# TREATMENT STRATEGIES
## HEPATOLOGY

Volume 8 Issue 1

- Congress Review - ILC 2022 - London
- Preview ILC 2023 - Vienna
- Advanced Liver Disease
- Acute Hepatic Porphyria
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- Hepatitis
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- Thrombocytopenia
- Ultrasound
- Wilson Disease

**Review of the Annual Meeting of EASL - ILC 2022 - London and Preview ILC 2023 - Vienna**

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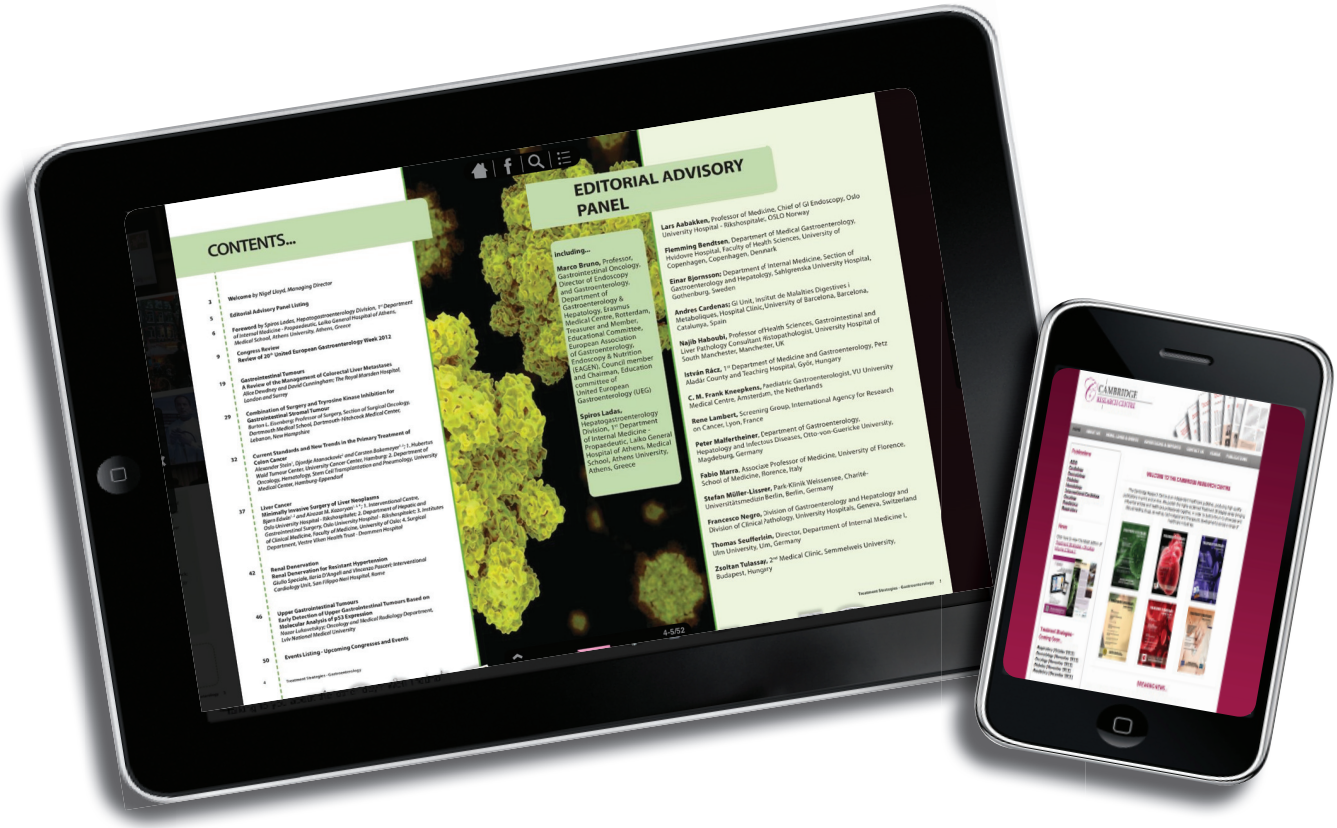


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# TREATMENT STRATEGIES - HEPATOLOGY - VOLUME 8 Issue 1

**TREATMENT STRATEGIES - HEPATOLOGY - August 2022**

**The Cambridge Research Centre**

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## Welcome...

Welcome to the latest issue of *Treatment Strategies Hepatology*, which provides a series of stories on the latest hepatology research and news from the International Liver Congress (ILC) 2022. This issue includes a comprehensive review of the entire congress from the biggest news stories to fascinating abstracts and peer-reviewed articles and posters, all for your perusal.

Perhaps the biggest news this last year was that, after two years of online meetings, the International Liver Congress (ILC), European Association for the Study of Liver's (EASL) annual meeting, was allowed to take place in person in London.

Following a three year wait to meet in-person since the 2019 Vienna congress, the European Association for the Study of Liver (EASL) International Liver Congress (ILC) was held in London, from 22nd– 26th June. This year marked the 57th anniversary of the annual ILC congress, and welcomed almost five and half thousand delegates on site, and close to one and half thousand virtually from over a hundred countries.

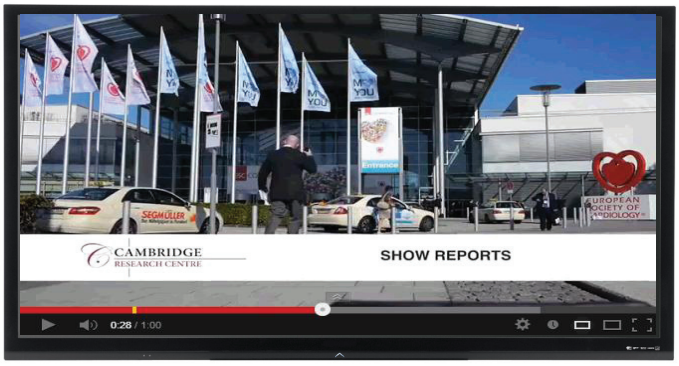
We hope this edition provides you with some fascinating insights in to the most up-to-date research in hepatology as well as information that you can incorporate into your daily practice. We are continuing to see many major developments in hepatology and hope to see more as the year continues.

See you all at next year's congress in Vienna.

**Nigel Lloyd,**
Managing Editor

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.





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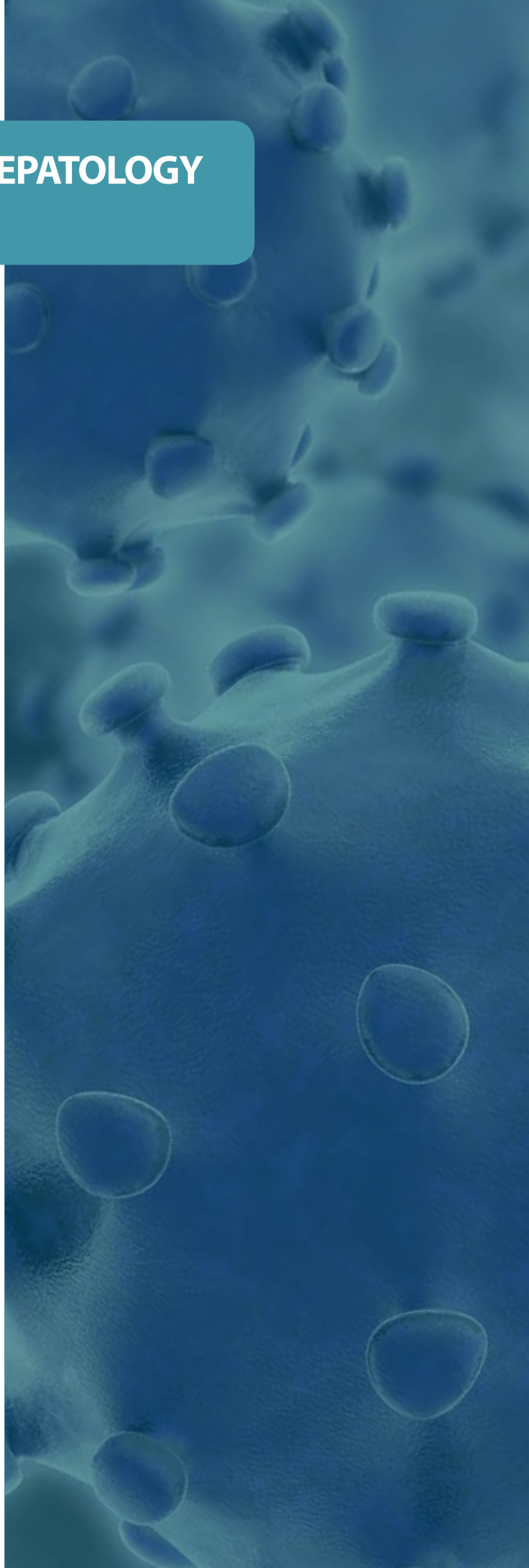
# TREATMENT STRATEGIES - HEPATOLOGY
## Editorial Advisory Panel





## Aims and Scope

*Treatment Strategies* (TS) is an online and in-print (to order), peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline. TS allows healthcare professionals to stay abreast of key advances and opinions across Europe. TS aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

TS is published throughout the year and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

TS publishes 13 therapeutic area journals, which provide concise coverage of salient developments at the leading European congresses. These are published throughout the year, approximately 4 weeks after the relevant meeting or congress.

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# The International Liver Congress™ 2022

## 22nd - 26th June 2022 - London

# Annual Meeting of the European Association for the Study of the Liver (EASL)

**Nigel Lloyd**

*Treatment Strategies*, Cambridge Research Centre.

Perhaps the biggest news this last year was that, after two years of online meetings, the International Liver Congress (ILC), European Association for the Study of Liver's (EASL) flagship annual meeting, has been allowed to take place in person in London.

Following an almost three year wait to meet in person since the 2019 Vienna congress, the European Association for the Study of Liver (EASL) International Liver Congress (ILC) was held in London, from 22nd– 26th June. This year marked the 57th anniversary of the annual ILC congress, and welcomed almost five and half thousand delegates on site, and close to one and half thousand virtually from over a hundred countries.

The opening ceremony, led by Thomas Berg, General Secretary of EASL, brought attendees through the array of interesting sessions that ILC 2022 had on offer this year, including exclusive online material for hybrid attendees. This year's theme for the ILC congress focused upon the association's mission to 'savour science together again'.

Berg communicated the importance of coming together to inspire communities, and celebrate science in unison in the aftermath of the COVID-19 pandemic. With the ILC's core mission succinctly conveyed, Berg presented the diverse array of hepatology-focused sessions taking place, including the new initiative of EASL's studio sessions broadcast live from this year's congress. The groundbreaking format of these exclusive sessions allowed leading lights in the field to interact with the attendees, sharing views on daily data interpretations and the associated clinical consequences. Berg elaborated further, on the development of the studio sessions, "necessity is the mother of invention," giving late-breaking updates to hepatologists around the world. The year-round online content, which consists of twenty three episodes, has already had over thirty thousand views in over fifty countries.

Berg presented and passed to Mario Rizzetto, Honorary President of ILC 2022. Rizzetto, who discovered hepatitis delta in 1977, began his talk by highlighting the significant impact of COVID-19 on the association. Following the challenges created by the pandemic, the governing board selected energy and efficiency, and decided to go digital for the last two meetings. With this year's congress almost being back to "business as usual," Rizzetto took the opportunity to convey the association's mission, of ensuring that the cohesion and scientific identity of European hepatologists remains untarnished. Rizzetto continued to

...Continued on page 15


# The International Liver Congress™ 2022
## 22nd - 26th June 2022 - London


# The International Liver Congress™ 2023
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# Prevention of Hepatitis C Viral Infection in Recipients of Viraemic Grafts - Pre-emptive Combination Therapy

*Treatment Strategies* reports from this year's International Liver Congress. Eight doses of combination therapy could prevent post-transplant complications associated with hepatitis C viral (HCV) transmission in patients receiving viraemic transplants. The combination therapy studied was glecaprevir/pibrentasivir (G/P) and ezetimibe, commencing on the day of surgery and continuing for 7 days after transplant of an hepatitis C virus viraemic, non-liver solid organ into HCV seronegative recipients.

The prospective, multicentre, open-label study, presented on 23rd June 2022 by Bashar Aqel (pictured above) of the Mayo Clinic College of Medicine in Phoenix, Arizona, USA, at the congress, assessed the efficacy and cost-effectiveness of pre-emptive combination of G/P plus ezetemibe therapy in thirty-eight HCV-seronegative patients receiving non-liver, HCV-viraemic, solid organ transplants.

Looking into the study, of the thirty-eight recipients, 63% were male and the median age was sixty years. Thirty-two patients received a kidney transplant, two received a kidney and pancreas transplant, three received a heart transplant, and one received a heart and kidney transplant.

To assess response to treatment, HCV RNA levels were monitored for twenty-four weeks post-transplant and patients were followed-up for one year to determine rates of patient and graft survival.

All recipients completed the eight-dose treatment course, which was assessed to be, well-tolerated. Post-operative monitoring revealed that twenty-eight patients had transient viraemia in the initial 2 weeks post-transplant, but all thirty-eight patients had undetectable HCV RNA levels by Week 4. These RNA levels remained undetectable at 13 weeks. One recipient died 65 days post-surgery secondary to acute subdural haematoma.

In terms of cost-effectiveness, Aqel presented that the cost of pre-emptive combination therapy was significantly less than standard therapy given in response to post-operative complications associated with HCV transmission.

In conclusion, Aqel reported that combination therapy with G/P and ezetemibe was effective at preventing HCV infection secondary to transplant of HCV viraemic non-liver, solid organs in 100% of HCV seronegative recipients.

Further to this, Aqel stated that the approach is cost-effective and could potentially eliminate the risk of post-transplant complications associated with HCV transmission. The findings from his work could increase the use of HCV viraemic grafts, which could, in turn, lead to reduced patient waiting times.

...Continued from page 11

share the visions and successes of the association. Their four-year plan was implemented to take strides in (Euorpean Union (EU)-level advocacy, with an aim of raising awareness of liver health in Europe. The EASL Campus platform has been an essential part of this mission; with over six thousand resources, twenty thousand registered users, and over a million page views, it has been a turning point in extending it's global digital reach. Clinical practice guideline sessions were presented, providing key updates to the attendees in conditions, including sclerosing cholangitis, haemochromatosis and pregnancy in liver disease, and cystic disease and hepatic encephalopathy.

The microphone was passed over to patient representatives affiliated with EASL. Marko Korenjak, President, European Liver Patients' Association, spoke at the ceremony of the importance and impact of patient groups, and how it is crucial to retain both passion and compassion. Korenjak detailed how by improving patient education to be as skilled as possible can greatly improve the management of conditions, all whilst retaining patient perspective.

Danjuma Adda, President, World Hepatitis Alliance (WHA), spoke of his personal life experience of both living with hepatitis B, and having people close to him also diagnosed with it. Resident in Nigeria, Adda explained how a cure for the disease is not currently affordable or accessible, which is a key factor in the alliance's aim to lead the fight against hepatitis. This important talk gave fascinating insights, and reiterated the importance of patient perspectives and representation.

Two members of the EASL Scientific Committee, Saskia van Mil and Virginia Hernández-Gea, presented the 2022 award ceremony. The EASL 2022 Emerging Leader Award recognises the outstanding achievements of young fellows. This year, Salavatore Piano, Assistant Professor, University of Padua, Italy, and María Jesús Perugorria, Principal Investigator in the Liver Diseases Group, Biodonostia Health Research Institute, San Sebastian, Spain, received this award for their respective research contributions. The EASL Nurses and Allied Health Professions Rising Star Award was presented to Catherine Wood, Hepatology Clinical Nurse Specialist, Royal Cornwall Hospital NHS Trust, UK, for her dedication to improving healthcare for all patients, specifically in the context of nonalcoholic fatty liver disease (NAFLD).

Berg closed the talks with a message to all attendees, wishing them an enjoyable congress whilst reminding them of the most engaging and interactive sessions available. With many networking sessions, interactive ePosters, and general assembly meetings, it is without doubt that this year's congress successfully allowed hepatologists around the world to 'savour science together'. Expert-led symposia presented emerging topics in the discipline, including hepatitis, cirrhosis, and optimal diagnosing strategies for liver disease. We, *Treatment Strategies*, were overjoyed to be a part of the in-attendance audience at the London event, and we look forward to next year's event which, as in 2019, will be held in Vienna.

# The Elimination of Viral Hepatitis C

*Treatment Strategies* reports from this year's International Liver Congress. The high intensity test and treat (HITT) programme, the result of a collaboration between the National Health Service (NHS) and the Hepatitis C Trust, a patient-led charity for those with viral hepatitis C (HCV), was presented at the congress, with data that highlighted the importance of the testing and treating inmates and the prevalence of the infection in different establishments throughout England. The programme was a sucess.

Successfully completed in thirty-four institutions in England (7 female prisons and 27 male prisons), the HITT programme saw NHS staff, nurses, and peers who have experience of HCV and prison life enter into prisons. Between June 2019 and September 2021, they offered 23,388 inmates prison-wing-based testing with point-of-care antibody tests, which were followed by blood draws or dried blood spot testing for conformation of viraemia in those who tested positive for HCV antibodies. 19,049 inmates agreed to testing and total of 1,234 inmates tested positive for HCV antibodies. Of these, 175 tested positive for the presence of HCV RNA. All individuals who were infected were offered therapy. A review of the data showed that HCV is more prevalent in prisons for females and that different prisons had different infection rates. The programme presented that remand prisons had a higher prevalence of HCV than re-settlement prisons.

The above results indicate that the HITT programme is invaluable to providing treatment to inmates, who are more likely to test positive for HCV than the general population, and to stop the infection from escalating. It also provided data for the prevalence of HCV in prisons and how it varies between the establishments.

# Let's Talk Primary Biliary Cholangitis

**Prof. Gideon Hirschfield**
University of Toronto, Canada

Given the online format of recent meetings, it was great to have the chance to interact, discuss and debate in person this year. A key focus of my clinical and academic work is primary biliary cholangitis (PBC), a so-called 'rare' liver disease that carries a substantial burden for patients, including an ongoing risk of developing cirrhosis. Given PBC is a less frequent condition than many other liver diseases (one in 1,000 women over the age of 40 years old live with PBC),[1] dynamic international meetings such as the ILC, enable us to raise awareness amongst those without specialist knowledge of how we can effectively diagnose, manage and monitor disease.

The industry sponsored symposium entitled "Current challenges in Primary Biliary Cholangitis: Debating the care odyssey" was a good example of an opportunity to discuss, learn and disseminate knowledge about PBC. This meeting captured many facets of PBC relevant to clinicians and patients. I was invited by Ipsen, along with two colleagues who are also experts in PBC, Prof. Cynthia Levy (USA) and Prof. David Jones (UK), to debate whether delayed diagnosis is the greatest challenge in PBC.

It was clear from the discussions that timely diagnosis was agreed to be key for the effective management of PBC, particularly as the disease can progress to a point at which a response to therapy becomes less likely. However, the counter argument highlighted that delayed diagnosis is not the only unmet need in PBC. Without effective, disease modifying treatments that also address symptoms, management of PBC can be challenging. Early-stage disease needs to be diagnosed efficiently and successfully, but this should not detract from the need for effective therapy in already identified high-risk patients. In addition, symptom control and quality of life matter greatly, and this should be considered when developing new treatments and making management decisions.

The debate led to many clinical points about PBC care being discussed. The management of PBC is rightly increasingly dynamic, as new pharmacological innovations are in development, and our practice needs to adapt to these changes.[2–4] We continue to step closer to the goal of providing the best care to every patient, no matter where they live.

PBC, and related cholestatic liver diseases, were hot topics throughout ILC, with presentations on research in the inflammatory and cholestatic components of disease, disease-specific quality of life assessment tools, and population-based data reporting care practices. Other important topics discussed included treatment targets and how we can provide lifelong and personalised treatment to patients with this chronic autoimmune liver disease. The identification of high-risk patients, with insufficient response to standard of care, who require second-line and subsequent treatment also remains a challenge. Finally, the vexed topic of overlap syndrome remains an important theme for many conversations about PBC. However, there is hope that as we are better able to treat patients with PBC with more effective therapies, earlier in their disease, we may indeed see less patients with overlap features as part of their disease course.

As we look to the future, we are entering a new era, where a greater understanding of the disease alongside therapeutic advances, will equip us to offer more impactful interventions for patients living with PBC.

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3. Louie JS *et al* Clinical Liver Disease 2020;15:100–104
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# Hepatitis Delta Clinical Trials - Results Announced

This year's congress saw significant attention given to hepatitis delta (HDV), as new treatments continue to move through the pipeline and more widespread approval for prescription of current treatments is sought.

