consultant and honorary senior lecturer in liver intensive care medicine, King’s College Hospital, London, noted an autoimmune attack is unlikely as the cells used are not immunogenic, with Samuel adding mesenchymal stem cells are usually well-tolerated. This is in contrast to mature cells where the risk of cell rejection is high, Samuel added. In the real world, stem cell inoculation of children with impaired liver synthesis is regarded as a safe process since it leads to limited systemic inflammation, and this could be expected with HepaStem, Arroyo said. But Bernal said it is challenging to speculate if AEs seen in other procedures would apply to HepaStem.

In any infusion of any biological product, AEs that could be expected include allergic reactions, Arroyo said. Bernal added the biological product could induce the accumulation of toxic substances like phenols and thus should be monitored. Bernal noted it is an advantage that HepaStem uses human cells because using animal-derived cells would have increased the likelihood of zoonosis or perhaps introducing latent viruses.

Arroyo added blood coagulation should also be monitored, since this could be significant in ACLF patients who already...
have poor liver function. Samuel said it is encouraging HepaStem has a two-dose approach since too much cells injected at one time could lead to thrombosis (blood clot) of the vessels.

In the long-term, a potential AE is tumour generation from the mesenchymal cells, as they could lead to clonal cell expansion, Samuel said. Immortalised cell lines have been observed to lead to tumours once injected in humans, Bernal said. Reassuringly, mesenchymal cells most likely die of senescence before tumour generation, Samuel noted. He added HepaStem has been investigated preclinically and has yet to show tumour risk.

**LACK OF OPTIONS DRAWS HOPE FOR EFFICACY**

Dhawan said it is challenging to predict efficacy, the secondary endpoints, with lacking data in humans. But with patients dying within less than six months, the need is there to expand available treatment options, Samuel and Bernal added. Samuel said the current standard of care is antibiotics at intensive care, then transplantation. If the patient has severe renal failure, generic terlipressin plus albumin is a specific organ failure treatment used, Arroyo said.

That said, the inclusion criteria focusing on mild ACLF means patients could be more susceptible to treatment, and thus there is a low success bar, Dhawan and Bernal said. More severe patients are very hard to treat, so enrolling milder patients is encouraging when an efficacy signal is needed to be seen in a few weeks, Dhawan said.

The inclusion criteria focusing on mild ACLF means patients could be more susceptible to treatment, and thus there is a low success bar.

The trial’s secondary efficacy endpoints are appropriate as they evaluate the evolution of the patient’s disease, Samuel said. Efficacy is assessed by mortality, liver transplantation, and disease scoring rates after 28 days, 3 months and one year, ClinicalTrials.gov shows. However, it could be hard to differentiate the effect of HepaStem and antibiotics, Samuel noted. To overcome this issue, biochemical changes are warranted to show an efficacy signal, he explained. Bilirubin, creatinine, liver function and albumin values are also secondary endpoints, ClinicalTrials.gov shows.

The question of whether HepaStem has enough stem cells for efficacy is hard to predict because this depends on the patient, Bernal said. Patients who have a single gene defect may not need a large mass of cells to see change but patients with compromised liver function may need a significant number of cells, Bernal added. Also, there needs to be enough stem cells injected that survive in a liver environment that is toxic (due to sepsis) and has inflammation, Bernal added. The advantage of 50 million stem cells is that it’s not too much that it would cause issues in preparation and injection, he said.

Because HepaStem’s stem cells do not have the same function as normal hepatocytes, it is worth noting the treatment is not designed to replace liver cells, Samuel said. This means that HepaStem may be ideal as a form of bridging therapy, where patients are treated with HepaStem to allow them to become qualified for liver transplant, Bernal and Samuel said. A significant number of patients may be ineligible for transplant immediately because they may be too vulnerable for transplant or due to their alcoholic steatohepatitis, Samuel said.
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Boston
41 Farnsworth St, 1st Fl
Boston, MA 02210
T +1 781 762-9450

New York
441 Lexington Ave
New York, NY 10017
T +1 646 395-5460

London
John Carpenter House
7 Carmelite St
London EC4Y 0BS, UK
T +44 (0) 20 7936 6400