

**THE INTERNATIONAL LIVER CONGRESS™  
PRESS KIT 2018**

**FRI/SAT**

## Background Media Information

The European Association for the Study of the Liver (EASL): Promoting liver research and education across Europe since 1966

The European Association for the Study of the Liver (EASL), The Home of Hepatology, is Europe's leading organisation dedicated to advancing the scientific, medical and public understanding of the liver and liver disease. Since its foundation in 1966, EASL has evolved into a driving force by supporting the education of healthcare professionals, promoting research in the field of liver disease and fostering policy changes to support liver health.

EASL – a not-for-profit organisation – is an ever-growing global liver community with over 4,000 members from all over the world. EASL provides an annual platform, The International Liver Congress™, for approximately 10,000 liver experts to meet and share best practices, research, new data and ideas for the future of hepatology. EASL's members include many of the world's leading hepatologists. The association has prompted a large number of clinical practice guidelines and international research collaborations in liver disease, to the benefit of patients all over the world.

EASL's mission is to ensure that all those who are involved with liver disease can realise their full potential to cure and prevent it. To achieve this mission, EASL has six key priorities, all of which contribute to the aim of ensuring better liver health across the world:

1. Promoting research in the science of liver disease (hepatology)
2. Providing state-of-the-art education for healthcare professionals and scientists
3. Improving public awareness of liver disease, diagnosis and management
4. Advising European health authorities on liver conditions
5. Facilitating scientific exchange and fostering European multi-centre controlled trials
6. Supporting young investigators to ensure that the liver remains at the forefront of research

### ***The International Liver Congress™***

The annual congress is the biggest event in the EASL calendar, attracting scientific and medical experts from around the world to learn more about the latest in liver research. Specialists share research studies and findings, and discuss prominent topics related to liver disease.

In 2017, EASL and the hepatology community celebrated the 52<sup>nd</sup> annual meeting, attracting over 10,000 delegates and around 110 media representatives from all corners of the globe.

**The International Liver Congress™ 2018 takes place 11-15 April, at the Paris expo  
Porte de Versailles, Paris, France.**

## Supporting research

Through its annual scientific meetings, official journal (the *Journal of Hepatology*), young investigator fellowships and support of multi-centre clinical trials, as well as the provision of funding, EASL promotes research into the liver and liver disease, and supports wide dissemination of vital research findings.

## Promoting education

Education is a priority for EASL and the association provides CME-accredited learning opportunities at every level from clinical fellow to professor. EASL runs a vast educational programme including a range of residential courses known as the EASL Schools of Hepatology, which are offered in formats suitable for both basic researchers and clinicians. EASL also provides specialist and monothematic conferences which focus on key topics in liver disease, research and management. Monothematic conferences provide a unique opportunity for industry-academia interaction. Further educational opportunities for investigators at the start of their careers are available through the EASL Masterclass Programme. Find out more about EASL's educational programme and upcoming events at: <http://www.easl.eu/discover/events/calendar/2018>

EASL also offers online and mobile-led education to its members:

- Liver Tree™, designed with healthcare professionals in mind, provides a comprehensive e-learning portal collating all EASL educational materials. It provides an online destination for up-to-date research and materials in the field of hepatology, recent and historical webcast presentations, abstracts, ePosters and learning quizzes
- iLiver, an interactive and dynamic app designed for professional use, delivers instant medical information and clinical recommendations to hepatologists, gastroenterologists and internal medicine specialists. The app contains rigorously reviewed and regularly updated information specifically related to liver disease management. The app is free and available on iPhone, iPad and Android devices

To further advocate research and education, EASL funds a range of activities from supporting PhD programmes dedicated to Hepatology, to post-doctoral fellowships and short-term grants for technical education. In addition, EASL provides funds for Registry Grants to support consortia groups. Information about EASL fellowships is available at: <http://www.easl.eu/research/support/easl-fellowship>.