The US-based pharmaceutical company Gilead Sciences, Inc. demonstrated with results from a Phase 3 clinical trial that treatment with Hepcludex (bulevirtide), the first medication ever approved for HDV, has been shown to achieve significant response in chronic HDV. After 48 weeks, 48% of study participants who received different doses of treatment with Hepcludex achieved virological response (meaning a decline in hepatitis delta viral load, ALT normalisation, and a change in liver stiffness), compared to only 2% of those who had not received any treatment. When compared to results from clinical trials after 24 weeks, response rates to HDV only improved, showing the drug to be even more effective over time. Throughout the clinical trials, there have been no adverse events reported that are attributable to this treatment.

*"These results...not only highlight the important clinical role that bulevirtide has to play as a safe and effective treatment option for chronic HDV, but critically also demonstrate that with prolonged treatment, we can achieve higher response rates so we can better manage this rare, life-threatening disease in more people"*

Hepcludex has also been found to have a positive impact on the quality of life of individuals living with hepatitis delta, and their overall ability to manage the condition. There were improvements found in health distress, performance of daily activities related to hepatitis, emotional impact of hepatitis, and ability to work. This data reinforces the efficacy and safety of Hepcludex and hopefully strengthens the case for approving the drug in more parts of the world.

"As the most severe form of viral hepatitis, HDV presents a significant disease burden with high healthcare-related costs and until recently, no approved treatment options," said Heiner Wedemeyer, MD, Director, Clinic for Gastroenterology, Hepatology and Endocrinology at Hannover Medical School, and principal investigator of the study. "These results presented at ILC 2022 not only highlight the important clinical role that bulevirtide has to play as a safe and effective treatment option for chronic HDV, but critically also demonstrate that with prolonged treatment, we can achieve higher response rates so we can better manage this rare, life-threatening disease in more people."

Currently, Hepcludex has been conditionally approved by the European Commission for prescription in France, Germany, and Austria. It has not yet been approved by the United States Food and Drug Administration (FDA) or in other countries. A Biologics License Application was submitted by Gilead to the FDA in late 2021 for injection of 2mg of Hepcludex to treat adults with HDV and compensated liver disease. Hepcludex had previously been granted Breakthrough Therapy and Orphan Drug designations by the FDA and PRIority MEdicines (PRIME) scheme eligibility by the European Medicines Agency (EMA).

The second company to present their research findings was US-based Eiger BioPharmaceuticals, Inc. The two primary hepatitis delta drugs that they have in the pipeline are called lonafarnib and peginterferon lambda. One abstract presentation indicated that peginterferon lambda (lambda) had better antiviral activity and tolerability than peginterferon alfa (the previous version of this drug that has been used as the only somewhat effective, but off-label treatment for hepatitis delta since the early 1980s). Lambda has been shown to block production of new hepatitis delta virus very effectively. Additionally, lambda in combination with lonafarnib was found to lower levels of HDV RNA and decrease its production and release, more effectively than lambda by itself. Patterns in HBV DNA, hepatitis B surface antigen, and ALT were also observed as part of this study. In its Phase 3 D-LIVR study, which is assessing the safety and efficacy of lonafarnib in combination with ritonavir, with and without peginterferon alfa, Eiger has assembled the largest cohort of global participants in an HDV study, and therefore the largest body of data. Results from this study are anticipated by the end of 2022.

Further HDV news to come out of the conference was the announcement from Vir Biotechnology Inc. that they are beginning a Phase 2 clinical trial for VIR-2218 in combination with VIR-3434 for the treatment of chronic hepatitis delta. Initial data from this study is anticipated in 2023.

HDV is now receiving more attention than ever before and there is only more hope as new treatments are created, investigated, approved, and made available.

# Closing the Treatment Gap for Wilson Disease Community

FoCus Phase III trial evaluates new approach to copper mobilisation for patients with Wilson disease who have not seen meaningful innovation in decades.

## About FoCus(301)

FoCus (301) is a pivotal Phase III, randomised, controlled, rater-blinded trial designed to evaluate the efficacy and safety of ALXN1840 versus SoC in patients with Wilson disease aged 12 years and older. The primary endpoint assessed copper mobilisation over 48 weeks, defined as daily mean AUEC for dNCC. In the trial, 214 patients were enrolled in one of two cohorts on a 3:1 basis (treatment-experienced:treatment-naïve). Each cohort was then randomised 2:1 (ALXN1840:SoC). The first cohort enrolled 161 patients who received SoC (chelation therapy with penicillamine or trientine, zinc therapy or a combination of both chelation and zinc therapy) for more than 28 days and the second cohort enrolled 53 patients who were treatment-naïve or had received SoC for 28 days or less.[1,5] Key secondary endpoints assessed over the 48-week period included change in neurological function as measured by the UWDRS Part II and III.[1]

## About Wilson Disease

Wilson disease is an inherited condition in which the body's pathway for removing excess copper is compromised. Over time, that results in the build-up of excess copper levels in the liver, brain and other organs leading to damage that greatly impacts patients.[2] Although the disease is present at birth, the age of diagnosis occurs between five to 35 years.3,4 People can develop a wide range of symptoms, including liver disease and/or psychiatric or neurological symptoms.[2,3,4] In Wilson disease, excess copper build-up in organs and tissues can lead to liver disease as well as neurological and psychiatric symptoms.

Detailed results from the positive FoCus Phase III trial in Wilson disease showed that ALXN1840, an investigational once-daily, oral medicine, met its primary endpoint demonstrating three-times greater copper mobilisation from tissues compared to the standard of care (SoC) arm (Least Square Mean Difference [LSM Diff] 2.18 µmol/L; p< 0.0001), including in patients who had been treated previously for an average of 10 years.[1]

In the trial, people taking ALXN1840 experienced rapid copper mobilisation, with a response at four weeks and sustained through 48 weeks.[1]

*"These results have the potential to reframe the way doctors can think about the disease given that current therapies focus on removing copper from the blood."*

**Professor Karl Heinz Weiss, MD, Director, Department of Internal Medicine, Salem Medical Centre, Heidelberg**

Results from the trial were presented on 23rd June at the 2022 International Liver Congress (ILC) in London.

Wilson disease is a rare and progressive genetic condition in which the body's pathway for removing excess copper is compromised. This may result in the accumulation of copper in a person's liver, brain or other vital organs. Damage from excess copper build-up in tissues and organs may lead to symptoms of liver, neurological and psychiatric diseases, which may be irreversible.[2,3,4] Even after SoC treatment is initiated, some patients experience worsening of disease, especially of neurologic symptoms.[3,4]

Change in neurological scale scores and clinician-reported functional assessments with ALXN1840 treatment were also evaluated in a post-hoc analysis as secondary endpoints in the Phase III trial.[1]

## About ALXN1840

ALXN1840 is a potential new once-daily, oral medicine in development for the treatment of Wilson disease. This investigational, novel molecule is designed to selectively and tightly bind to and remove copper from the body's tissues and blood. ALXN1840 has been granted Orphan Drug Designation in the United States and orphan designation in the European Union

for Wilson disease.

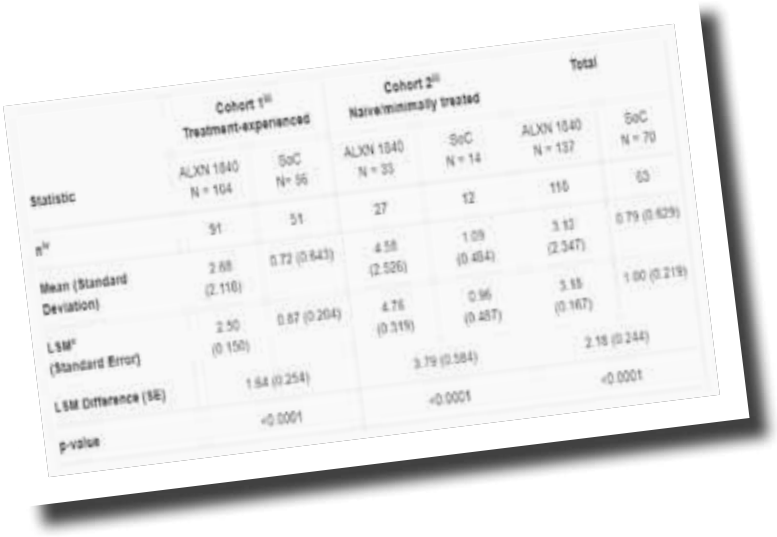
In patients who were symptomatic at baseline, there were greater improvements in neurological scores for those treated with ALXN1840 compared to SoC (Unified Wilson Disease Rating Scale [UWDRS] part II symptomatic ALXN1840 -1.7, SoC -0.8; UWDRS Part III symptomatic ALXN1840 -2.91, SoC -1.31). However, there were no significant differences between treatment groups observed at 48 weeks.[1]

Most patients in the trial had low symptom scores at baseline, so there was minimal room for total score improvement (UWDRS Part II ALXN1840 -0.6, SoC -0.3; UWDRS Part III ALXN1840 -2.20, SoC -1.02).1 As people with Wilson disease experience a highly varied degree of symptoms[4], this total score may not reflect the extent of disease severity.

ALXN1840 was well tolerated and the long-term safety and efficacy of ALXN1840 is being assessed in an up to 60-month extension period.[1]

Professor Karl Heinz Weiss, MD, Director of the Department of Internal Medicine at Salem Medical Centre Heidelberg and investigator in the FoCus Phase III trial, said: "These data from the largest global trial in Wilson disease to date show significant copper mobilisation from the tissues with ALXN1840, even in patients who were on standard of care for over a decade on average. These results have the potential to reframe the way doctors can think about the disease given that current therapies focus on removing copper from the blood. We are also encouraged by initial neurological improvement with ALXN1840 in those who were symptomatic and believe that assessing individual patient experiences may provide a better understanding of the impact on daily life."

Marc Dunoyer, Chief Executive Officer, Alexion, said: "Many people with Wilson disease continue to experience symptoms even after years of intervention with current therapies, illuminating an urgent need to re-evaluate the standard of care. Applying our 30 years of experience in rare disease clinical development, Alexion has conducted rigorous scientific research to bring fresh thinking to Wilson disease around the importance of copper mobilisation from the tissues. These data further our efforts to potentially introduce a novel treatment for patients who have gone decades without meaningful innovation."



| Statistic | Cohort 1[iii] Treatment-experienced | | Cohort 2[iii] Naive/minimally treated | | Total | |
|---|---|---|---|---|---|---|
| | ALXN 1840 N = 104 | SoC N= 96 | ALXN 1840 N = 33 | SoC N = 14 | ALXN 1840 N = 137 | SoC N = 70 |
| n[iv] | 91 | 51 | 27 | 12 | 118 | 63 |
| Mean (Standard Deviation) | 2.68 (2.110) | 0.72 (0.643) | 4.58 (2.526) | 1.09 (0.464) | 3.12 (2.347) | 0.79 (0.629) |
| LSM[v] (Standard Error) | 2.50 (0.150) | 0.87 (0.204) | 4.76 (0.319) | 0.96 (0.487) | 3.18 (0.167) | 1.00 (0.219) |
| LSM Difference (SE) | 1.64 (0.254) | | 3.79 (0.584) | | 2.18 (0.244) | |
| p-value | <0.0001 | | <0.0001 | | <0.0001 | |

## Summary of Efficacy and Safety Results

The primary endpoint gauged the daily mean Area Under the Effect Curve (AUEC) for directly measured non-ceruloplasmin-bound copper (dNCC)ii over 48 weeks. The dNCC parameter includes copper bound in an inert complex with ALXN1840.[1]

Most adverse events (AEs) were not considered serious (ALXN1840, 85.4%; SoC, 75.7%) and/or were not considered related to trial treatment (ALXN1840, 77.4%; SoC, 75.7%). The most common AE associated with ALXN1840 was a reversible increase in alanine aminotransferase levels (ALXN1840, 14.6%; SoC, 2.9%). Two deaths were also reported but were unrelated to ALXN1840.[1]

In addition to the Phase III trial, two ongoing mechanistic trials in Wilson disease are also underway. Alexion is working closely with health authorities worldwide and intends to submit these data for review.

*"These data further our efforts to potentially introduce a novel treatment for patients who have gone decades without meaningful innovation."*

**Marc Dunoyer, Chief Executive Officer, Alexion**

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# Dissemination of Knowledge Beyond the Event - ILC 2022

When the International Liver Congress arrived at London ExCeL in June 2022, it came with a three-layered legacy approach that focused on liver disease prevention, early diagnosis, and research.

The first layer, 'Love your liver' saw liver specialists deliver workshops in primary schools for pupils who were then invited to the congress to present what they had learned.

The second layer, 'Be nice to your liver' consisted of an on-site liver-screening booth for attendees and staff. Of those screened, three per cent were referred for further investigation.



The third layer, 'Hepatology is hot' ensured medical students participated in the congress to showcase the opportunities for a hepatology career.

*Treatment Strategies* report on the congress' legacy mission, how it fulfilled that mission and how next year's International Liver Congress in Vienna, Austria, will level up the three-layered legacy approach.

Maraika Geisterfer-Black, Advocacy. Policy and Public Health Intern, European Association for the Study of the Liver
"Impact and legacy are two distinct things and they are really coming up in the events industry. I think for associations, especially, it is important and in the next few years, maybe in the next decade, I think it will become almost a requirment for associations to expand their horizons beyond simply the event that they are hosting or the ecomonimic impact that we are bringing to host destinations and show our host cities that we are bringing social impact to them as well. As a medical association we want to create value for our delegates, of course, but we also want to improve the public health level for the cities we are working in. We want to disseminate knowledge beyond the event space"

The EASL/Lancet Commission : protecting the next generation of Europeans against liver disease complications and premature mortality.

Dr Emmanouil Tsochatzis, Senior Clinical Lecturer and Honorary Consultant in Hepatology, Royal Free London NHS Foundation Trust
" The EASL/Lancet Commission was published in 2022 after many years of hard work. It was a joint venture from the European Study of the Liver and The Lancet and the aim was to highlight the burden of liver disease in Europe and to provide actionable recommendations"

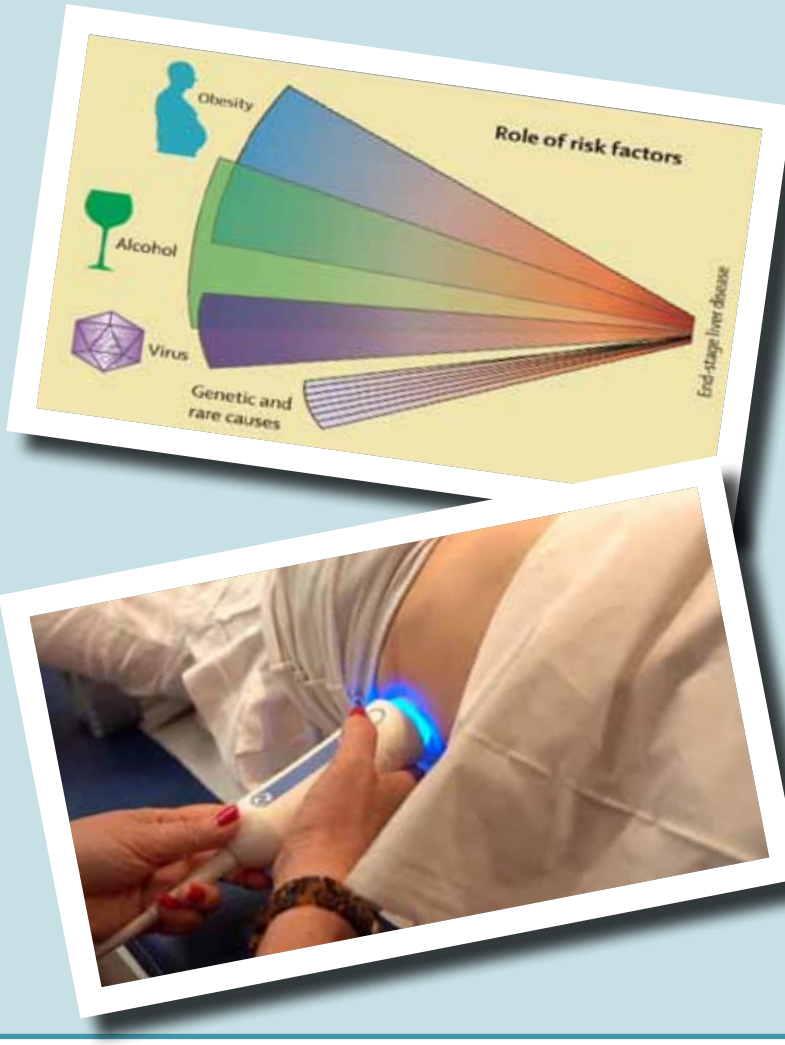
Professor Dr Thomas Berg, Division of Hepatology, University of Leipzig, comments "The EASL annual meeting, the International Liver Congress is one of the most important annual events in liver disease in hepatology worldwide and it sets the stage of our current knowledge and evidence"

**Do you love your liver?**

Maraika Geisterfer-Black, Advocacy. Policy and Public Health Intern, European Association for the Study of the Liver, "We partnered with the British Liver Trust and we offered congress delegates and staff members the oportunity to have their livers screened and have consultations based off of those screenings"

"Having our unit at the ILC was really helpful in terms of raising public awarenesss"
Pamela Healy, OBE, Chief Executive, British Liver Trust.

The Love Your Liver Campaign seeks to raise awareness of the major risk factors that can cause liver damage and encourage those who are at risk to get tested. It includes a free online screener that assesses whether you are at risk of liver disease and provides information on what to do if you are, a year round awareness campaign with the media and through promotional displays, targeted activity in 'Liver Awareness month' and in 'Love Your Liver week' and Love Your Liver community screening events held in association with local liver clinicians around the UK.




# Alcohol-Related Cirrhosis - Genetic Variation of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common form of liver cancer, and is often seen in patients with chronic liver diseases, such as cirrhosis. HCC occurs most often in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection.

Presented at this year's congress, the aim of the study was to identify novel risk factors for HCC developing in patients with ArC. Genetic variation in telomerase reverse transcriptase modifies the risk of patients diagnosed with alcohol-related cirrhosis (ArC) developing HCC. Patients with ArC have an annual risk of up to 2.9% of developing HCC. In previous research, some host genetic risk factors have been discovered, but these do not provide a full explanation for the majority of variances in occurrence.

The study was made up of a cohort of patients with ArC who developed HCC (cases: n=1,214), and another with ArC who did not have HCC (controls: n=1,866). These patients resided in Austria, Germany, Italy, Switzerland, and the UK. All patients were included in a two-stage genome-wide association study, which used a case-control design.

Made up of 1,520 individuals, researchers included a validation cohort, who misused alcohol, but had no evidence of liver disease. The cohort was added as a control regarding possible association effects of alcohol misuse. Researchers performed genotyping using both the Infinium®Global Screening Array (version 24v2; Illumina, San Diego, California, USA) and the OmniExpress Array (version 24v1-0a; Illumina). Confirmation of two variants were found, previously associated with HCC in patients who have ArC at a genome-wide significance. They also identified a novel locus rs2242652 in telomerase reverse transcriptase, which continued to be significant following correction for age, ancestry, BMI, sex, and Type 2 diabetes.

In conclusion, rs2242652 in telomerase reverse transcriptase is a novel protective factor against developing HCC in patients who have ArC.

# Impact of Pruritus on Quality of Life for Patients with Primary Sclerosing Cholangitis

Mirum Pharmaceuticals, Inc., a biopharmaceutical company dedicated to transforming the treatment of rare liver diseases, presented data at this year's International Liver Congress™ (ILC). The first analysis featured a multinational survey of patient-reported outcomes showing the effects of pruritus in patients with primary sclerosing cholangitis (PSC). A second poster assessed gastrointestinal (GI) tolerability on time of dosing with ileal bile acid transporter inhibitors (IBATis) relative to meals.

"We are pleased to share new data at the 2022 EASL congress," said Dr. Pam Vig, head of research and development at Mirum. "The large multinational PSC survey shows that adults with PSC often experience significant and debilitating pruritus which impacts their day-to-day quality of life, despite use of off-label antipruritic medications. Thus, there remains an urgency for a treatment to address this most burdensome symptom, and we are excited to be evaluating the potential of volixibat, a minimally absorbed IBAT inhibitor, in patients with PSC."

*Treatment Strategies* presents the summaries of data presented during the congress along with the on-line links to view the presentations in full within the Publications & Presentations section of the Mirum website.

**Poster 756: Impact of pruritus in primary sclerosing cholangitis (PSC): a multinational survey**

By Dr. Kris Kowdley, *et al*.

The multinational survey, conducted by Hetz Israel, PSC Australia, PSC Partners, and PSC Support, assessed results from a collection of patient-reported outcomes from people living with PSC (n=482). The aim of the survey was to assess the presentation and severity of cholestatic pruritus and its broader burden on patients with this rare liver disease. The 39-question survey captured the age and gender of respondents as well as whether they also have inflammatory bowel disease. In addition to pruritus, inflammatory bowel disease and chronic liver disease associated with PSC can negatively impact the quality of life and can lead to depression and anxiety.

*"The large multinational PSC survey shows that adults with PSC often experience significant and debilitating pruritus which impacts their day-to-day quality of life, despite use of off-label antipruritic medications."*

**Dr. Pam Vig, Head of Research and Development, Mirum Pharmaceuticals**

The survey results showed that: Of the 91% of patients who reported experiencing itch following their diagnosis, 46.4% of respondents experienced >15 episodes (an episode is defined as a prolonged period of itching for at least 7 days).

Respondents were asked to rate the worst itch experienced in the last 24 hours, and the median worst itch was 6 out of 10 in those who responded (scale from 0-10). Their previous itching episode was reported as 8 out of 10. Thirty-one percent of patients who reported having a current itching episode stated that they have been

continuously itching for >12 months.

The survey assessed the overall impact of pruritus on respondents' lives with responses indicating:
Itch was worst in the evening or nighttime (96%)
Mood changes including but not limited to anxiety, irritability, and feelings of hopelessness (58%)
Itch led to disruption of day-to-day activities (50%)
Itch lasted ≥1 month in duration (45%)
Disruption of daily responsibilities due to itch that lasted >30 days (32%), and reported it lasting >12 months (18%)
Missing school or work (22%)

Other findings showed that almost half of respondents (235/482) reported using ≥2 medications but 75% (177/235) described only partial or no relief with the interventions.

Data from the survey concluded that pruritus related to PSC has a major adverse impact on quality of life (e.g., sleep, mood, fatigue), and interferes with daily activities in a substantial proportion of patients, yet it remains inadequately treated in most patients. There is a high unmet need for the development of safe and effective therapies to treat PSC.

View the presentation. Click here.

**Poster 634: Dosing ileal bile acid transporter inhibitors in the fasted state minimises gastrointestinal adverse effects while maintaining pharmacodynamic effect**

By Dr. Cory Kostrub, *et al*.

The analysis sought to assess the impact of timing of IBATis dosing relative to food, and the impact on gastrointestinal adverse events and pharmacodynamic effects to inform the optimal dosing approach for IBATis.

Adverse event data from three Phase 1 clinical studies of maralixibat and volixibat in healthy participants were compiled to assess the relative tolerability with different timing of dosing versus mealtime. Fecal bile acids (fBA) data were assessed from nonclinical studies and used as a marker of efficacy since fBA is often difficult to assess in clinical trials.

The data demonstrated that: There were 0% GI-related adverse events in the fasted state in two out of the three fasted studies. In all three studies where the drug was dosed at mealtime, there were 75%, 33% and 100% GI-related events, respectively. In general, lower rates of GI adverse events occurred when IBATis were dosed in a fasted state versus at mealtime. Non-clinical pharmacodynamic data demonstrate that fasted versus fed dosing had no impact on fBA excretion.

Maralixibat significantly increased fBA excretion across all dosing time schedules, relative to a daily meal.

The highest increases in fBA excretion were seen when dosing 30 minutes prior to or four hours after mealtime, indicating flexibility in the timing of IBATi dosing versus mealtime to maintain maximal pharmacodynamic effect.

The analysis concluded that in healthy human participants, gastrointestinal tolerability was improved when dosing IBATis in a fasted state versus dosing immediately before or at mealtime. The data from animal studies showed that fBA excretion was maintained regardless of dosing time relative to mealtime, indicating that there is flexibility in the dosing of IBATis relative to food.

View the presentation.
Click here.

# Fibrosis Treatment - A Novel Continuous Scoring System

PathAI, a global leader in AI-powered pathology, presented three presentations at this year's ILC congress in London.

*Treatment Strategies* highlights the three abstracts. The abstracts detail a novel machine learning-enabled continuous scoring system for nonalcoholic steatohepatitis (NASH) that allows for both nuanced analysis of treatment efficacy and capabilities to predict disease progression in patients with advanced fibrosis due to NASH. Furthermore, the research details a novel method to image fibrosis in liver biopsy slides, potentially eliminating the second set of trichrome stain slides that historically have been required.

"Until now, no one has a proven method for quantifying subtleties in fibrosis progression, nor a way to predict that progression reliably," said Andy Beck, CEO and Co-founder of PathAI. "We are excited to discuss these findings at ILC and explore the implications for advancing the standard of care for fibrosis treatment."

The first abstract demonstrates the utility of AI Measured (AIM)-NASH by PathAI, a tool for scoring NASH histology in a retrospective analysis of liver biopsies from the Phase 2 trial of resmetirom. All biopsy-based endpoints that were evaluated via manual histologic scoring were also analysed by AIM-NASH. Standard histologic assessment of fibrosis labels patients with scores of 1 to 4, much like labels for the stages of cancer. PathAI developed a novel continuous scoring system to allow for more nuanced analysis of a given treatment's efficacy, such as 3.6 or 2.4. Analysis of these continuous scores revealed a statistically significant increase in NASH resolution and a greater reduction in fibrosis in treated versus placebo subjects.

"Previously studies would score patients at the onset and culmination of a study using a standardised ordinal scale. However, such scoring misses nuanced improvements that our continuous scoring system brings to light," said Dr. Mike Montalto, Chief Scientific Officer at PathAI. "For example, a patient may start at 3.8, but be a 3.2 by the end of the study, pointing to benefits of the treatment that traditional scoring would have missed by labeling the patient a 3 at both the start and endpoint."

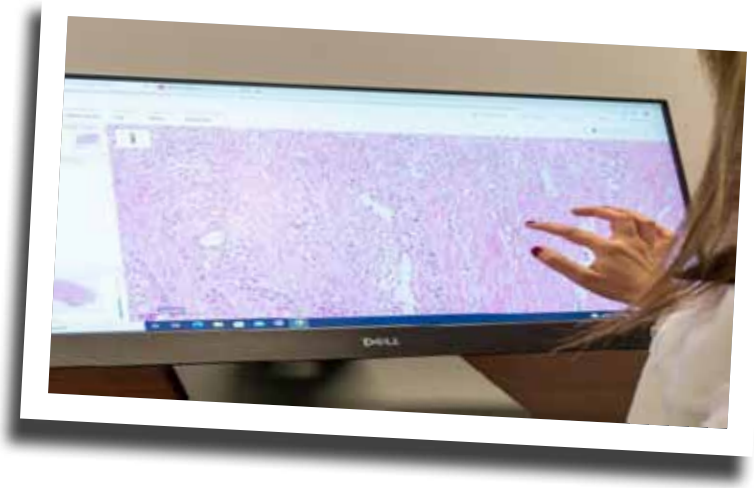
The second abstract accepted at ILC dovetails with the first abstract and details employing PathAI's proprietary continuous scoring to predict disease progression in patients with NASH. By leveraging continuous scores, prediction of clinical disease progression in patients with NASH is possible. The results of this abstract support further investigation into the value of machine learning-based continuous histologic scoring methods for detecting small but clinically meaningful therapeutic effects in NASH clinical trials.

The final abstract presents PathAI's novel method for imaging fibrosis in liver biopsies, potentially allowing for removal of trichrome stain slides that historically have been necessary. Eliminating the need for trichrome-stained slides may have several benefits, the most prominent of which could be improved accuracy. Liver biopsy segments taken from a given patient can have variations unrelated to disease activity but due to heterogeneity in liver tissue. Obtaining all necessary information to assess a patient's disease state from a single biopsy slide allows for a more consistent analysis of the patient's disease and may improve accuracy on determining their risk for disease progression.

**Title: Retrospective AI-based Measurement of NASH Histology (AIM-NASH) analysis of biopsies from Phase 2 study of Resmetirom confirms significant treatment-induced changes in histologic features of non-alcoholic steatohepatitis**
Session Date and Time: June 25, 2022. 9:00 am -18:00 pm GMT
Abstract: #3625
Developed in partnership with Madrigal Pharmaceuticals

**Title: Machine learning-enabled continuous scoring of histologic features facilitates prediction of clinical disease progression in patients with non-alcoholic steatohepatitis**
Session Date and Time: June 25, 2022. 9:00 am -18:00 pm GMT
Abstract: #3788
Developed in partnership with Gilead Sciences

**Title: Quantitative multimodal anisotropy imaging enables automated fibrosis assessment of H&E-stained tissue**
Session Date and Time: June 25, 2022. 9:00 am -18:00 pm GMT
Abstract: #3370



# Turn Up the Volume on Heptocellular Carcinoma

Roche Diagnostics Intenational Ltd were on hand at ILC 2022 to showcase the Elecsys® Gaad technology, an *in vitro* diagnostic multivariate index assay. Elecsys® GAAD test for the aid in diagnosis of early-stage Heptocellular Carcinoma (HCC).

Heptocellular Carcinoma is a "silent killer". It develops unseen, often only to be found when it's too late to save patients. It is already the third leading cause of cancer death,[1] and the global incidence of HCC is increasing, especially in developed countries.[2] But it doesn't have to be that way.

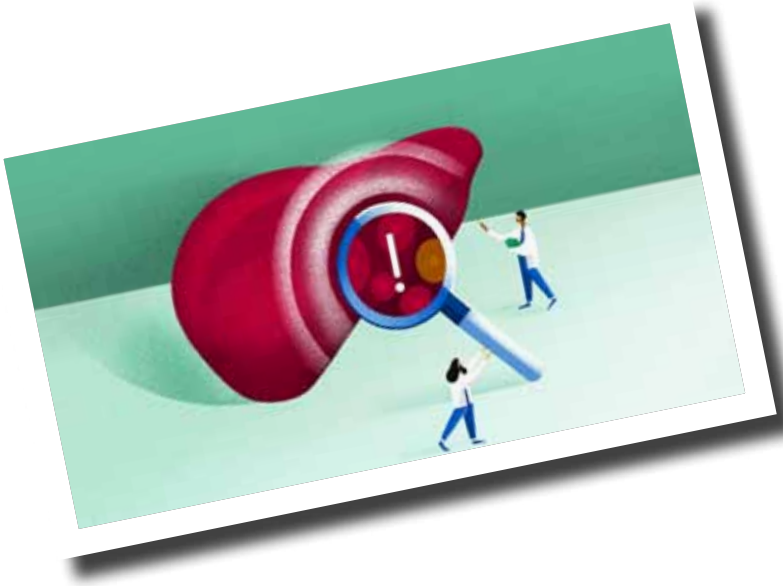
Healthcare is rapidly shifting, towards more personalised care that's more in tune with patients, embracing digital technologies that enable new possibilities. Roche are shaping a new class of diagnostic algorithms.

Introducing the Elecsys® GAAD *in-vitro* diagnostic multivariate index assay. It is a CE-marked algorithm to help diagnose early stage HCC and save lives. Combining Elecsys® AFP and Elecsys® PIVKA-II assay results, along with gender and age, Elecsys® GAAD communicates patients' risk factor clearly, so you may be able to evaluate earlier and save more lives.

It's simple and intuitive to use, and can be adapted to current workflow, so there should be no disruption.

Elecsys® GAAD is an *in vitro* diagnostic multivariate index assay intended to provide a semi-quantitative result by combining in an algorithm the quantitative measurements of Elecsys® AFP assay and Elecsys® PIVKA II assay in human serum and plasma with gender and age. Elecsys® GAAD is intended as an aid in diagnosis of early stage HCC.

Elecsys® GAAD is indicated for adults who meet the following criteria: diagnosis of chronic liver disease and recommended for surveillance due to increased risk of developing HCC.
Elecsys® GAAD must be interpreted in conjunction with other diagnostic findings and clinical information in accordance with standard clinical management guidelines.



# Humanised Liver Technology

*Treatment Strategies* met up with PhoenixBio at the congress. Here we highlight absratcts on future therapies for HBV, HDV/HBV, HCV, NASH/NAFLD, Gene Editing, Gene Therapy, Drug Metabolism, Pharmacokinetics, and Toxicology.

Posters featuring PhoenixBio's humanised liver technology & study services:

**• Abstract "THU319": Understanding acute HCV infection kinetics in humanised mice via an agent-based modeling approach**

**• Abstract "THU303": A persistent HBV infection features spontaneous cccDNA loss and new rounds of infection**

**• Abstract "SAT426": The discovery of AMS-I-1274, a high potent and orally active capsid-assembly modulator against hepatitis B virus**

**• Abstract "SAT434": VIR-2218 plus VIR-3434 combination therapy reduces hepatitis B virus surface antigen levels in vivo**

**• Abstract "SAT117": Combination of an Acetyl-CoA carboxylase inhibitor and obeticholic acid reduced lipids and bile acids and altered lipid and amino acid metabolism in the liver of humanised mice**

# A Multi-parametric Reporting Tool for Liver Imaging

*Treatment Strategies* visited Canon Medical Systems to get more information on the Aplio 1800 that was being showcased at this year's congress.

The Aplio i800 is designed to deliver outstanding clinical precision and departmental productivity.


*"At the core, we believe users will be delighted with the power of the B-mode imaging performance but will also appreciate the many new applications that have been introduced on this machine for a broad range of clinical areas."*

Crystal-clear images with enhanced resolution and penetration as well as an abundance of expert tools help you get your diagnostic answer quickly and reliably.

From the smallest to the toughest patients, Aplio's revolutionary iBeam architecture with dramatically increased processing power provides unprecedented imaging clarity and definition while significantly enhancing penetration.


Akihiro Sano, Ultrasound General Manager at Canon Medical says of the development, "At the core, we believe users will be delighted with the power of the B-mode imaging performance but will also appreciate the many new applications that have been introduced on this machine for a broad range of clinical areas".

Canon CANON MEDICAL SYSTEMS

# Chronic Hepatitis B and Primary Liver Cancer: Is Ultrasound an Effective Surveillance Modality?

Chronic hepatitis B patients under surveillance for primary liver cancer (PLC), who receive poor ultrasound liver imaging reporting and data system (US LI-RADS) visualisation scores, have higher false negative rates and an increased risk of PLC than those with good scores.

Chronic hepatitis B is a risk factor for PLC, particularly hepatocellular carcinoma (HCC); as a result of this, regular surveillance is required for patients considered high-risk with ultrasound being the standard imaging technique used in surveillance.

A cohort study was presented at the congress with the lead study author being Min Kyung Park of The Department of Internal Medicine and Liver Research at Seoul National University College of Medicine, Korea, Republic of South Korea. The study highlights that ultrasound may not be the optimal imaging modality for PLC surveillance in those with poorer visualisation scores.

The study included 2,002 patients with chronic hepatitis B under regular HCC surveillance, with the goal of assessing the efficacy of ultrasound for detection of PLC according to US LI-RADS visualisation scores.

Patients were stratified into visualisation scores A and B/C, with visualisation score A being top and C being lowest. There were 972 patients with visualisation score A, 1,003 with visualisation score B, and 27 with visualisation score C. Once stratified, the researchers analysed the incidence of PLC and ultrasound false negatives and the median follow-up period was seventy-five months.

Of the 2,002 patients that the study enrolled, 166 developed PLC (158 HCC, 8 other PLC). The researchers found that those with visualisation scores B/C had a significantly higher risk ($p<0.001$) of developing PLC (2.41% /year) than those in group A (0.5% /year), as well as higher false negative rates with ultrasound surveillance (43.5% versus 20.0%). Additionally, researchers found that very early-stage PLC was less likely to be picked up by ultrasound in visualisation group B/C.

The conclusions from this study infer that ultrasound may not be the optimal surveillance imaging modality for patients with poor US LI-RADS visualisation scores. The study researchers recommended that CT or MRI could be considered as alternative surveillance techniques in this patient cohort.

# It's all about Uniting the Community

*Treatment Strategies* visited Health Solutions, a part of BCB Medical, a solution provider for gathering, analysing and reporting clinical data, at the ILC 2022 congress exhibition hall, to find out how they are contributing to the hepatology community.

Modern healthcare is generating a huge amount of data. The problem with this is that the industry is so much better at producing data than it is at capturing it. This is where Health Solutions comes in. By taking the relevant data and using it to help their customers, the patients. The industy creates health by using what it already has at their disposal - healthcare generated data.

One of the systems in focus during the conference is HepCARE. HepCARE is a Digital Clinical Decision Management System for Hepatitis B, C and D. It is designed and developed together with clinical experts based on real world needs in daily practice. HepCARE offers an effective tool for healthcare professionals in diagnostics, treatment and follow-up of the patients with Hepatitis B, C or D and offers standardised processes and reduced costs of delivering care.

HepCARE is currently used in key hospitals in UK, covering approximately 30 different hospitals, hundreds of end users and thousands of patients. HepCARE provides the healthcare professional with a comprehensive view on the patient's treatment and state of health and supports them in daily treatment decisions.

Among HepCARE's features are patient overview, real-time statistics for patient cohort follow-up and structured manual data feeds. It is the leading Hepatitis Decision Support System, long established and successfully implemented in UK Trusts for the last couple of years. Whatsmore, HepCARE is more than just a digital tool. It is a powerful community uniting clinicians, patients, researchers, commissioners and patients.

In addition, HepCARE has multiple integrations. HepCARE gathers data from Lab and Patient Administration systems (PAS) at respective trusts around the UK and sends data automatically to The NHS England national HCV registry as well as exports to the Health Informatics Collaborative (HIC) NIHR Biomedical Research study.

### HepCARE key features and benefits

- Online Multidisciplinary Team (MDT) approval & management process
- Patient overview for Hepatitis C and B & D
- Improved outcomes monitoring with real time statistics
- Improved data collection in structured form
- Supports the Operational Delivery Network (ODN)
- Improved research environment
- Outcome auditing
- Simple cohort assessment

# Outbreak of Acute Hepatitis - Global Data Review

During a media briefing at the International Liver Congress, it was reported that an outbreak of acute, severe hepatitis of unknown etiology in children has increased to 894 cases across 33 countries, according

Philippa Easterbrook, MD, senior scientist at the Global HIV, Hepatitis and STI Programs at WHO headquarters in Geneva, told delegates. "As of June 20, we now have 894 probable cases reported in 33 countries in five WHO regions. Since the last WHO public communication on May 27, this represents 244 additional cases over a space of about a month. However, it's important to remember that this includes both new cases as well as retrospectively identified cases."

Easterbrook commented that over half of these cases (n = 449) are from Europe, with the U.K. alone accounting for 262 cases — nearly 30% of the global total. The second highest reporting population is the Americas with 368 cases; as with the U.K., the United States harbors a disproportionate number of cases at 290, over a third of the global total.

"Together the United States and the United Kingdom account for 65% of the global total cases," she said. "The majority of cases — 75% — are among children less than five years of age. Forty-four children have required liver transplantation, and there have been 18 reported deaths. Fortunately, in both the European and United States data, there does appear to be a declining trajectory in terms of reports of new cases, which is a positive development."

Early in the investigation, adenovirus along with past or current COVID-19 infection were the primary suspects and that is still the case. Easterbrook commented further, noting that these viruses are most likely independent or collaborative causes that result in hepatitis.

"Adenovirus remains the most detected of all viral infections with a rate of detection of about 53% across Europe and bit higher in the U.K., but they are not in all cases," she stated. "There does seem to be a higher rate of detection in the younger age groups and in those developing severe disease, so perhaps there is some link to severity."

In terms of current COVID infection, in both Europe and the U.S. rates of detection are approximately 10%, which is what researchers expect, given the rate of transmission in the general population around that time.

"Some of the emerging hypotheses are [whether this outbreak] represents a post-COVID phenomenon," she stated. "Is this a variant of the rare but recognised multisystem inflammatory syndrome condition in children? It often occurs one to two months after COVID-19, causing widespread organ damage, but it is rare, and the cases of hepatitis that have been reported don't seem to fit those features."

However, Easterbrook noted that early on researchers were able to rule out COVID-19 vaccination as a potential contributor. "The majority of children [in these cases] had not been vaccinated, particularly the younger age groups, consistent with the vaccination policy in place at the time," she said. "The clear message is 85% were unvaccinated, which is why that cause was excluded."

The steady growth in cases and a still unknown etiology have highlighted the importance of capturing consistent data from multiple countries.

"We are seeing a somewhat mixed picture globally, with two countries reporting the majority of cases in large numbers," she said. "We are seeing differences in age distribution; we are seeing some differences in the rate of adenovirus detection and COVID-19. It's a mixed picture, and we really need to have good quality data collected in a standardised way from other countries."