EASL also provides dedicated mentorship programmes to support investigators during the first stages of their careers. The events and opportunities offered by EASL expose attendees to some of the most important opinion leaders in hepatology, giving them invaluable time for scientific exchange and conversations with senior hepatologists with many years of experience. Information about the EASL mentorship programme is available at: <http://www.easl.eu/research/support/mentorship-programme>.

## Providing clinical guidance

EASL develops and disseminates Clinical Practice Guidelines to assist physicians and other healthcare providers in the clinical decision-making process to help ensure optimal care across various aspects of liver disease. EASL has developed Clinical Practice Guidelines on managing the following conditions:

- HCV recommendations
- Autoimmune hepatitis
- Vascular liver disease

- Liver transplantation
- Gallstones
- Benign liver tumours
- Non-alcoholic fatty liver disease (NAFLD)

New EASL Clinical Practice Guidelines will be presented at The International Liver Congress™ 2018 and published in the *Journal of Hepatology*:

- EASL Recommendations on Treatment of Hepatitis C 2018
- EASL Clinical Practical Guidelines: Management of patients with decompensated cirrhosis
- EASL Clinical Practice Guidelines: Management of alcohol-related liver disease
- EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma
- EASL Clinical Practice Guidelines: Management of Hepatitis E virus infection

The Clinical Practice Guidelines can be accessed at: [www.easl.eu/clinical-practice-guideline](http://www.easl.eu/clinical-practice-guideline).

**For more information about EASL and its activities, please  
visit: [www.easl.eu](http://www.easl.eu)**

#### References

- 1 Jurgen R, et al. Global burden of alcoholic liver diseases. *Journal of Hepatology*. 2013;(59):160-168.
- 2 Globocan 2012. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Available from: [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). Last accessed: March 2018.
- 3 EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Journal of Hepatology*. 2016;64(6):1388–1402.
- 4 European Association for the Study of the Liver. The Burden of Liver Disease in Europe. Available from: [http://www.easl.eu/medias/EASLimg/Discover/EU/54ae845caec619f\\_file.pdf](http://www.easl.eu/medias/EASLimg/Discover/EU/54ae845caec619f_file.pdf). Last accessed: March 2018.
- 5 European Association for the Study of the Liver. EASL recommendations on treatment of Hepatitis C 2016. Available from: <http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2016>. Last accessed: March 2018.

Press Conference 3: Friday 13 April, 14:00 – 15:30

EAST 3 Hall 7.3

**The official ILC 2018 Press Conference webcast will be available after the ILC.**

<u>Time</u>	<u>Content</u>	<u>Speaker</u>
14:00	Welcome and introductions	Prof Markus Cornberg, Hannover Medical School, Hannover, Germany
14:05	<b>LBP-021</b> The percentage of patients with HCV infection in need of a liver transplant is rapidly declining while their survival after transplantation is improving: A study based on European Liver Transplant Registry	Dr Chiara Mazzarelli, Ospedale Niguarda, Milan, Italy
14:15	<b>PS-063</b> Cases of transfusion-transmitted hepatitis E Virus infections at a tertiary referral center	Dr Ansgar Lohse, Hamburg, Germany
14:25	<b>LBP-014</b> Long-Term Obeticholic Acid (OCA) Treatment Associated with Reversal or Stabilization of Fibrosis/Cirrhosis in Patients with Primary Biliary Cholangitis (PBC)	Dr Christopher Bowlus, UC Davis, California, United States
14:35	<b>PS-057</b> Substantial comorbidities and rising economic burden in real-world non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) patients with compensated cirrhosis (CC): A large German claims database study	Dr Ali Canbay, University of Magdeburg Medical School, Germany

**14:45**      **LBO-002** NGM282, an Engineered Analogue of FGF19, Significantly Improves Markers of Bile Acid Synthesis, Hepatic Injury and Fibrosis in PSC Patients: Results of a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