> **"Fortunately, in both the European and United States data, there does appear to be a declining trajectory in terms of reports of new cases, which is a positive development."**
>
> **Philippa Easterbrook, MD, Senior Scientist, Global HIV, Hepatitis and STI Programs, WHO**

# Low-Carbohydrate, High-Fat Dietary Intervention for Non-alcoholic Fatty Liver Disease

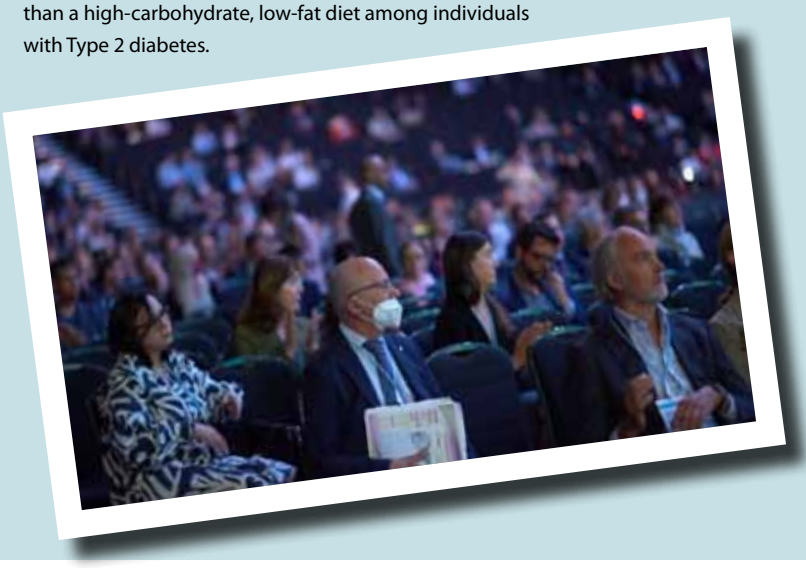
More than half (55%) of those with Type 2 diabetes also have non-alcoholic fatty liver disease (NAFLD). Glycaemic control predicts severity of hepatocyte escalating and hepatic fibrosis in NAFLD. Although dietary interventions with low carbohydrates assist glycaemic control, the effect on NAFLD remains to be resolved.

Results of the following investigation were presented at ILC 2022. A group of researchers investigated the impact of a 6-month low-carbohydrate, high-fat diet on NAFLD. The effect of this dietary intervention was assessed by ≥2 points improvement in the NAFLD Activity Score (NAS).

The researchers performed liver biopsies and measured HbA1c at baseline and after 6 months. One hundred and eighty-five individuals with Type 2 diabetes were randomised 2:1 to a diet consisting of low carbohydrates and high fat or one comprising high carbohydrates and low fat. Non-calorie-restricted diets were used in both cases.

One hundred and sixty-five, the total, of the randomised participants commenced the allocated intervention and were included in the analysis. After intervention, no significant difference was observed between the groups with respect to improvement of ≥2 points in NAS (p=0.587). Of significantce, a higher proportion of patients in the low-carbohydrate, high-fat group improved NAS with ≥1 point relative to the high-carbohydrate, low-fat group (70% and 49%, respectively; p=0.028). Furthermore, fewer in the low-carbohydrate, high-fat group experienced a worsening of NAS (1% versus 23% for the high-carbohydrate, low-fat group; p<0.001). Those in the low-carbohydrate, high-fat group improved HbA1c with -9.5 versus -3.4 in the high-carbohydrate, low-fat group.

One can conclude that a 6-month non-calorie-restricted low-carbohydrate, high-fat diet improves NAS and HbA1c significantly more than a high-carbohydrate, low-fat diet among individuals with Type 2 diabetes.



# ILTS 2023 - Rotterdam

Mark your calendar for the world's premier congress on liver transplantation in Rotterdam, Netherlands, May 3-6, 2023!

Hosted jointly by The Netherlands' three outstanding liver transplant centers (Groningen, Leiden and Rotterdam), this will feature 60+ invited lectures, 700+ abstracts, technical workshops, case discussions, and unique networking opportunities for all disciplines engaged in this rapidly evolving field.

ILTS Special Interest Groups and specialist committees will be closely involved, focusing on the latest science and consensus-driven trends.

Special topics will include advances in preservation, surgical techniques and robotics, biliary disorders, transplant oncology, and management of complex liver disease.

**Find out more: https://2023.ilts.org/**

# WHO: HCV Elimination by 2030

During a joint WHO-EASL-CDC symposium at this year's congress, World Health Organization (WHO) presented updated guidance on hepatitis C, calling for siignificant simplification of care pathways to alleviate access gaps in HCV testing and treatment.

Philippa Easterbrook, MD, senior scientist at the Global HIV, Hepatitis and STI Programs at WHO headquarters in Geneva, informed attendees, "In 2016, when WHO launched its global strategy, there were ambitious plans for elimination, defined as a 90% reduction in incidence and a 65% reduction in mortality. These could be delivered through the scale-up of six synergistic interventions, including testing and treatment, to achieve by 2030 towards elimination: 90% of those infected diagnosed, and 80% of those diagnosed treated."

Furthermore, "Although excellent progress has been made in many champion countries, and more than 10 million have been treated, based on the global hepatitis report from WHO a year ago, still only 21% of those infected have been diagnosed and 13% treated. If we are to reach the goals of elimination, there needs to be a substantial scale up and simplification of care pathways."

Among its initial recommendations, the updated WHO guidance pushed for decentralisation, integration and task shifting in HCV care. In particular, WHO recommended moving the treatment and care of HCV out of specialty clinics and into more peripheral health or community-based facilities where trained non-specialist physicians and nurses can be assigned with patient care to expand access.


"We are recommending delivery of hepatitis C testing and treatment at peripheral health or community-based facilities, ideally at the same site to increase access to diagnosis, care and treatment," Easterbrook remarked. "These facilities may include primary care, harm reduction sites, prisons, HIV clinics, as well as community-based organisations. We recommend integration of the hepatitis testing and treatment within existing services at these health facilities."

The World Health Organization made this a robust recommendation, based upon moderate certainty of evidence, other than for the general population where there were less data. The rationale for these recommendations was founded on evidence review, 2021, of 142 studies from 33 countries — 14% of which were low- or middle-income countries — that compared full decentralisation or integration vs. partial or none, as well as task sharing to non-specialists compared with specialists.

In the second updated guidance, WHO presented a number of conditional recommendations on the use of HCV point-of-care viral load RNA testing, specifically, that this can be utilised as an alternative approach to laboratory-based HCV RNA nucleic acid testing to diagnose HCV viremic infection. Furthermore, point-of-care HCV RNA assays with comparable limit of detection to lab-based assays may be used an alternative approach as a test of cure, as stated by the WHO recommendations.

"The rationale for this was based on an evidence review of 45 studies of 27,364 patients, in which 50% of studies were from low- and middle-income countries, that compared point-of-care viral load with lab-based assays," Easterbrook remarked.

"The main message here was that there were better outcomes with point-of-care assays, with a short turnaround time between antibody test and treatment initiation, increased viral load uptake and increased treatment uptake. Diagnostic performance in terms of sensitivity and specificity compared to lab-based assays was also very high."

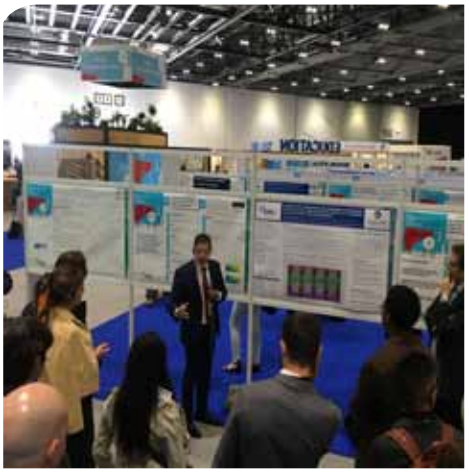
Further benefits of point-of-care HCV RNA testing involve its use in lower-level health facilities near where patients receive care, as well as the opportunity for integration with other point-of-care molecular platforms for diseases such as HIV,

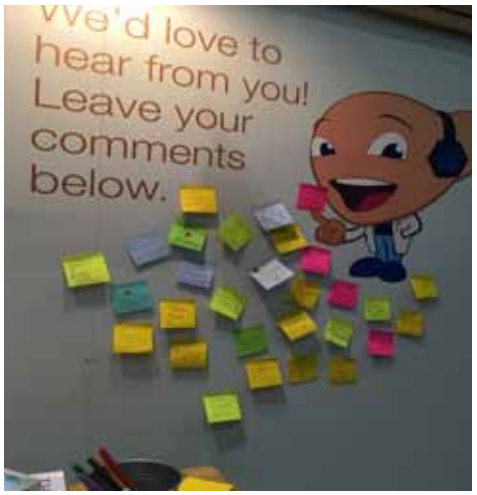
tuberculosis and COVID-19.

Finally, WHO guidance robustly recommended the use of pangenotypic direct-acting antiviral regimens for all adults, adolescents and children aged older than 6 years with chronic HCV, regardless of stage of disease. Children aged 3 to 5 years were given a conditional recommendation, based on very low certainty of evidence.

Additionally, for direct-acting antiviral regimens, WHO robustly recommended the use of sofosbuvir/daclatasvir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir among adolescents and older children, while children aged 3 to 5 years were again given a conditional recommendation.

"The rationale was based on a systematic review of 49 studies in adolescents, older children and younger children, with [sustained virologic response] rates at least 95% in all age groups across all regimens," Easterbrook noted. "Serious adverse events and treatment discontinuations were uncommon and, of course, [the benefit of earlier treatment] is to achieve a cure before the onset of disease progression and into the associated liver damage."






# Progressive Familial Intrahepatic Cholestasis

*Treatment Strategies Haematology* visited with Albireo Pharma, a rare liver disease company developing novel bile acid modulators, and reports on several abstracts and posters at the European Association for the Study of the Liver (EASL) International Liver Congress (ILC).

Here are the details of the abstracts on offer. Long-term data confirmed durable efficacy with Bylvay™ (odevixibat), with demonstrated improvement in quality of life, growth, and sleep measurements, and hepatic biomarkers in children with all types of progressive familial intrahepatic cholestasis (PFIC). Two abstracts describe data on early-stage NTCP and ASBT inhibitor assets in development for adult cholestatic and viral liver disease. Data includes analyses of the landmark Phase 3 PEDFIC 1 study and PEDFIC 2 long-term extension study of Bylvay in children with progressive familial intrahepatic cholestasis, with some patients on Bylvay for up to 128 weeks. Albireo also presented pre-clinical data on its pipeline program for A2342 for the treatment of Hepatitis B and D, as well as data on dual ileal/renal and liver bile acid transport inhibitors.

Abstracts of the following posters are available on the EASL website. PLease click here.

**Pediatric Liver Presentations: Bylvay PEDFIC 1 & 2 Clinical Trial Data**

**Poster (Abstract #850): Changes in Hepatic Parameters, Growth, Sleep, and Biochemical Markers With Odevixibat Treatment Across Patients With Various Types of Progressive Familial Intrahepatic Cholestasis**
Lead Author: Dr. Lorenzo D'Antiga, Department of Paediatric Hepatology, Gastroenterology, and Transplantation, Azienda Ospedaliera Papa Giovanni XXIII
Session Title: Rare liver diseases (including paediatric and genetic)
Date & Time: Thursday, June 23, 12:30 BST

**Poster (Abstract #865): Analysis of Quality of Life, Hepatic Biochemical Markers, and Sleep in Patients With Progressive Familial Intrahepatic Cholestasis Who Had a Pruritus Response With Odevixibat Treatment**
Lead Author: Dr. Girish Gupte, Liver Unit and Small Bowel Transplantation, Birmingham Women's and Children's NHS Foundation Trust
Session Title: Rare liver diseases (including paediatric and genetic)
Date & Time: Thursday, June 23, 12:30 BST

**Poster (Abstract #763): Improvements in Quality of Life in Odevixibat Responders and Nonresponders: An Analysis of Pooled Data from the PEDFIC 1 and PEDFIC 2 Studies**
Lead Author: Dr. Cara L. Mack, Children's Hospital Colorado, University of Colorado School of Medicine
Session Title: Rare liver diseases (including paediatric and genetic)
Date & Time: Thursday, June 23, 12:30 BST

**Poster (Abstract #1197): Efficacy and Safety of Odevixibat Over 72 Weeks of Treatment in Patients With Progressive Familial Intrahepatic Cholestasis**
Lead Author: Dr. Richard J. Thompson, Institute of Liver Studies, King's College London
Session Title: Rare liver diseases (including paediatric and genetic)
Date & Time: Thursday, June 23, 12:30 BST

**Poster (Abstract #847): Total, Primary, and Secondary Serum Bile Acid Changes and Pruritus Improvement During Odevixibat Treatment in Patients With Progressive Familial Intrahepatic Cholestasis**
Lead Author: Dr. Henkjan J. Verkade, Department of Paediatrics, University of Groningen, Beatrix Children's Hospital/University Medical Centre Groningen
Session Title: Rare liver diseases (including paediatric and genetic)
Date & Time: Friday, June 24, 12:00 BST

**Adult Liver Presentations**

**Poster (Abstract #1226): The Orally Available Sodium/Taurocholate Co-Transporting Polypeptide Inhibitor A2342 Blocks Hepatitis B and D Entry In Vitro**
Lead Author: Dr. Britta Bonn, Albireo Pharma
Session Title: Viral hepatitis B/D: therapy
Date & Time: Saturday, June 25, 12:30 BST

**Poster (Abstract #1238): Dual Ileal/Renal-Liver Bile Acid Transporter Inhibitors with Different Transporter Selectivity In Vitro Differentially Increase Faecal and Urinary Bile Acid Excretion in Organic Anion Transporting Polypeptide 1a/1b Knockout Mice In Vivo**
Lead Author: Ellen Strängberg, Albireo Pharma
Session Title: Molecular and cellular biology
Date & Time: Saturday, June 25, 12:30 BST

**Sponsored Symposium**
On June 23rd 2022, the Albireo-sponsored symposium, Idiopathic Cholestasis and Targeted Next-Generation Sequencing Panels: A Case Blended Approach, took place.

The lunchtime symposium and discussion was held at the Hepatology Arena and was also broadcast live on-demand on the EASL website. Delegates were welcomed with an introduction and overview of the genetics of progressive familial intrahepatic cholestasis (PFIC) by the chair, Professor Richard Thompson, King's College, London, UK.
PFIC in practice, a paediatric and adult case studies of patients with idiopathic cholestasis were presented followed by a questions and answers session.

Expert panel: Prof. Richard Thompson, King's College, London, UK, Dr. Silvia Vilarinho, Yale School of Medicine, Connecticut, US and Prof. Verena Keitel-Anselmino, University Hospital, Magdeburg, Germany
Date & Time: Thursday, June 23, 12:30-13:30 BST at ExCel London.

# Chronic Liver Disease and Liver Cancer: Non–alcoholic Fatty Liver Disease

The global burden of chronic liver disease (CLD) and liver cancer has historically been attributed to alcohol-associated liver disease (ALD), chronic hepatitis B, and chronic hepatitis C viral infections. Yet, at this year's ILC, new evidence was presented by lead author James Paik, Betty and Guy Beatty Center for Integrated research, Inova Health System, Falls Church, Virginia, USA, and Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, Virginia, USA, that shows that non-alcoholic fatty liver disease (NAFLD) has become an emerging driver for the accelarating incidence and occurance of CLD and liver cancer worldwide, between 2009 and 2019.

Using data gained from the Global Burden of Disease Study 2019, the authors analysed changes in incidence, prevalence, morbidity and mortality, and disability-adjusted life–years (DALYs) for liver cancer and CLD over the preceding decade. With this data, the team calculated annual percentage change (APC) using the Joinpoint Regression Program, National Cancer Institute. Prevalence and incidence both increased for liver cancer and CLD during the period studied (Liver cancer: +33.7% and +30%; CLD: +22.7% and +14.8%, respectively). Deaths and DALYs also increased for both conditions. Review of the APC for liver cancer death rate considered the impact of different aetiologies, with the greatest impact driven by NAFLD (APC +2.47%). NAFLD also had the greatest impact on CLD death rate (APC +1.33%), although the overall APC for CLD death rate decreased by 0.18% during the studied period.

Variations geographically in the aetiology and burden of liver cancer and CLD were also noted. Central Latin America showed the highest APC increase in NAFLD and hepatitis B and C virus-related liver cancer deaths; whereas, in the North American region, the highest APC increase in liver cancer deaths was due to ALD.

The findings from this work showed increases in NAFLD and ALD driving the increasing burden of liver cancer and CLD. This emphasises how disease aetiology can change over time and that there is the need to continually evaluate these factors in order to improve understanding.

# Presenting a New DIO-NASH Mouse Study

*Treatment Strategies* met up with Physiogenex, a leading preclinical research organisation providing non clinical services in metabolic disorders and complications, at ILC 2022.

A new DIO-NASH mouse study (abstract#258) was presented at the ILC-EASL in London, UK, on June 25th, 2022.

The poster presentation (#SAT110), entitled "Weight loss with semaglutide treatment or time-restricted feeding differentially improves non-alcoholic steatohepatitis in diet-induced obese insulin resistant mice" was delivered by Dr. François Briand, Physiogenex's Director of Research and Development.

Due to its positive correlation with obesity/type 2 diabetes, the prevelance of non-alcoholic steatohepatitis (NASH) is increasing globally. Weight loss represents a promising therapeutic strategy for NASH and liver fibrosis. In the paper, Briand compared the weight loss benefits of the glucagon-like peptide-1 (GLP-1) receptor against semaglutide (SEMA) or time-restricted feeding (TRF) on NASH/liver fibrosis in diet-induced obese insulin resistant mice.

In conclusion, SEMA markedly reduced body weight and liver steatosis but did not improve hepatic fibrosis. Although its weight loss effect was less pronounced. TRF improved both NASH and liver fibrosis. Briand cocluded that these benefits should be further investigated in the clinical setting.

# HBV - Antiviral Combination Plus Standard Therapy

According to a speaker at this year's ILC congress, therapy combining small interfering RNA, capsid assembly modulator and nucleotide analogue decreased HBsAg levels over 24 weeks compared with standard therapy.

Kosh Agarwal, MD, from the Institute of Liver Studies at King's College Hospital in London, informed attendees "It's important that we think about public health and global viruses and liver disease, and hepatitis B is a globally relevant virus. I believe the latest estimates suggest that almost 300 million people in the world are affected with hepatitis B, and almost every 30 seconds, someone dies of hepatitis B somewhere in the world."

"We have good treatments that can control hepatitis B, but we do not have treatments that cure hepatitis B. On the back of the stunning success of hepatitis C, there is within the field, a wish to try and achieve cure of hepatitis B, and we characterise that by losing surface antigen, a marker of hepatitis B."

Agarwal and colleagues , in the phase 2b REEF-2 study, took 130 non-cirrhotic HBeAg-negative chronic hepatitis B patients with HBsAg greater than 100 IU/mL and nucleotide analogue treatment for at least 2 years, and randomly assigned them to add on an investigational small interfering RNA (siRNA; JNJ-3989, Arrowhead Pharmaceuticals) plus a capsid assembly modulator (JNJ-6379, Janssen Pharmaceuticals) or placebo. The primary endpoint for the study was the proportion of patients who achieved HBsAg levels less than 0.05 IU/mL at follow-up week 24 without restarting nucleotide analogue therapy.

"The unique aspect of this study is that after 48 weeks, all treatment was stopped," Agarwal noted. "If you want to get to a cure, you have to think about a finite duration of therapy, and currently, we don't have that."

Researchers found, at baseline, 80% patients in the combination therapy group had HBsAg levels of at least 1,000 IU/mL and a mean duration of previous nucleotide analogue use of 8.4 years, while 76% of the standard therapy group exhibited HBsAg levels of at least 1,000 IU/mL with prior mean nucleotide analogue use of 8.1 years.

Following the end of treatment, mean reductions in HBsAg from baseline were –1.89 (0.060) log10 IU/mL in the combination group and –0.06 (0.012) log10 IU/mL in the control group. In the combination group, 71.1% of patients achieved HBsAg of less than 100 IU/mL, 19.7% less than 10 IU/mL and 2.6% less than 1 IU/mL. In the control group, only 2.4% of patients achieved HBsAg of less than 100 IU/mL; however, no patient in either group achieved HBsAg seroclearance.

*"On the back of the stunning success of hepatitis C, there is within the field, a wish to try and achieve cure of hepatitis B, and we characterise that by losing surface antigen, a marker of hepatitis B."*

**Kosh Agarwal, MD, Institute of Liver Studies, King's College Hospital, London**

"After 24 weeks of follow up, no patients in this study lost their surface antigen — ie, were cured of hepatitis B — in either the active arm or the control arm," Agarwal commented. "However, there is evidence to show that the combination of these drugs, and one particular aspect of siRNA, shows a significant decrease in some of the markers that we are interested in for hepatitis B, and this is at 24 weeks."

Agarwal stated: "So we didn't achieve a cure, but at the end of follow-up, a significant proportion of patients were in a 'controlled biological state' — is that good enough? Is that going to be followed through when we report 48 weeks? This will take us back to the drawing board to think about whether we need better antiviral treatments, whether we need to think about different combinations and whether stopping all treatment is the right strategy to take."

# Research Rodent Models

Research rodent models play a major role as they closely mimic the changes in humans and provide translational data, essential to improve understanding of human diseases and develop new drugs successfully. Chronic diseases such as obesity, diabetes, hypertension and other metabolic syndromes and disease and mortality.

At the ILC 2022, Janvier Lavs, experts in rodent research models, highlighted information on the B6 obese mouse (ob/ob), strain name B6.V-Lepob/ob/JRj.

The B6.V-Lepob/ob/JRj from Janvier Labs is used to model obesity and phases I and II of diabetes type II disease. This model has been well characterised as a model of obesity, exhibiting commonly published metaboloc symptoms including hyperinsulinemia and hyperphagia. B6.V-Lepob/ob/JRj replicates human obesity pathology model associated with hypergycemia and insulin resistance.

**For more information visit - www.janvier-labs.com**

# Proton Pump Inhibitors - Severe Infection, Decompensation in Patients with Cirrhosis

According to research presented at the International Liver Congress, exposure to proton pump inhibitors (PPI) correlated with an increased risk for severe infection and cirrhosis decompensation among a subset of patients with cirrhosis.

Nadim Mahmud, MD, MS, MPH, MSCE, assistant professor of medicine and epidemiology at the University of Pennsylvania Perelman School of Medicine, informed attendees, "The safety of PPIs in cirrhosis remains quite controversial. There is conflicting data regarding the impact of PPIs on several key liver-related adverse events, including infections, decompensation and mortality. There is plausibility to this potential association. ... However, prior studies are limited."

Mahmud and colleagues, in a retrospective cohort study, included 76,251 patients with compensated cirrhosis from the Veterans Health Administration, of whom 23,628 were on PPI at baseline. Researchers time-updated PPI exposure every 30 days and utilsed inverse probability treatment weighting and Cox regression analysis to evaluate incidence of infection, decompensation and all-cause mortality, adjusting for time-updated cardiovascular comorbidities, statin use, antiplatelet medication and hospitalisation for gastrointestinal bleed.

Results from the study revealed, PPI use was associated with a reduced risk for mortality among patients hospitalised for GI bleeds (HR = 0.88; 95% CI, 0.84-0.92) but was not associated with all-cause mortality among patients who were not hospitalised for GI bleeds (HR = 0.99; 95% CI, 0.97-1.02). However, PPI use was associated with an escalated risk for cirrhosis decompensation (HR = 1.64; 95% CI, 1.61-1.68) and severe infection (HR = 1.21; 95% CI, 1.18-1.24) with risk growing with higher dose exposure. The strongest observed infection association was with spontaneous bacterial peritonitis (HR = 1.77; 95% CI, 1.66-1.88), where PPI use correlated with a 77% increased risk.

*"In summary, PPIs should not be avoided solely due to concerns of liver-related adverse events."*

**Nadim Mahmud, Assistant Professor of Medicine and Epidemiology, Perelman School of Medicine, University of Pennsylvania**

"PPI exposure is associated with severe infections and cirrhosis decompensation in this broad cohort of veterans in the United States," Mahmud added. "This observation may mediate the observed association between PPI exposure and liver-related mortality.

"In summary, PPIs should not be avoided solely due to concerns of liver-related adverse events. However, their prescription should be limited to appropriate indications at the lowest effective dose."

# Givosiran Increases Quality of Life, Reduces Attacks in Acute Hepatic Porphyria

According to research presented at the International Liver Congress, long-term givosiran treatment provided sustained benefit and improved quality of life among patients with acute hepatic porphyria.

Manish Thapar, MD, Director of the Center for Genetic and Metabolic Liver Disease at Thomas Jefferson University, stated, "Acute hepatic porphyria is a rare genetic disorder that causes acute neurovisceral symptoms caused by defects in hepatic heme biosynthesis leading to accumulation of neurotoxic heme intermediates 5-aminolevulinic acid and porphobilinogen, which can be life-threatening in a small proportion of patients. It can also lead to chronic debilitating symptoms in a subtype of patients. In this meeting, we will be presenting data from a long-term study of a novel treatment called givosiran, which has been approved and is commercially available."

In the phase 3, randomised, placebo-controlled ENVISION study, givosiran treatment led to sustained clinical benefit among patients aged 12 years and older with acute hepatic porphyria who experienced at least two attacks that required hospitalisation, urgent care or intravenous hemin in the past 6 months. More than 75% of patients were attack-free at 21 to 24 months.

Of ninty-three patients who enrolled in the open-label extension period, data at 36 months showed givosiran treatment induced sustained reduction in median urinary 5-aminolevulinic acid to near-normal levels and decreases in porphobilinogen levels by more than 90%. Continued treatment brought about sustained reduction in attacks and hemin use in both arms.

During the open-label extension period, the proportion of patients who experienced zero attacks per 3-month interval improved, with 86% of patients in the continuous treatment group and 92% of patients in the placebo crossover group attack-free at 33 to 36 months. Similarly, 88% of continuous-treatment patients and 90% of placebo-crossover patients reported no hemin use in the same time frame.

Thapar confirmed that further improvements were observed in quality of life and activities of daily living during the open-label extension period. The most common treatment-related adverse events were injection site reactions, nausea and fatigue. Six patients discontinued treatment.

"Over 3 years the efficacy is maintained," Thapar added. "It does improve the patient's overall quality of life, their attack rates by approximately 90% and they continue to perform well in normal life."

# Genetics of Haemochromatosis


Haemochromatosis is a genetic disorder causing the body to absorb too much iron from the diet, characterised by joint pain and disease, chronic fatigue and weakness, psychological and cognitive difficulties, abnormal liver function , diabetes and cardiomyopathy.

Haemochromatosis UK was founded as The Haemochromatosis Society in 1991, by people affected by genetic haemochromatosis. The founder, Janet Fernau was recognised for her charitable work in 2014 with a MBE. The charity is still run by people with genetic haemochromatosis.

The socity works to support anyone affected by the condition, across three key areas :

- **Support**
- **Education & Awareness**
- **Medical Research**

The charity works closely with other voluntary sector organisations and is a member of the Genetic Alliance UK.

"Haemochromatosis is a genteic condition that is remarkably common in the UK but is rarely diagnosed and for those people who have the condition many of them will go on to develop iron overload." Neil McClements, Chief Executive, Haemochromatosis UK

Haemochromatosis·UK
Helping people live with iron overload

# An End-to-end Liver Diagnostic Service from a Single Blood Sample

BioPredictive S.A., an independent bio-pharmaceutical company, based in France, which designs and markets diagnostic tests for liver diseases, in particular FibroTest and NASH-FibroTest, highlighted 12 key publications 2021/22, available at the free-to-access resource - library.biopredictive.com - within the Fibro Test/ NASH-FibroTest Scientific Publications information pamphlet.

**External validation of LCR1-LCR2, a multivariable HCC risk calculator, in patients with chronic HCV**
Thierry Poynard *et al*, jhepr.2021.100298

**External Validation of LCR1-LCR2, a Multivariable Hepatocellular Carcinoma Risk Calculator, in a Multiethnic Cohort of Patients With Chronic Hepatitis B**
Thierry Poynard *et al*, Gastro Hep Advances 2022, 604-617

**Clinical Interest of Serum Alpha-2 Macroglobulin, Apolipoprotein A1, and Haptoglobin in Patients with Non-Alcoholic Fatty Liver Disease, with and without Type 2 Diabetes, before or during COVID-19**
Olivier Deckmyn, *et al*. Biomedicines10030699.

**Prospective external validation of a new non-invasive test for the diagnosis of non-alcoholic steatohepatitis in patients with type 2 diabetes**
Thierry Poynard *et al*, Aliment Pharmacol Ther. 2021 Oct.

**Impact of Type 2 Diabetes on the Accuracy of Noninvasive Tests of Liver Fibrosis With Resulting Clinical Implications**
Jérôme Boursier , *et al*, Clin Gastroenterol Hepatol. 2022.

**Response to: Impact of Type 2 Diabetes on the Accuracy of Noninvasive Tests of Liver Fibrosis With Resulting Clinical Implications**
Thierry Poynard *et al.* Clin Gastroenterol Hepatol. 2023 Feb.

**Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study**
Mary E Rinella , *et al*. jhep.2022, 536-548

**Evolution of Non-alcoholic Fatty Liver Disease (NAFLD) Biomarkers in Response to Weight Loss 1 Year After Bariatric Surgery-a Post Hoc Analysis of the FibroTest Prospective Study**
Tatiana Codjia *et al.* Obes Surg. 2021 Aug.

**Non-invasive diagnosis and follow-up of chronic infection with Hepatitis C Virus**
Albert Tran *et al.* Clin Res Hepatol Gastroenterol. 2022 Jan.

**Validation of the Performance of A1HPV6, a Triage Blood Test for the Early Diagnosis and Prognosis of SARS-CoV-2 Infection**
Pauline Maisonnasse *et al*. Gastro Hep Adv. 2022.

**Biomarkers for liver disease in urea cycle disorders**
Sandesh C S Nagamani *et al.* Mol Genet Metab. 2021 Jun.

**Assessment of Selected Parameters of Liver Fibrosis and Inflammation in Patients with Diagnosed Cystic Fibrosis**
Sabina Więcek *et al*. Mediators Inflamm. 2021.

NASH-FibroTest is a complete diagnostic test for the liver. It is pain-free, simple to use, and affordable, while offering high standards of performance. NASH-FibroTest™ offers an end-to-end liver diagnostic service from a single blood sample.

# Characterisation of Primary Hepatic Cells

*Treatment Strategies* caught up with Cytes Biotechnologies, a biotechnological company that offers products and services (CRO) based on tissue procurement, cell isolation and cell solutions for *in vitro* models addressed to the research community worldwide, at ILC 2022.

The company's main focus is the isolation and full characterisation of primary human and animal hepatic and skin cells, as well as providing different tissue explants (pathological and healthy donors). They offer an extensive portfolio of fresh and cryopreserved human and animal cells. Among others, plateable and suspension hepatocytes, stellates, Kupffer's, hepatic endothelial, liver sinusoidal endothelial cells, liver subcellular fractions, skin fibroblasts, and keratinocytes.

**Human Hepatocytes**
Human Hepatocytes represent 70 to 80% of the total liver cells population and have become the "gold standard" for drug development and for evaluating hepatic metabolism and toxicity of drugs and other xenobiotics in vitro. In addition, they are becoming utilised more extensively for many kinds of biomedical research, including a variety of biological, pharmacological, and toxicological studies.

continued p 39

The company offers a large stock of fresh, cryopreserved, and plated high-quality human hepatocytes which are presented in two different formats: plateable or suspension. They ensure the best quality of hepatocytes by controlling every step from organ procurement, cell isolation process, and cell distribution. In addition, logistics expertise is also offered, to distribute fresh and cryopreserved cells worldwide with personalised follow-up service.

Their products are provided with a certificate of analysis with data related to the donor's medical record, as well as hepatocyte's characterisation including the number of cells per vial, viability after thawing, optimal cell seeding concentration, and days in cultures. Also, hepatocytes are certified for *in-vitro* like enzyme expression levels, induction studies, and spheroid formation.

**Human Non Parenchymal Cells**

Human liver tissue is highly complex and consists of two different cell entities, hepatocytes, and non-parenchymal cells. The NPC fraction constitutes about 30% of the total liver cell population which includes liver endothelial and sinusoidal endothelial cells, Kupffer cells, cholangiocytes, and hepatic stellate cells. This heterogeneous cell fraction in collaboration with hepatocytes plays a role in physiological liver functions, as well as mediating acute liver damage, drug-induced liver injury (DILI), and chronic liver injuries, such as cirrhosis.

Because liver function relies on so much more than hepatocytes themselves, co-cultures with NPCs are critical for every *in vitro* liver model. The advantage of having a stable co-culture system is to mimic the intrinsic environment of the liver such as the contributions and interactions within the liver cell population. NPCs are suitable for use in many cell-based assays including toxicity tests, drug screening, and metabolism tests, and are powerful tools to study liver function, physiology, and liver diseases.

Cytes offers each of these cell types individually as well as a mix of Kupffer cells (KC), liver endothelial cells that include sinusoidal endothelial cells (LSEC), and and stellate cells (HSC). Each product is fully characterised in terms of cell number, viability, and morphology. Mixed NPCs are also characterised by flow cytometry analysing the principal markers expressed in the different cell types presented in the mix. The stellate cells and liver endothelial cells are additionally characterised by immunofluorescence by using important makers present in these cells. Cytes can also offer human hepatocytes and NPCs matched from the same donor.

**www.cytesbiotechnologies.com/**

# Rise in Global Liver Cancer Deaths

Nonalcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease are among the main contributors of increased mortality related to chronic liver disease and liver cancer burden.

"Although viral hepatitis B and C and alcohol liver disease have historically been the drivers of burden of chronic liver disease and liver cancer, NAFLD and nonalcoholic steatohepatitis have increasingly become more prominent," Zobair Younossi, MD, MPH, President of Inova Health System Center for Liver Diseases, stated. "The most recent meta-analysis suggests that the global prevalence of NAFLD is 29%, and in 2020 NAFLD was the second indication for all liver transplants in the U.S."

Younossi and colleagues analysed data from the 2019 Global Burden of Disease Study, to assess changes in the global prevalence, incidence, mortality and morbidity [disability-adjusted life-years (DALYs)] related to liver cancer and chronic liver disease.

The prevalence, incidence, mortality and DALYs from liver disease in 2019, according to study results, was 1.69 billion (liver cancer: 0.04% and chronic liver disease: 99.96%), 2.59 million (20.7% and 79.3%), 1.95 million (24.8% and 75.3%) and 58.7 million (21.3% and 78.7%). From 2009 to 2019, researchers reported a 33.7% increase in liver cancer prevalence as well as a 22.7% increase in chronic liver disease prevalence. Incidence (30% and 14.8%), deaths (27.2% and 10.6%) and DALYs (21.9% and 5.1%) also increased.

Furthermore, increases in worldwide liver cancer deaths [per 100,000; annual percent change (APC) = 1.33%] during that decade were driven by NAFLD (0.36 to 0.45; APC = 2.47%], alcohol-associated liver disease (0.97 to 1.17; APC = 1.91%), HBV (2.25 to 2.48; APC = 0.21%) and HCV (1.64 to 1.83; APC = 1.12%) . In the same time period, a drop in global chronic liver disease rates (per 100,000; APC = –0.18%) was attributed to a decrease in HBV (5.07 to 4.28; APC = –1.83%), although HCV (4.9 to 5.11; APC = 0.37%), alcohol-associated liver disease (4.67 to 4.81; APC = 0.45%) and NAFLD (1.53 to 1.74; APC = 1.33%) increased.

"NALFD is responsible for the greatest increase in mortality related to liver cancer and chronic liver disease," Younossi added. "Despite this increasing burden, awareness about NAFLD is very low. To address these increasing trends and low awareness, regional and global policies and programs need to be established."

# The Management of Hepatocellular Carcinoma

The debate on whether aetiology matters in the management of hepatocellular carcinoma continues and was the topic for discussion at the well-attended lunchtime sympoium on June 24th at ILC 2022.

Capital Suite 16 was the venue for the lunchtime symposium, offering insights from the esteemed faculty of Professor Tom Ludde (Chair, pictured left), Department of Gastroenterology, Hepatology and Infectious Diseases at the University Hospital Düsseldorf (Germany), Professor Bruno Sangro (pictured right), Head of Hepatology Unit, Clinica Universidad de Navarra and Professor Andrea Casadei Gardini, senior researcher and Consultant Medical Oncologist at San Raffaele Hospital (University Vita e Salute), Milan.

The three speakers discussed the latest statistics on the NASH pandemic, gave commentary on controversies from the recent phase III trials and provided an overview of the real-world therapeutic efficacy and safety of Lenvima (c) (lenvatinib) in hepatocellular carcinoma (HCC).



# Hepatocellular Carcinoma MR Imaging

Attendees at the International Liver Congress 2022 were offered the opportunity to learn more on Hepatocellular Carcinoma MR Imaging from Dr Keisuke Hino, Department of Hepatology and Pancreatology, Kawasaki Medical School and Dr Katsuyoshi Ito, Department of Diagnostic Radiology, brochure , Kawasaki Medical School through the Bayer funded and distributed brochure entitled *Hepatocellular Carcinoma MR Imaging for Referrers.*

The informative brochure was created both to help gastroenterologists understand liver MRI and use it in diagnosis in the everyday clinical setting as well as to summarise the procedure for interpreting liver MRI images, along with useful innovations. tips on interpretation of characteristics and contrast patterns of Gd-EOB-DTPA-enhanced MRI.

Dr Keisuke Hino presents from the standpoint of the gastroenterologist. "It is no exageration to call the advent of Primovist (Gd-EOB-DTPA) Gd-EOB-DTPA-enhanced MRI a real progress in diagnostic imaging for hepatocellular carcinoma. With the means of distinguishing cancerous from non-cancerous area on the basis of hepatocellular function, it has become possible to detect even minute lesions that would previously have gone undetected. At the same time, the new issue has arisen of how to handle mass lesions appearing as images with enhancement defects in the hepatobiliary phase alone. With Gd-EOB-DTPA-enhanced MRI, gastroenterologists now have the opportunity to further improve the prognosis of hepatocellular carcinoma patients through early diagnosis".

Dr Katsuyoshi Ito presents from the standpoint of the radiologist. "With Gd-EOB-DTPA-enhanced MRI, we must interpret the hepatocyte phase images differently, as the contrast enhancement effect will differ depending upon the extent to which transporters appear, as well as upon hepatocyte function. This interpretation transcends the existing concept of 'contrast enhancement effect' based on haemodynamics and histopathology. Implicit in this is the possibility of determining new aspects of the biological characteristics of hepatocellular nodules. An MRI provides highly specific images for various types of tissues which contain water, fat, blood from haemorrhage or others, with the development of more and more imaging techniques, and therefore, the imaging sequence obtained in a single examination becomes truly varied. If we factor in the use of contrast agent Gd-EOB-DTPA, it becomes necessary to appropriately grasp which series corresponds to which image in order to interpret images efficiently"

# Hepatocellular Carcinoma Progression in Patients with Diabetes

According to data presented at the International Liver Congress, alcohol misuse was a primary trigger for progression of liver disease to hepatocellular carcinoma among a subset of French patients with type 2 diabetes.

Lucia Parlati, a PhD student at the Cochin Institute in Paris, commented, "A history of alcohol use disorders accounted for more than half of the HCC burden of patients with type 2 diabetes in France from 2011 to 2020. Male patients with type 2 diabetes, aged between 65 and 70, with a history of alcohol use disorders were at a higher risk of HCC."

Parlati and colleagues, in a longitudinal, retrospective study, analysed 2,883,684 patients (mean age, 67 years; 54% men) with type 2 diabetes using the 2011 to 2020 National Hospital Discharge database. Researchers measured incidences of HCC, liver disease progression and death.

HCC incidence was 1.19 (95% CI, 1.17-1.21) per 1,000 person-years at risk, which totaled 26,136 cases (0.9%) over 12,504,690 patient-years according to results. Researchers further recorded a history of alcohol use disorders among 55% of patients and non-metabolic liver-related risk factors among 21% of patients.

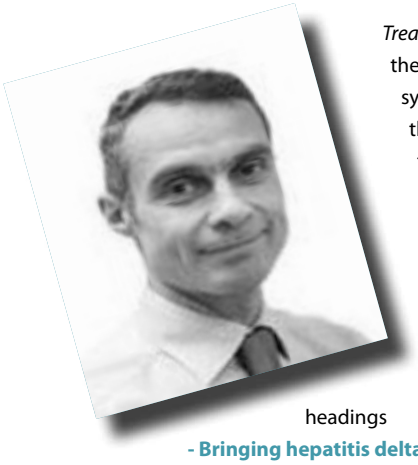
In patients without well-identified risk factors for liver disease progression, HCC incidence was 0.57 (95% CI, 0.55-0.58) per 1,000 person-years at risk.

A higher risk for HCC was independently associated with male sex, age 40 to 70 years, alcohol use disorders (adjusted OR = 20.8; 95% CI, 20-21.5) and obesity (aOR = 1.24; 95% CI, 1.2-1.28).

"Alcohol use is a modifiable risk factor and patients with type 2 diabetes should be advised to abstain from alcohol," Parlati stated.

Presenter of "Modeling regional variation in the return on investment of VCTE for fatty liver disease (FLD) in the U.S.". Mazen Noureddin, M.D., director, Fatty Liver Program, Cedars-Sinai Medical Center, commented, "Broad deployment of VCTE devices, like FibroScan, is a financially advantageous solution to address the fatty liver disease (FLD) epidemic, with the South and Midwest regions standing to benefit the most, likely due to a combination of the higher prevalence rates of FLD and relevant comorbidities, as well as medical utilisation and costs."

# See B. Think D



*Treatment Strategies* attended the lunchtime Gilead-sponsored symposium entitled 'Lighting the Path forward to Innovative treatment in Hepatitis Delta' that took place on Friday 24th June in the Capital Hall at this years International Liver Congress.

The well-attended symposium was presented under the following programme headings

- **Bringing hepatitis delta out of the shadows**
- **See B. think D: The path to care begins with screening**
- **Bulevtride: What can be acheived today in hepatitis delta**
- **Question and answers and panel discussion**
- **Keeping the spotlight on hepatitis delta**

GILEAD

The symposium was chaired by Patrick Kennedy, Consultant Hepatologist and Gastroenterologist at Barts Health NHS Trust (pictured left) with further presentations from Pietro Lampertico, 1st Division of Gastroenterology, Fondazione Cà Granda IRCCS Ospedale Maggiore Policlinico, Università degli Studi di Milano, Victor de Ledinghen, Professor of Hepatology and Head of the Hepatology and Liver Transplantation Unit, Haut Lévêque Hospital (pictured above right) and Tatyana Kushner, Associate Professor of Medicine in the Division of Liver Diseases at the Icahn School of Medicine at Mount Sinai (pictured right).



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# Facilitating Drug Development for the Treatment of Liver Disease

Non-alcoholic fatty liver disease (NAFLD) comprising both non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), has emerged as a leading cause of chronic liver disease. NAFLD affects approximately 25% of adults and 10% of children in the U.S.[1,2] and is associated with obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension.[3] Patients with NASH may progress to cirrhosis, increasing the risk of liver-related morbidity and mortality, including hepatocellular carcinoma.[4] In addition to liver-related outcomes, patients with NASH also have an increased risk of cardiovascular disease,[5] chronic kidney disease,[6] and non-liver cancers.[7] NASH is now the leading indication for liver transplantation in women, and the second leading cause in men.[8]

With the growing burden of end stage liver disease, and the inherent limitations of transplantation (access, cost, and availability), it is critical to increase the pace of development of safe and effective therapies to prevent and treat NASH, fibrosis and cirrhosis to reduce morbidity and mortality.

Interest in the development of therapeutic options to prevent and treat NASH is high; however, the drug development field is challenged by the complexity of the disease etiology and pathophysiology, natural course of disease and the resulting divergent strategies for therapeutic approaches.

The Forum's aim is to advance the regulatory sciences for the treatment of NAFLD/NASH and liver fibrosis by providing an independent and neutral venue for ongoing multi-stakeholder dialogue. Its work will facilitate making the best science-based decisions on how to study efficacy and safety in real time, as thier collective knowledge and experience with therapies for liver diseases advances.

Once new drug candidates and therapeutic strategies are identified, their rapid, safe development is in the best interest of all stakeholders, most of all, the patients.[9] Careful deliberation on issues of common interest and concern by an independent body whose neutrality and objectivity is ensured through representation and active engagement of scientific experts from all stakeholder groups, including academia, industry, patient community and regulatory agencies, in a non-competitive and safe environment, breaks down inefficiencies by increasing clarity and standardisation and decreasing uncertainty, and allows the whole field to benefit from valuable lessons learned. The Liver Forum provides a platform for such a process.

Traditional FDA approval mechanisms require demonstration of benefit based on hard clinical endpoints. For conditions with a long asymptomatic natural history such as NASH, the time to reach hard endpoints such as cirrhosis, hepatocellular carcinoma and death can be a significant barrier for clinical trials. The potential for accelerated approval, requiring identification and validation of surrogate markers, is hampered by the heterogeneity of disease presentation, underlying disease mechanisms, and progression. The field also lacks ideal standards for assessing and staging fibrosis, NAFLD, NASH, and cirrhosis. Effective therapeutic strategies will likely require combination therapies, personalised according to patient characteristics. The regulatory pathway for combination therapies can be complex, full of uncertainties and burdensome for patients, clinical researchers, regulators and industry.

The Trial Designs and Endpoints for Liver Disease Secondary to Nonalcoholic Fatty Liver Disease[10] meeting sponsored by the U.S. Food and Drug Administration (FDA) and the American Association for the Study of Liver Disease (AASLD) highlighted these concerns and issues. Consensus emerged that the field of hepatology would benefit from continuing the multi-stakeholder dialogue initiated at that meeting, as this rapidly moving and dynamic field will require collaborative bridges and coordinated effort between many parties. Thus the Liver Forum was established.

The Forum is led by a Steering Committee which provides overall scientific leadership and guidance, and is managed by Forum staff. Throughout the year, the Liver Forum convenes working group conference calls, email/web-based communication, in-person meetings, webinars, and workshops as needed. Presentations and materials from previous meetings are posted, with permission, on the forum's website.

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THE FORUM
For Collaborative Research™

# Innovation and Collaboration at the Global Liver Institute

The Global Liver Institute (GLI) is a patient-driven 501(c)3 nonprofit organisation headquartered in Washington, DC, with offices in the EU and UK, founded in the belief that liver health must take its place on the global public health agenda commensurate with the prevalence and impact of liver disease and the importance of liver health to well-being.

Global Liver Institute promotes innovation, encourages collaboration, and supports the scaling of optimal approaches to improve research, care, and policy.

By bringing together more than 200 community-based, national, and international organisations across its Councils, Campaigns, and events, GLI equips advocates to identify and solve the problems that matter to liver patients.

Follow GLI on Twitter, Facebook, Instagram, LinkedIn, and YouTube.

GLI is the global host of International NASH Day, held annually on the second Thursday in June.

*"The gaps in liver health advocacy have resulted in one and a half billion people living with liver diseases, most of whom are undiagnosed, undertreated, and over-stigmatised. I know because I am one of these people"*

**Donna R. Cryer, JD, founder, CEO, Global Liver Institute**

### Mission

To improve the lives of individuals and families impacted by liver disease through promoting innovation, encouraging collaboration, and scaling optimal approaches to help eradicate liver diseases.

### Nash Day

Let's Step Up for NASH this June and raise awareness about nonalcoholic fatty liver disease (NAFLD) and its more advanced form, nonalcoholic steatohepatitis (NASH), in your communities.

NAFLD is the leading cause of chronic liver disease globally, affecting 1 in 4 people. Of that, 1 in 5 will develop NASH, which can progress to advanced liver fibrosis, cirrhosis, or liver cancer. The diagnosis and treatment of liver disease has advanced significantly in recent decades, but many patients go undiagnosed, which results in poor long-term outcomes.

"The gaps in liver health advocacy have resulted in one and a half billion people living with liver diseases, most of whom are undiagnosed,undertreated, and over-stigmatised. I know because I am one of these people" comments Donna R. Cryer, JD, founder, CEO, Global Liver Institute.

# Understanding Advanced Liver Disease

**About The British Liver Trust**

The British Liver Trust, are the UK's leading liver health charity working to improve liver health for all and supporting those affected by liver disease or cancer, reaching millions of people each year through various campaigns and services.

The British Liver Trust, are the largest UK liver charity for adults and we lead the fight against liver disease and liver cancer. The trust reaches over a million people each year; raising awareness of the risk factors of liver disease and providing vital advice to help people improve their liver health. They provide patients with up to date information and support including a free nurse-led helpline and online community.

The patient leaflet, 'A Guide to Understanding Advanced Liver Disease Varices and Variceal Bleeding' was distributed at this years International Liver Congress. The production of the patient leaflets have been supported by Norgine as a service to medicine.
The eighteen page leaflet is a guide to understanding Varices and Variceal Bleeding and is available below.

https://britishlivertrust.org.uk

BRITISH LIVER TRUST

# The First Disease-modifying Therapy for Patients with Alcohol-associated Hepatitis

Durect, a California-based biopharmaceutical company was delighted to attend this year's International Liver Congress™ and share information about alcohol-associated hepatitis (AH) and its ongoing AHFIRM study, a Phase 2b trial in subjects with alcohol-associated Hepatitis to evaluate safety and efflcacy of larsucosterol (DUR-928) treatment. The study is a randomised, double-blind, placebo-controlled trial being conducted at more than 60 clinical trial sites across the US, Europe, UK, and Australia.

The six team members from Durect on site engaged with physicians from all over the world who visited the company's booth. Most of the discussions revolved around the unmet needs in AH and the challenges of treating these patients in the absence of effective or approved therapies. AH is a life-threatening disease caused by chronic heavy alcohol use, frequently precipitated by a recent binge. It is characterised by inflammation in the liver and may lead to liver and other organ failure. AH accounts for roughly 137,000 hospitalisations per year in the US. Approximately 30% of patients die within 90 days of hospitalisation. The cost of each fatal hospitalisation episode is approximately $151,000. There is currently no approved treatment for AH, presenting a large unmet need.

Larsucosterol is an endogenous epigenetic regulator administered intravenously. It improves cellular function and regulates the expression of many different genes and has the potential to treat acute organ injuries such as AH. Larsucosterol was evaluated in a Phase 2a study in 19 patients with severe or moderate AH. Notably, all patients treated with larsucosterol survived the 28-day follow-up period compared to a 26% historical 28-day mortality rate.

At the International Liver Congress, DURECT also had the opportunity to reveal its refreshed company branding, which echoes Durect's evolution into an epigenetics company and its forward-looking focus in unlocking the potential of these therapeutics to revolutionise medicine.

For more information on the company's ongoing study in AH, AHFIRM, please visit: https://clinicaltrials.gov/ct2/show/NCT04563026?term=AHFIRM&draw=2&rank=1

For more information on Durect and larsucosterol visit,

**https://www.durect.com**

# Liver Disease Development - Key Oral Presentations and Posters

More than 80 abstracts were presented at the International Liver Congress™ (ILC) 2022 and key oral presentations included Week 48 primary endpoint data from the Pivotal Phase 3 program of Hepcludex® (bulevirtide) evaluating its efficacy and safety for the treatment of hepatitis delta virus (HDV) and the impact of the treatment on patient-reported outcomes.

Gilead presented real-world data on global efforts to support the World Health Organization's (WHO) goal of hepatitis C (HCV) elimination, long-term results from studies in the treatment of chronic hepatitis B (HBV) and ongoing research in nonalcoholic steatohepatitis (NASH) and primary sclerosing cholangitis (PSC).

"We are very proud to share such a broad range of research and progress at this year's International Liver Congress as we continue to pursue solutions to some of the greatest unmet needs for people living with liver disease," said Merdad Parsey, MD, PhD, Chief Medical Officer, Gilead Sciences. "As a leader in liver disease, with more than two decades of experience in HCV and HBV, we are applying our expertise to develop treatments for HDV and pioneering research into NASH, PSC and HBV cure."

Driving Innovation in HDV Research

Gilead presented the latest data from the Phase 3 MYR301 study on the safety and efficacy (Oral 0509) of bulevirtide in chronic HDV at Week 48 and patient-reported outcomes (Oral 3237) in adults with chronic HDV and compensated liver disease. These results underscore the utility of bulevirtide as the first-in-class treatment for chronic HDV.

In addition to advancing scientific innovation in HDV, Gilead is working in partnership with the liver community to increase understanding of the burden and impact of HDV for patients and health systems. At ILC 2022, nine studies were presented further characterising the HDV burden, prevalence, epidemiology, patient characteristics and resulting economic impact on health systems. This included an analysis of the U.S. All-Payer Claims Database (Posters 1436 and 1326) which found that 4.8% of the adults with HBV also had an HDV diagnosis. Adults with HDV also had high rates of baseline comorbidities, liver disease severity and experienced significantly greater overall healthcare resource utilisation and costs. These findings highlight the need for more effective strategies to screen, diagnose and treat HDV, which may also translate into cost savings for the healthcare system.

Impact of Treatment in Viral Hepatitis

Data

| Abstract | Abstract Title |
|---|---|
| **HDV** | |
| Oral 0509 | Efficacy and Safety of Bulevirtide Monotherapy Given at 2 mg or 10 mg Dose Level Once Daily for Treatment of Chronic Hepatitis Delta: Week 48 Primary Endpoint Results From a Phase 3 Randomized, Multicenter, Parallel Design Study |
| Oral 3237 | Treatment With Bulevirtide Improves Patient-Reported Outcomes in Patients With Chronic Hepatitis Delta: An Exploratory Analysis of a Phase 3 Trial at 48 Weeks |
| Poster 0557 | Integrated Efficacy Analysis of 24-week Data From Two Phase 2 and One Phase 3 Clinical Trials of Bulevirtide Monotherapy Given at 2 mg or 10 mg Dose Level for Treatment of Chronic Hepatitis Delta |
| Poster 0597 | Integrated Safety Analysis of 24-week Data From Three Phase 2 and One Phase 3 Clinical Trials of Bulevirtide Monotherapy Given at 2 mg and 10 mg Dose Level for Treatment of Chronic Hepatitis Delta |
| Poster 1326 | Healthcare Resource Utilization and Costs of Hepatitis Delta in the United States: An Analysis of All-Payer Claims Database |
| Poster 1436 | Evaluating Hepatitis Delta Virus Disease Prevalence and Patient Characteristics Among Adults in the United States: An Analysis of All-Payer Claims Database |
| Poster 1456 | Hepatitis Delta Management in the United States: An Analysis of All-Payer Claims Database |
| Poster 1758 | Rising Clinical and Economic Burden Among Hepatitis D Patients Who Attended Spanish Hospitals |
| Poster 1769 | Analysis From National Hospital Discharge Records Database in Spain: Increased Baseline Comorbidity Burden Including Liver Severity Among HDV Coinfection Versus HBV Monoinfection Patients |

presented on HCV will further explore the benefit of treatment with direct-acting antivirals (DAAs) on clinical markers, quality of life, cost effectiveness and progress toward the WHO goal of HCV elimination. Of note, Gilead presented data from two analyses in Spain which found that scaling up testing and treatment with DAA's reduced the prevalence and incidence of HCV over time (Poster 3205) and over five years, treatment with Epclusa® (sofosbuvir/velpatasvir) significantly reduced morbidity and mortality (Poster 3201).

| | |
|---|---|
| **HCV** | |
| Poster 2954 | Real-World Value and Innovation of Direct-Acting Antivirals for the Treatment of Chronic Hepatitis C at Kaiser Permanente Southern California |
| Poster 3021 | Evaluation of the Clinical and Economic Value of Sofosbuvir/Velpatasvir (SOF/VEL) in Patients With Chronic Hepatitis C in Spain During the Last 5 Years |
| Poster 3205 | The Value of Increased HCV Testing and Treatment Strategies in Spain to Achieve Elimination Goals |
| **HBV** | |
| Poster 0660 | Quantification Of HBV Hepatocyte Burden Using Novel Multiplex Immunofluorescence Staining and Image Analysis Reveals Substantial Reduction in HBV Liver Burden With Anti-Viral Treatment |
| Poster 0832 | Evaluation of Renal and Bone Safety at 4 Years in Post-Liver Transplant Patients With Chronic Kidney Disease Receiving Tenofovir Alafenamide for HBV Prophylaxis |
| **Liver Fibrosis** | |
| Poster 1403 | The MRI and AST (MAST) Score is Correlated With Noninvasive and Histologic Markers of Fibrosis in Patients With Advanced Fibrosis Due to NASH |
| Poster 1405 | Safety and Efficacy of the Farnesoid X Receptor (FXR) Agonist Cilofexor in a Proof-of-Concept Study in Patients With Compensated Cirrhosis Due to Primary Sclerosing Cholangitis (PSC) |
| Poster 2202 | Inhibition of Tumor Progression Locus 2 (TPL2) Halts the Progression of Liver Fibrosis in a Stringent Long Term Choline-Deficient High-Fat Diet (CDHFD) Rat Model |

Real-world evidence from the Kaiser Permanente Southern California healthcare system was also presented (Poster 2954), showing a reduction in HCV-related morbidity and mortality, and a significant improvement in quality-adjusted life-years (QALYs) in patients treated with DAAs like sofosbuvir/velpatasvir. Furthermore, the use of DAAs in this setting resulted in cost savings within the healthcare system.

These data provide additional support for the effectiveness of utilising testing and treatment of HCV with DAAs within key populations as a promising strategy to not only reduce the clinical and economic burden of HCV, but as strategies to ultimately achieve the WHO's goal of viral hepatitis elimination by 2030.

In HBV, data presented highlighted the long-term results of switching to Vemlidy® (tenofovir alafenamide 25 mg, TAF) for HBV prophylaxis in post-liver transplant patients with chronic kidney disease, providing sustained improvements in bone and renal safety parameters (Poster 0832). In addition, Gilead presented results from a study in which a new multiplex imaging method was used to quantify HBV hepatocyte burden, demonstrating a substantial reduction in HBV liver burden with anti-viral treatment (Poster 0660).

Advancing Liver Fibrosis Monitoring and Treatment

Five presentations included a range of early data from the company's broader liver disease research and development program as Gilead continues its work to pursue new approaches in the potential treatment and monitoring of NASH and PSC.

Non-invasive measures of treatment response that avoid the need for liver biopsy remain a significant unmet need in NASH clinical research and patient care. New data was presented assessing the associations between treatment-induced changes in the MRI-aspartate aminotransferase (MAST) Risk score, and non-invasive and histologic measures of fibrosis in patients with advanced fibrosis due to NASH (Poster 1403). The study found the MAST Risk score is correlated with non-invasive and histologic measures of fibrosis and may be a useful marker of treatment response beyond conventional histologic methods.

In addition, Gilead presented a proof-of-concept study, evaluating the safety and efficacy of escalating doses of investigational cilofexor (GS-9674) in patients with compensated cirrhosis due to PSC (Poster 1405). The study found escalating doses of cilofexor over 12 weeks were well tolerated and showed improved markers of cholestasis and liver biochemistry. Cilofexor is undergoing evaluation in the ongoing Phase 3 PRIMIS study of PSC patients without cirrhosis.

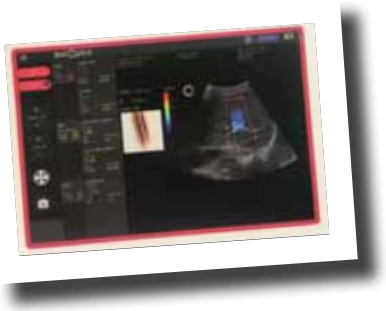
# An App for Chronic Liver Disease Management

The various digital Industries have gone through major transformations: smartphones have dematerialised cameras or sound systems and democratised these technologies. Ultrasound is a digital industry. It has been miniaturised since 2000. Dematerialisation pushes the boundaries of miniaturised ultrasound and transforms cart-based ultrasound system into an app-based service.

E-Scopics develops low power digital transducers connected to Ultrasound SaaS. Without any compromise on quality, its proprietary computerised ultrasonography technology leverages processing power from consumer devices and the cloud and delivers premium diagnostic performance.

Acquisition guidance, image automation and AI-based controls remove the need for expertise and ease adoption of ultrasound amongst all healthcare professionals.


Currently liver biopsy and histological assessment of liver tissue is the only way to diagnose NASH and assess the disease severity. Owing to the large population at risk, the lack of early symptoms and the invasiveness of liver biopsy, the medical community lacks an easy, non-invasive diagnostic tool for NASH. The expected approval of NASH pharmaceutical treatments in the coming months urges the development of such biomarkers of NASH severity so as to implement surveillance programs.



E-Scopics dematerialised ultrasound system supports quantitative elastography methods that estimate liver fibrosis severity via tissue stiffness. Liver elastography has proven to be a reliable method for liver fibrosis assessment in several chronic liver diseases like viral hepatitis.

The modality provides an overall estimation of liver tissue stiffness, and thereby overcomes sampling errors from biopsy. In addition liver elastography offers a continuous measurement of liver stiffness, which gets round quantisation errors related to fibrosis histological scoring systems. These issues of liver biopsy have recently been highlighted by the analysis of the placebo arms of several NASH drugs pharmaceutical trials.

**https://www.e-scopics.com**

# Data Presented on Terlipressin in Adult Patients with Hepatorenal Syndrome

At the European Association for the Study of the Liver (EASL) International Liver Congress, Mallinckrodt plc, a global biopharmaceutical company, developing, manufacturing, marketing and distributing specialty pharmaceutical products and therapies, presented two scientific posters on the disease progression and treatment paradigms for patients with hepatorenal syndrome (HRS) involving rapid reduction in kidney function.[1]

Terlipressin is an investigational agent being evaluated for the treatment of HRS involving rapid reduction in kidney function[1] in the U.S., and its safety and effectiveness have not yet been established by the FDA. It is one of the most studied pharmacological agents in HRS with more than 70 published manuscripts and presented abstracts on clinical data to date.[3] It has been approved outside the U.S. for more than 30 years and is available on five continents for its two indications in the countries where it is approved.[4,5,6]

Hepatorenal syndrome (HRS) involving rapid reduction in kidney function[1] is an acute and life-threatening syndrome involving acute kidney failure in people with advanced liver disease.[2] HRS is classified into two distinct types – a rapidly progressive type that leads to acute renal failure and a more chronic type that progresses over weeks to months.[2] HRS is estimated to affect between 30,000 and 40,000 Americans annually.[7,8] If left untreated, the rapid reduction in kidney function associated with HRS[1] has a median survival time of approximately two weeks and greater than 80 percent mortality within three months.[9]

Khurram Jamil, Vice President, Hepatology, Clinical Development & Critical Care, said, "It is our hope that this research may help inform clinicians on the early identification and management of adult patients with HRS with rapid reduction in kidney function.[1] We look forward to sharing new data from a retrospective analysis that uncovers the influence of baseline serum creatinine (SCr) levels on clinical outcomes for patients with HRS involving rapid reduction in kidney function,[1] and resharing the findings of our subgroup analysis examining HRS gender differences and response to treatment – recently presented at the 2022 American Transplant Congress."

These studies are sponsored by Mallinckrodt Pharmaceuticals and include:

**Abstract 2952 Title: Early Treatment with Terlipressin in Patients with Hepatorenal Syndrome Yields Improved Clinical Outcomes in 3 Phase III North American Studies**
Presenter: Michael Curry, MD
Poster #: FRI537

**Abstract 564 (Encore) Title: Gender Affects the Association Between Serum Creatinine Levels and Clinical Response to Terlipressin in Patients with Hepatorenal Syndrome Type of Acute Kidney Injury**
Presenter: Khurram Jamil, MD
Presentation Date: June 24, 2022; 9AM – 6PM BST
Poster #: FRI490

***"It is our hope that this research may help inform clinicians on the early identification and management of adult patients with HRS with rapid reduction in kidney function"***
**Khurram Jamil, Vice President, Hepatology, Clinical Development & Critical Care, Mallinckrodt plc**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# Advances in Non-invasive Technologies


Perspectum, a global medical technology company with offices in the US, the UK, Portugal, and Singapore, delivers leading digital technologies that help clinicians provide better care for patients with chronic metabolic diseases, multi-organ pathology, and cancer. With a strong focus on precision medicine using advanced imaging and genetics, Perspectum's vision is to empower patients and clinicians through quantitative assessments of health enabling early detection, diagnosis, and targeted treatment.

LiverMultiScan is a non-invasive MRI scan that accurately assesses signs of liver disease, offering a complete picture of liver health.

LiverMultiScan is a unique non-invasive tool offering you and your patients an easy-to-understand report to provide quantitative metrics that may empower clinicians with information to assess the current state of liver disease. Treatments exist today that enable patients to manage and even reverse liver disease. Life-style adjustments and some additional approaches have been employed successfully. LiverMultiScan offers a comprehensive view of liver health and allows monitoring of the effectiveness of treatment.

Perspectum symposium ILC 2022

Advances in Non-invasive Imaging for NAFLD/NASH

System-based Solutions for NAFLD in the UK

Dr Saima Ajaz, Clinical Research Fellow
Institute of Liver Studies, Kings College Hospital, London

Current Landscape of Non-invasive Technologies and the Role of LiverMultiScan Quantititative Multiparametric MRI for Patient Risk Stratification, Prognosis and Treatment Decisions in Today's Clinical Practice

Dr Naim Alkhouri, VP of Academic Affairs;, Director, Fatty Liver Program, Arizona Liver Health

Upcoming NASH Therapeutics; the Need for Non-invasive Technollogies

Dr Stephen Harrison, Hepatologist Medical Director, Pinnacle Clinical Rsearch

Perspectum

# Diet - a Critical Part of Study Design

When designing experiments with animal models, the importance and variety of dietary choices is typically overlooked, especially if diet is not the main focus of the study. This can be seen in the methods sections of many publications in lab animal science, where it is common to read vague terms such as 'standard chow' or 'regular diet' which do not provide readers with useful information. There are many reasons to consider the diet carefully for each and every experiment, especially given that dietary factors are known to affect nearly every phenotype, including health to disease characteristics.

Most all of us are aware that certain dietary choices can increase or decrease the likelihood of developing certain diseases. Our diets can also change our metabolism as well the levels of circulating factors (hormones, lipids, etc.) which may be markers for disease risk. What is often overlooked is the fact that these concepts also apply to laboratory animals, making diet a critical part of study design.

"We're committed to our customers doing preclinical research and passionate about formulating custom purified diets to meet their particular needs. ILC 2022 was a great meeting for us to talk with researchers using animal models to study fatty liver disease. Diet is a key driver in the development of fatty liver disease in animal models, and there are many different components in the diet that can be manipulated to allow for various levels of disease to occur." Michael Pellizzon, Ph.D. | Science Director.

Research Diets' scientists consult with our scientist customers around the world. In our conversation, we integrate information about the animal model, the desired phenotype and the published literature to arrive at suggested diet formulas.

Unlike other diet manufacturers, custom purified ingredient diet formulations are standard procedure for Research Diets. By carefully designing the diet formulas, researchers can test the effects of small or large controlled changes in nutrient composition.

Research Diets, Inc. (RDI) has over 25 years of collaborative research experience in the study of dietary factors on phenotype expression or NutriPhenomics.

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# Late-breaking Data from Phase 3 MAESTRO NAFLD-1

Madrigal Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), announced data from multiple resmetirom abstracts presented at the International Liver Congress (EASL 2022), including a late-breaking presentation of data from the Phase 3 MAESTRO-NAFLD-1 study and three additional oral presentations from the resmetirom clinical development program.

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, "Today's late-breaking presentation at EASL is our first opportunity to share the double-blind results from the MAESTRO-NAFLD-1 safety study in a major scientific meeting. The data from this study will play an important role in the planned new drug application submission for resmetirom and help shape the non-invasive testing strategies that guide patient care in 'real world' clinical practice."

Becky Taub, M.D., Chief Medical Officer and President of Research & Development of Madrigal, added, "In addition to the late-breaker, we are sharing new safety and efficacy data from patients with compensated NASH cirrhosis who participated in an open-label portion of MAESTRO NAFLD-1; these data informed our decision to initiate a new Phase 3 outcomes study in this more advanced NASH patient population."

*"The data from this study will play an important role in the planned new drug application submission for resmetirom and help shape the non-invasive testing strategies that guide patient care in 'real world' clinical practice."*
**Paul Friedman, M.D., Chief Executive Officer, Madrigal**

Stephen Harrison, M.D., Medical Director for Pinnacle Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and Principal Investigator of the MAESTRO studies, commented, "The MAESTRO-NAFLD-1 data we are presenting at EASL continue to reinforce confidence in the favorable safety profile of resmetirom and provide a deeper view of efficacy in patients with both early-to-moderate fibrosis and compensated NASH cirrhosis. The marked reductions in non-invasive measures of fibrosis, liver fat, and liver volume observed at 52 weeks in the open-label cirrhosis portion of the trial are particularly encouraging; this is a difficult-to-treat population at elevated risk of progressing to negative outcomes."

**Late-Breaking Oral Presentation: "Primary data analyses of MAESTRO-NAFLD-1, a 52 week double-blind placebo-controlled phase 3 clinical trial of resmetirom in patients with NAFLD" (LB005)**

Primary and key secondary endpoints from the double-blind, placebo-controlled, 969-patient MAESTRO-NAFLD-1 safety study were achieved; resmetirom was safe and well tolerated and provided significant reductions in liver fat (measured using magnetic resonance imaging proton density fraction (MRI-PDFF) and FibroScan controlled attenuation parameter (CAP)), LDL-C, and other atherogenic lipids vs placebo. Patients treated with resmetirom also achieved significant reductions relative to placebo in ALT, AST, and GGT. For those patients with sufficient baseline liver stiffness, as measured by FibroScan vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE), responder analyses showed statistically significant VCTE and MRE responses in the resmetirom groups compared to placebo. Adverse event-related withdrawals were uncommon in the MAESTRO-NAFLD-1 study. The most common adverse event reported with greater frequency in the resmetirom groups vs placebo was generally mild diarrhea or increased stool frequency at the beginning of therapy.

**Oral Presentation: "Biomarkers, imaging and safety in a well-compensated NASH cirrhotic cohort treated with resmetirom, a thyroid hormone receptor beta agonist, for 52 weeks" (OS121)**

105 patients with well-compensated NASH cirrhosis were enrolled in the open-label arm of the MAESTRO-NAFLD-1 study. Baseline FibroScan VCTE (kPa 24.6) and MRE (5.7) scores were consistent with F4 fibrosis. Patients with lower MRI-PDFF (≤5%) at baseline had more progressed cirrhosis and greater spleen volumes. Similar to patients with non-cirrhotic NASH, liver volume was greatly elevated compared to normal at baseline. Resmetirom reduced MRI-PDFF and LDL-C and other atherogenic lipids in patients with NASH cirrhosis and reduced FibroScan controlled attenuation parameter (CAP), VCTE, and MRE in a significant fraction of patients. The largest reduction in FibroScan VCTE (mean reduction of 9 kPa) occurred in the more advanced group (baseline PDFF ≤5%). Similar improvements were observed in MRE. 73% of patients, independent of baseline cirrhosis severity, had at least 15% reduction in liver volume at Week 52. Spleen volume was also reduced and was strongly correlated with liver volume change and exposure to resmetirom. Reductions in liver enzymes and atherogenic lipids were similar across patient subgroups. Resmetirom was safe

and well tolerated. As observed in patients with noncirrhotic NASH, mild GI adverse events were seen at the beginning of therapy. No differences in safety parameters between patients with cirrhosis compared to noncirrhotic NASH patients were noted. No thyroid axis changes or hyper- or hypothyroid symptoms were observed.

**Oral Presentations and Posters**

Abstracts from the resmetirom development program provide new insights to inform non-invasive testing strategies, improve artificial intelligence-based evaluation of treatment response, and better characterise the cost burden of NASH.

**Oral presentation: "Utility of FIB-4 thresholds to identify patients with at-risk F2-F3 NASH based on screening data from a 2,000 patient biopsy confirmed cohort of resmetirom Phase 3 clinical trial, MAESTRO-NASH" (OS101)**

**Oral presentation: "Impact of resmetirom-mediated reductions in liver volume and steatosis compared with placebo on the quantification of fibrosis using second harmonic generation in a serial liver biopsy study" (OS030)**

***"The MAESTRO-NAFLD-1 data we are presenting at EASL continue to reinforce confidence in the favorable safety profile of resmetirom and provide a deeper view of efficacy in patients with both early-to-moderate fibrosis and compensated NASH cirrhosis."***

**Stephen Harrison, M.D., Medical Director for Pinnacle Clinical Research**

**Poster: "Retrospective AI-based measurement of NASH histology (AIM-NASH) analysis of biopsies from Phase 2 study of Resmetirom confirms significant treatment-induced changes in histologic features of nonalcoholic steatohepatitis" (SAT094)**

**Poster: "A higher FIB-4 score is associated with higher healthcare costs and hospitalisations in patients with nonalcoholic steatohepatitis" (THU094)**

**About the Resmetirom Phase 3 Registration Program for the Treatment of NASH**

Madrigal is currently conducting two Phase 3 clinical trials, MAESTRO-NASH and MAESTRO-NAFLD-1, to demonstrate the safety and efficacy of resmetirom for the treatment of NASH.

MAESTRO-NASH is a multicenter, randomised, double-blind, placebo-controlled Phase 3 study of resmetirom in patients with liver biopsy confirmed NASH and was initiated in March 2019. The study targeted enrollment of 900 patients with biopsy-proven NASH (fibrosis stage 2 or 3, at least 450 fibrosis stage 3), randomised 1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, or placebo. After 52 weeks of treatment, a second biopsy is performed. The dual primary surrogate endpoints on biopsy are NASH resolution with ≥2-point reduction in NAS (NAFLD Activity Score), and with no worsening of fibrosis OR a 1-point decrease in fibrosis with no worsening of NASH. Either primary endpoint can be achieved for a successful trial outcome. A key secondary endpoint is lowering of LDL-C. The planned target enrollment was announced as completed on June 30, 2021. The first 900 patients in the MAESTRO-NASH study will continue on therapy after the initial 52-week treatment period; up to another 1,100 patients are to be added using the same randomisation plan. The study is expected to continue for up to 54 months to accrue and measure hepatic clinical outcome events including progression to cirrhosis on biopsy (52 weeks and 54 months) and hepatic decompensation events. MAESTRO-NAFLD-1 was initiated in December 2019 and the 52-week multicenter, randomised, double-blind, placebo-controlled Phase 3 study of resmetirom in over 1,200 patients with NAFLD, presumed NASH, has completed the double-blind arms and an open-label 100 mg arm. An additional open-label active treatment arm in patients with early (well-compensated) NASH cirrhosis is ongoing. The primary endpoint is to evaluate the safety and tolerability of resmetirom. An open-label extension study (MAESTRO-NAFLD-OLE) is ongoing.

Patients in the 52-week blinded phase of MAESTRO-NAFLD-1 were randomised 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, placebo or a resmetirom 100 mg in an open-label arm. MAESTRO-NAFLD-1 (unlike MAESTRO-NASH), did not include a liver biopsy and represents a "real-life" NASH study. Patients with 3 metabolic risk factors were documented with NASH or NAFLD by historical liver biopsy or non-invasive techniques. Using non-invasive measures, MAESTRO-NAFLD-1 was designed to provide incremental safety information to support the NASH indication as well as provide additional data regarding clinically relevant key secondary efficacy endpoints to better characterise the potential clinical benefits of resmetirom on cardiovascular- and liver-related endpoints. These key secondary endpoints included LDL-C, apolipoprotein B, and triglyceride lowering; and reduction of liver fat as determined by MRI-PDFF. Additional secondary and exploratory endpoints were assessed including reduction in liver enzymes, FibroScan, and MRE scores and other NASH biomarkers.

Data from the 52-week portion of MAESTRO-NASH, together with data from MAESTRO-NAFLD-1 and other data, including safety parameters, will form the basis for a potential subpart H submission to FDA for accelerated approval of resmetirom for treatment of NASH.

In May 2022, Madrigal announced plans to expand the resmetirom development program by initiating MAESTRO-NASH Outcomes, a randomised double-blind placebo-controlled study in approximately 700 patients with early NASH cirrhosis to allow for non-invasive monitoring of progression to liver decompensation events. A positive outcome is expected to support the full approval of resmetirom for noncirrhotic NASH, potentially accelerating the timeline to full approval. In addition, this study has the potential to broaden the label for resmetirom to include NASH patients with compensated cirrhosis.

For more information, visit **www.madrigalpharma.com.**

# Treatment of Thrombocytopenia

At the International Liver Congress 2022, Shionogi, a leading global research-driven pharmaceutical company based in Osaka, distributed reprints as part of the MulpleoR (Lusutrombopag) information pack.

Mulpleo is indicated for the treatment of severe thrombocytopenia in adults with chronic liver diseae undergoing invasicve procedures, a prescription medicine, which is taken orally to help increase the number of platelets in the blood before a procedure.

### Lusutrombopag Reduces Need for Platelet Transfusion in Patients With Thrombocytopenia Undergoing Invasive Procedures

Hisashi Hidaka et al. Clin Gastroenterol Hepatol. 2019 May. doi: 10.1016/j.cgh.2018.11.047. Epub 2018 Nov 28.

Background & aims: Platelet transfusion is used to prevent hemorrhagic events in patients with thrombocytopenia undergoing invasive procedures, but there are many disadvantages. We evaluated the efficacy and safety of lusutrombopag in patients with chronic liver disease and thrombocytopenia undergoing invasive procedures. Conclusion: In a placebo-controlled trial, lusutrombopag was effective in achieving and maintaining the target platelet count in patients with chronic liver disease and thrombocytopenia undergoing invasive procedures. No significant safety concerns were raised. Japanese clinical trial registration no: JapicCTI-132323.

### Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease Undergoing Invasive Procedures (L-PLUS 2)

Markus Peck-Radosavljevic et al. Hepatology. 2019 Oct. doi: 10.1002/hep.30561. Epub 2019 Mar 15.

Thrombocytopenia may be associated with increased bleeding risk impacting timing and outcome of invasive procedures in patients with chronic liver disease (CLD). Lusutrombopag, a small-molecule, thrombopoietin (TPO) receptor agonist, was evaluated as a treatment to raise platelet counts (PCs) in patients with thrombocytopenia and CLD undergoing invasive procedures. L-PLUS 2 was a global, phase 3, randomised, double-blind, placebo-controlled study. Adults with CLD and baseline PCs < 50 × 109 /L were randomised to receive once-daily lusutrombopag 3 mg or placebo ≤ 7 days before an invasive procedure scheduled 2-7 days after the last dose. The primary endpoint was avoidance of preprocedure platelet transfusion and avoidance of rescue therapy for bleeding. A key secondary endpoint was number of days PCs were ≥ 50 × 109 /L throughout the study. Safety analysis was performed on patients who received at least one dose of study drug. This study occurred between June 15, 2015, and April 19, 2017, with a total of 215 randomised patients (lusutrombopag, 108; placebo, 107); 64.8% (70/108) of patients in the lusutrombopag group versus 29.0% (31/107) in the placebo group met the primary endpoint (P < 0.0001; difference of proportion 95% confidence interval [CI], 36.7 [24.9, 48.5]). The median duration of PCs ≥ 50 × 109 /L was 19.2 days with lusutrombopag (without platelet transfusion) compared with 0.0 in the placebo group (with platelet transfusion) (P = 0.0001). Most adverse events were mild or moderate in severity, and rates were similar in the lusutrombopag and placebo groups (47.7% and 48.6%, respectively). Conclusion: Lusutrombopag was superior to placebo for reducing the need for platelet transfusions and achieved durable PC response in patients with thrombocytopenia and CLD undergoing invasive procedures, with a safety profile similar to placebo.

### How common is thrombocytopenia in patients with chronic liver disease (CLD)?

Thrombocytopenia (a platelet count of <150x109/L) is a common haematological complication in patients with CLD1, with 64–78% of adult patients with cirrhosis having thrombocytopenia, and 1% of adult patients with advanced fibrosis or cirrhosis having severe thrombocytopenia (a platelet count of <50x109/L).[1–5]

### What effect does thrombocytopenia have on this patient group and their ongoing care?

As part of their ongoing care, adult patients with CLD will often require numerous medical procedures throughout their diagnosis and therapy, some of which are invasive procedures.[6] Severe thrombocytopenia significantly increases the risk of bleeding events during these invasive procedures when compared to mild to moderate thrombocytopenia.6 Not only is this an issue for the patient and their safety, but it also comes with a significant disease burden and associated costs.[6–8] A study which investigated this burden found that compared to patients with CLD and a platelet count >100x109/L, patients with CLD and a platelet count ≤100x109/L experience:[7]
2.5x more liver disease-related ambulatory visits (p<0.01)
Nearly 4x greater likelihood of liver disease-related emergency hospital visits (p<0.01) 13x greater likelihood of having to have liver disease-related inpatient hospital stays (p<0.01)

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SHIONOGI

# Non-invasive Liver Diagnostic System

*Treatment Strategies* caught up with Smeda Medica Co, Ltd., at The International Liver Congress 2022 to discuss transient elastography (TE).

Transient elastography gives a quantitative one-dimensional (i.e. a line) measure of tissue stiffness. It functions by vibrating the skin with a motor to create a passing distortion in the tissue (a shear wave) and imaging the motion or propagation of that distortion as it passes deep into the body using a one-dimensional ultrasound beam. It then displays a quantitative image of tissue stiffness data, as well as the Young's modulus.

Transient elastography relies on a transient mechanical vibration which is used to induce a shear wave into the tissue. The propagation of the shear wave is tracked using ultrasound in order to assess the shear wave speed from which the Young's modulus is deduced under the hypothesis of homogeneity, isotropy, infinite and pure elasticity ($E=3\rho V^2$).

The technology is non-invasive, which can be used to assess the degree of liver fibrosis by Liver Stiffness Measurement (LSM). Due to the advantage of being non-invasive, simple, rapid, easy to perform, reproducible, safe, and well-tolerated, TE has been recommended and recognised by major clinical guidelines and consensus, including the EASL, AASLD, APASL,CMA, and WHO.

Smeda Medical's devices are based on proven existing transient elastography technology, making them easier to use, more intuitive for the user, and cost-effective, without compromising accuracy or safety.

Smeda Medical is led by a European based team that has exclusively licensed the technology from the market-leading TE company in Asia. The hardware and software have been redesigned and updated to meet the needs of the European market. The core algorithms and the platform are based on technologies that have over 2000 installations in Asia as well as the rest of the world. The devices are CE marked and conform to ISO 13485.

Smeda Medical provide non-invasive, reliable, and cost-effective liver diagnosis solutions to European standards.

### Broadband Probe

- One broadband probe for multiple uses.

- One single probe is applicable to patients of different body sizes (adults, overweight/obese patients, children).
- No need to change probe for patients of different body sizes, easy to operate.
- Cost-effective in terms of procurement and maintenance.

### Portable Non-Invasive Liver Diagnostic System

One broadband probe can be used for all morphologies, including pediatrics, adults, and overweight patients without changing the probe.
LT P1 is compact lightweight and easy to transport. It can be used in a fixed location or transported easily to outreach clinics.
The intuitive user interface reduces training time and easy operation allowing the operator to focus on the patient rather than the equipment.
Quick measurement time, time-saving for both operator and patient, more examinations can be done for outpatient department (OPD) patients.
Ergonomic design using a convenient foot switch to ensure probe placement is not affected during scanning.
Measurements: liver stiffness (kPa) and ultrasound attenuation parameter (UAP)

### Non-Invasive Liver Diagnostic System

The ultrasound imaging system ensures accurate consistent measurements as the position of the liver can easily be identified on screen before measurements are taken.
One broadband probe can be used for all morphologies, including pediatrics, adults, and overweight patients without changing the probe.
The intuitive user interface reduces training time and easy operation allowing the operator to focus on the patient rather than the equipment.
Quick measurement time, time-saving for both operator and patient, more examinations can be done for the OPD patients.
Ergonomic design using a convenient foot switch to ensure probe placement is not affected during scanning.
Measurements: liver stiffness (kPa) and UAP.

For more information visit - **info@smedamedical.com**

# Hepatitis B Vaccine - New Long-term Follow-up Clinical Data Announced

VBI Vaccines Inc., a biopharmaceutical company driven by immunology in the pursuit of powerful prevention and treatment of disease, announced that new data from a follow-up analysis of a subset of participants from the pivotal Phase 3 study (PROTECT) of the Company's 3-antigen prophylactic hepatitis B (HBV) vaccine, were presented in an oral presentation at The International Liver Congress™ 2022 (ILC).

Timo Vesikari, M.D., Ph.D., Professor Emeritus and Director of the Nordic Vaccine Research Network in Finland, and principal investigator of the PROTECT and CONSTANT Phase 3 clinical studies of VBI's 3-antigen HBV vaccine, highlighted data from his investigator-initiated analysis that evaluated duration of immune response approximately 2.5 years after completion of vaccination. Immunogenicity was assessed using frozen sera samples from a subset of participants (n=465) who had been enrolled at five clinical sites in Finland as part of PROTECT. In the follow-up analysis, participants in PROTECT who received VBI's 3-antigen HBV vaccine had 5.5-fold higher mean anti-HBs titers (GMC: 1382.9 mIU/mL vs. 251.4 mIU/mL) and a higher seroprotection rate (SPR: 88.1% vs. 72.4%) compared to those who received Engerix-B. Additionally, 72.9% of participants who received VBI's 3-antigen HBV vaccine retained anti-HBs titers ≥ 100 mIU/mL compared to 32.6% of those who received Engerix-B.

"In the PROTECT study, more adults were protected with VBI's 3-antigen vaccine than with the single-antigen vaccine, and in this follow-up analysis we continued to see the benefit of the 3-antigen vaccine," said Francisco Diaz-Mitoma, M.D., Ph.D., VBI's Chief Medical Officer. "As we focus on the road ahead and our commitment to broadening access to this vaccine in Europe and North America, we continue to believe that our 3-antigen vaccine has the potential to be a meaningful new intervention in the public health battle to eradicate hepatitis B."

**Detailed Results of the Follow-Up Study:**

- Higher SPRs observed in participants who received VBI's 3-antigen HBV vaccine (3A-HBV) vs. Engerix-B (1A-HBV) across all key subgroups after 2.5 years of follow up
- Adults age 18+: 88.1% 3A-HBV vs. 72.4% 1A-HBV [difference: 15.7%]
- Adults 18-44 years: 96.2% 3A-HBV vs. 81.3% 1A-HBV [difference: 14.9%]
- Adults 45-64 years: 90.3% 3A-HBV vs. 75.0% 1A-HBV [difference: 15.3%]
- Adults ≥ 65 years: 81.8% 3A-HBV vs. 65.2% 1A-HBV [difference: 16.6%]

Individuals with obesity (BMI > 30): 86.3% 3A-HBV vs. 69.6% 1A-HBV [difference: 16.7%]

- A higher percentage of participants who received 3A-HBV retained anti-HBs titers above 100 mIU/mL (72.9% vs. 32.6% - difference: 40.3%) increase in anti-HBs titers observed in participants who received 3A-HBV vs. 1A-HBV

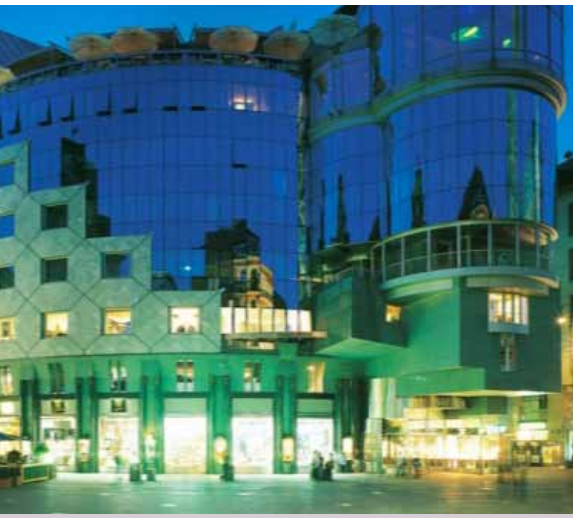
In the PROTECT study, peak antibody titers (Day 196) were 2.1x higher in participants who received 3A-HBV vs. those who received 1A-HBV [8021.9 mIU/mL vs. 3787.3 mIU/mL]

In the 2.5-year follow-up study, mean peak antibody titers were 5.5x higher in participants who received 3A-HBV vs. those who received 1A-HBV [1382.9 mIU/mL vs. 251.4 mIU/mL]

*"As we focus on the road ahead and our commitment to broadening access to this vaccine in Europe and North America, we continue to believe that our 3-antigen vaccine has the potential to be a meaningful new intervention in the public health battle to eradicate hepatitis B."*
**Diaz-Mitoma, M.D., Ph.D., Chief Medical Officer, VBI Vaccines**

The PROTECT follow-up analysis was investigator-initiated and conducted at five clinical sites in Finland, following 465 participants who received all three doses of study vaccines – either VBI's 3-antigen HBV vaccine or the comparator vaccine, Engerix-B®. To conduct immunogenicity testing, frozen sera samples were sent to the same central laboratory for evaluation using the same validated anti-HBs quantitative assay that was used in the PROTECT study. The objectives were to determine the durability of immune response as measured by serum levels of HBV surface antibodies (anti-HBs titers) 2.5 years after completion of vaccination as part of the PROTECT study. Additional objectives were to determine the proportion of participants who retained anti-HBs titers ≥ 10 mIU/mL and anti-HBs titers ≥ 100 mIU/mL 2.5 years after the completion of vaccination.


**Hotel Beethoven**



**DO & CO Hotel**

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# *ILC 2023...*

## The 2023 ILC Congress takes place in Vienna between 21st and 24th June 2023

## *Treatment Strategies* takes a look at a number of the finest hotels Vienna has to offer...

**Hotel Beethoven**
**Location - Papagenogasse 6, 1060 Vienna**
www.hotel-beethoven.at

The 4-star Hotel Beethoven is nestled in culture and cuisine on the "bohemian" Naschmarkt, opposite the Papagenotor of the Theater an der Wien, just a few minutes walk from the Vienna State Opera, Musikverein, Museumsquartier, traditional Viennese coffee houses, and vibrant shopping streets.
The hotel is family owned and operated. Barbara Ludwig explains her relationship with Vienna. "In our beautiful glazed lounge on the mezzanine floor you will find yourselves eye to eye with the stone figures of Papageno and his children, who give the name to Papagenotor of Theater an der Wien. Feel at home in the historic building of our hotel on the traffic-calmed Papagenogasse."

**DO & CO Hotel Vienna**
**Location - Stephansplatz 12 Haas Haus, 1010 Vienna**
www.docohotel.com

Located right in the centre of Vienna, in front of St. Stephen's cathedral the DO & CO Hotel is the perfect starting point for your stay. Whether on a business trip or on holiday the hotel is in walking distance from Vienna's most famous attractions; the Viennese opera house, the Hofburg Imperial Castle or the Albertina museum. Shopaholics will find themselves in paradise as our boutique hotel is situated on corner to Graben, Kärntner Strasse and Kohlmarkt.
The Design Hotel with its 43 rooms and suites offers round the clock personal service and numerous luxurious amenities to make one feel at home.
At the DO & CO Restaurant on the top floor of the building one can enjoy a magnificent view to the cathedral while indulging onesself with the best tastes of the world.
Located on the 6th floor, the new ONYX restaurant brings contemporary Japanese cuisine to the heart of Vienna. The conceptual small plate style of service encourages a shared dining experience.
Event rooms on the 7th and 8th floor are ideal for meetings up to 24 guests.

**Hotel Imperial**
**Location - Kaerntner Ring 16, 1015 Vienna**
www.marriott.com

Home to such iconic classical composers as Mozart, Beethoven,

Schubert and Strauss, Vienna boasts more than 50 theaters and opera houses. The Vienna waltz originated here and its centuries-old spirit still permeates the city's dancehalls.

Hotel Imperial's expert concierge and butlers attend to all wishes and desires before they are expressed, such as having a hand-ironed newspaper delivered bedside morning tea. Tastefully furnished with precious, authentic antiques, walls cocooned in jewel-toned silk, and bathrooms made of marble, our 79 rooms and 59 suites blend the timeless elegance of 19th Century Vienna with state-of-the-art facilities and amenities. Voted amongst Travel + Leisure 500 Best Hotels in the World in 2022 and earning the Travellers' Choice Best of the Best Award 2022, this renowned hotel awaits with a matchless experience.

**The Ritz-Carlton**
**Location - Schubertring 5-7, 1010 Vienna**
www.ritzcarlton.com

The Ritz-Carlton, Vienna, a casual yet impeccably luxurious retreat on the iconic Ring Boulevard in Vienna's cultural heart. Offering a holistic 21st-century guest experience, this is where legendary service and imagination are innate. Staying here crafts memorable experiences, bringing together a destination-inspired restaurant and bar scene, splendid accommodation and an enriching spa.

**Rosewood Vienna**
**Location - Petersplatz 7, 1010 Vienna**
www.rosewoodhotels.com

Rosewood Vienna is housed in a beautifully restored, historic 19th-century building. Ideally situated on Petersplatz, one of the most famous squares in Vienna's Old Town, Rosewood Vienna is located just steps away from the city's most luxurious shopping and dining and its most famous historical sites.

Rosewood Vienna offers 99 spacious guestrooms and suites that merge past and present through a thoughtful combination of elegant textural and artistic elements and the latest technological features.

The Pavilion at Rosewood Vienna offers a unique event concept space, ideal for festive social gatherings or formal business occasions alike. Its distinct and flexible design reflects a more residential and intimate approach to gatherings, all supported with top-of-the-line audio and visual systems and bespoke services.

**The Topazz**
**Location - Parkring 10, 1010 Vienna**
www.hoteltopazzlamee.com

With its breathtaking, award-winning architecture, enormously comfortable furnishings and at the same time sustainable, resource-saving philosophy, The Topazz sets standards that once enjoyed, one would not want to do without. A gem beyond all conventions, which is not for nothing one of the best hotels in Vienna. A place where one feels comfortable and at home from the first moment.

**Vienna Marriott Hotel**
**Location - Parkring 12A, 1010 Vienna**
www.marritt.com

Located within Vienna's vibrant city center, the Vienna Marriott Hotel welcomes you to your daycation. If one needs a location for a photo- or video shoot. It is here. Maximize your time in Vienna and rewind in the newly opened M Club Lounge on the 8th floor.

With outdoor seating and a marvelous view over Vienna's City Park, the elegant Lounge is the perfect place to relax and get some rest from the bustle of the city. A separate Business Center and high-speed internet offer the perfect environment to work.

**The Rosewood**


**The Topazz**

**Vienna Marriott Hotel**

# *ILC 2023...Vienna*

Vienna is the host city for the International Liver Congress™ (ILC) 2023. *Treatment Strategies* offers a glimpse of what this wonderful city has to offer next year's congress attendees.

Austria's capital Vienna offers a real mix of imperial traditions, music, and endearing charm. A city that inspires with the old and the new alike, and always has a cosy place around the corner in a coffee house or wine tavern.

Vienna, also described as Europe's cultural capital, is a metropolis with unique charm, vibrancy and flair. It boasts outstanding infrastructure, is clean and safe, and has all the inspiration that one could wish for in order to discover this wonderful part of central Europe.

## Vienna - The History

If one were to look down from the nearby Kahlenberg mountain and pinpoint Vienna, one will see what a fascinating tapestry this city is. There are green, rolling vineyards, and then there are the magnificent, imperial stately buildings Vienna is famed for. After all, Vienna is a city where world history was written for half a millennium. Art history, as well.

## Must-see Attractions in Vienna

On a daytrip along the Ringstrasse, one passes the Vienna State Opera, the Museum of Art History and its counterpart, the Museum of Natural History, the Parliament, the Burgtheater, and the City Hall.

Right in the centre of the city, the Gothic St. Stephen's Cathedral casts its shadows through narrow cobblestone streets. The palaces and parks of the Habsburg age - Schönbrunn Palace with the Gloriette and the zoo, Belvedere Palace, and the Hofburg palace - give the city an imperial royal air, enriched by beautiful buildings from the Art Nouveau period.

## Vienna - a Romantically Imperial City

Vienna is a dream destination for anyone with a romantic streak or an interest in history. Sightseeing opportunities are to be found in abundance.

Meander along narrow, medieval alleyways or across imperial squares, view Schönbrunn Palace or the Imperial Palace (Hofburg) in the footsteps of Sissi and Emperor Franz Josef, and marvel at the majestic architecture along the Ring boulevard. Be inspired by an atmosphere steeped in history - which also boasts the comforts and infrastructure of a modern city.

## Vienna - City of Culture

Vienna possesses a lively and vast array of cultural attractions. Whether classical or experimental theatre, film or dance festivals, opera or operetta, or exhibitions and concerts - no matter when one visits and how long one stays, there is sure to be something exciting for you to discover.

Perhaps if one's tastes are not quite so culturally refined, then one can visit one of Vienna's famous coffee houses or traditional wine taverns ("Heurige") and work one's way through famous culinary specialities.

## Vienna - City of Music

Vienna has been synonymous with music for centuries, and was home to Mozart, Beethoven, Schubert and Johann Strauss.

Vienna's outstanding musical heritage has been preserved right to the present day. The Wiener Philharmoniker is one of the world's top orchestras, the Vienna Boys' Choir is triumphantly successful wherever it tours, and the Vienna Conservatorium has produced innumerable international award-winners in all musical disciplines.

Vienna also boasts a lively scene for young people - if one loves music, one is sure to profit from Vienna.

## Vienna - City of Art

Down the centuries, Vienna has always produced and nurtured world-famous artists. The collecting passion of art-loving rulers and monarchs has made Vienna a treasure house par excellence.

The Museum of Fine Arts, for instance, is one of the world's largest and most distinguished museums, housing priceless works of art.

Art accompanies the visitor wherever you go in Vienna - even some of its underground stations are listed properties (on account of their elegant, ornamental Jugendstil style designed by Otto Wagner)! And Vienna is also uniquely zestful as far as its literature is concerned. After all, where else in the world will you find a city with its own "coffee house literature"?


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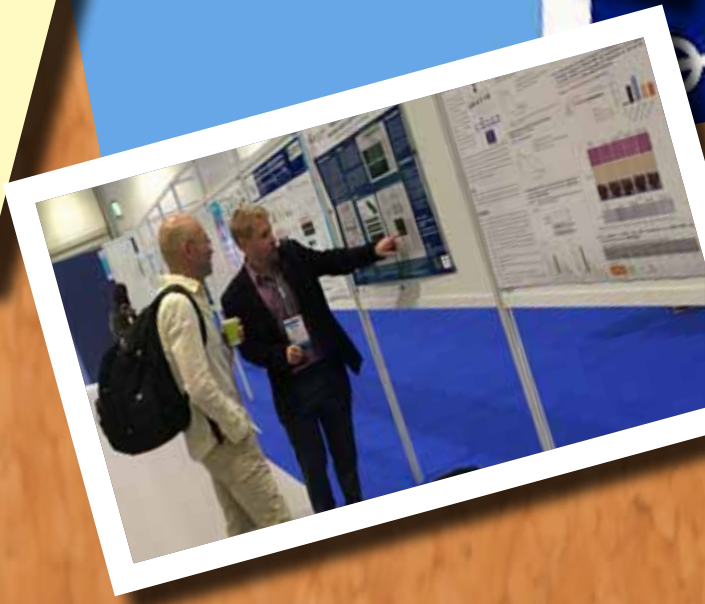
To do list

Register...
ILC2023
Book...
flights
Hotel

# The International Liver Congress™ 2023
## 21st - 24th June 2023 - Vienna

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# Company Listing - Hepatology...

- ABBVIE
- ABSOLUTE MEDIA
- ALBIREO PHARMA
- APOLLO ENDOSURGERY
- ARBUTUS BIOPHARMA
- BAYER RADIOLOGY
- BIOPREDICTIVE
- CAMBRIDGE RESEARCH
- CANON MEDICAL
- CEPHEID
- CYMABAY THERAPEUTICS
- CYTES BIOTECHNOLOGIES
- DR. FALK
- DURECT
- ECHOSENS
- EIGER BIOPHARMACEUTICALS
- EISAI
- ENDRA LIFE SCIENCES
- E-SCOPICS
- F.HOFFMANN-LA ROCHE
- GE HEALTHCARE
- GILEAD SCIENCES EUROPE
- GLAXOSMITHKLINE
- GORE & ASSOCIATES
- HEALTH SOLUTIONS
- INCYTE BIOSCIENCES
- INTERCEPT PHARMA
- INVENTIVA PHARMA
- IPSEN
- MADRIGAL
- MALLINCKRODT
- MILTENYI BIOTEC
- MIRIUM PHARMACEUTICAL
- NORGINE
- NOVO NORDISK
- ORPHALON
- PERSPECTUM
- PHILIPS HEALTHCARE
- PHYSIOGENEX
- PROSCIENTO
- RESEARCH DIETS
- RESOUNDANT
- ROCKET MEDICAL
- SHIONOGI EUROPE
- SIEMENS HEALTHCARE
- SMEDA
- TAKEDA
- UNIVAR SOLUTIONS
- VBI VACCINES INC
- VLV BIO
- WAYEMEDE PLC

# Association Listing - Hepatology...

- AASLD
- ALEH
- APASL
- British Liver Foundation
- CLDF
- EASL
- FCR
- Global Liver Institute
- Haemochromatosis UK
- ICE-HBV
- ILTS
- Lifenet Health lifesciences
- TASL
- WGO
- WHA

# Upcoming Congresses and Meetings

### 14th International Conference on Liver Diseases & Hepatology

**17-18 May, 2023**

**Amsterdam, Netherlands**

The main objective of the conference is to bring together leading academicians, scientists, researchers, graduate students, (gastroenterologists, hepatologists, pathologists, oncologists) environmental specialist & pharmaceutical specialist and others from all over the world.

Liver Diseases 2023 is a two-day conference.

https://liverdiseases.gastroconferences.com/

### International Conference on Pediatric Hepatology - ICPH

**10-11 June, 2023**

**Barcelona, Spain**

### Global Congress on Advances in Gastroenterology and Hepatology

**19 - 20 Jun 2023**

**Sheraton Heathrow Hotel, London, UK**

Global Congress on Advances in Gastroenterology and Hepatology makes a perfect platform for global networking as it brings together gastroenterologists, hepatologists, colorectal surgeons, physician assistants and nurse practitioners, clinical researchers & scientists, public health professionals, pathologists, medical practitioners, professors, and students across the globe to a most exciting, exceptional, a memorable scientific leading event to report and witness the latest scientific developments in gastroenterology and hepatology.

### EASL Congress 2023 - The International Liver Congress

**www.easlcongress.eu**

**21-24 June 2023**

**Vienna, Austria**

### European Meeting on HIV & Hepatitis

**7-9 June 2023**

**Rome, Italy**

Founded nineteen years ago as the European HIV Resistance Workshop, the European Meeting on HIV & Hepatitis - Treatment Strategies & Antiviral Drug Resistance has evolved to embrace all aspects of the clinical care of people living with HIV in Europe. Particular emphasis is put on optimal treatment strategies, clinical virology, molecular epidemiology, and public health aspects of HIV, HBV, HCV, and emerging viruses throughout Europe.

### International Conference on Hepatology ICH

**19-20 July, 2023**

**Paris, France**

### The International Liver Cancer Association (ILCA) Congress 2023

**7-9 September 2023**

**Amsterdam, Netherlands**

### AHA 2023 - Australasian Hepatology Association Conference

**8-10 September 2023**

**Melbourne, Australia**

### International Conference on Gastroenterology, Hepatology and Nutrition ICGHN

**23-24 September, 2023**

**London, UK**

### International Conference on Gastroenterology and Hepatology ICGH

**4-5 November, 2023**

**Cape Town, South Africa**

**The Cambridge Research Centre**

The Cambridge Research Centre is completely independent of the review events (ILC 2022) and the use of the organisation and event hyperlink does not constitute endorsement or media partnership in any form whatsoever.