**Prof Gideon Hirschfield, University of Birmingham, United Kingdom**

**14:55**      WHO update on global access to hepatitis C treatment, and upcoming guidelines

**Dr Gottfried Hirnschall, Global Hepatitis Programme, World Health Organization (WHO), Switzerland**

**15:05**      **LBO-005** The impact of combining Selective Internal Radiation Therapy (SIRT) with sorafenib on overall survival in patients with advanced hepatocellular carcinoma: the SORAMIC trial palliative cohort

**Prof Jens Ricke, LMU - Munich, Germany**

**15:15**      **PS-060** Food insecurity increases the risk of advanced fibrosis in diabetics with non-alcoholic fatty liver disease

**Dr Sonal Kumar, New York Presbyterian Hospital, United States**

**15:25**      **Question and answer session**

**15:30**      **Close**

**PUBLIC RELEASE: 13 APRIL 2018**

## US study reports dramatic reduction in likelihood of liver transplantation in patients with hepatocellular carcinoma

*ILC 2018: Although hepatocellular carcinoma is now the leading indication for liver transplantation in the USA, the probability of patients receiving a transplant has declined significantly in recent years*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: Patients with hepatocellular carcinoma (HCC) waiting for a liver transplant in the USA are now significantly less likely to receive a new liver than they were around a decade ago. A nationwide study presented today at The International Liver Congress™ 2018 in Paris, France, has confirmed that patients with HCC on the liver transplant list in the USA were more than 50% less likely to receive a transplant in 2014–2016 than they were in 2005–2007. Patients with Medicaid insurance were also significantly less likely to undergo liver transplantation than those with private/commercial insurance.

‘This is a very worrying trend and reflects the continued imbalance between the number of patients with HCC in need of liver transplantation and the limited number of donor livers available’, said Dr Jennifer Wang from the California Pacific Medical Center, San Francisco, USA, who presented the study findings today.

Hepatocellular carcinoma is the most common primary tumour of the liver, with average survival estimated to be 18 months.<sup>1,2</sup> Liver transplantation is a guideline-recommended treatment for people with HCC,<sup>3</sup> although individuals must meet strict criteria in order to join the waiting list.<sup>1,3</sup> A recent study has shown that HCC is the most common indication for liver transplantation and placement on the waiting list in the USA.<sup>4</sup> However, limited organ availability and an increasing demand has extended transplant waiting times, and increased morbidity and mortality amongst those listed.<sup>3</sup>

The study presented today was undertaken to evaluate overall trends in the probability of receiving a liver transplant among US adults with HCC on the transplant list. Data from the United Network for Organ Sharing Liver Transplant Registry were analyzed by year of listing (2005–2007, 2008–2010, 2011–2013, and 2014–2016), and stratified by age and insurance type. When stratified by age, the probability of receiving a liver transplant within 1 year of listing

was highest amongst HCC patients aged 50–59 years (64.6%) and lowest amongst those aged 60–69 years (58.1%) ( $p < 0.01$ ). When stratified by insurance type, the probability of receiving a liver transplant within 1 year was highest amongst those with private/commercial insurance (63.6%) and lowest amongst those with Medicare insurance (52.8%) ( $p < 0.001$ ). In 2005–2007, the probability of receiving a liver transplant in the first year of joining the waiting list was 81.5% compared with just 51.7% in 2014–2016 ( $p < 0.001$ ). A multivariate regression analysis confirmed that HCC patients who joined the liver transplant waiting list in 2014–2016 were significantly less likely to receive a transplant than those who joined the list in 2005–2007 (HR 0.43; 95% CI 0.40, 0.46;  $p < 0.001$ ).

‘This means that, despite the increasing numbers of adults with HCC waiting for a liver transplant in the USA, patients are now 57% less likely to receive one than they were in the mid-2000s’, said Dr Wang.

As well as the lack of donor livers, Dr Wang believes that the findings from her study also reflect disparities in the rates of liver transplantation amongst HCC patients – especially patients from ethnic minority backgrounds and those with Medicaid-type insurance. She also believes that the increasing burden of non-alcoholic fatty liver disease as a cause of HCC and the increasing numbers of patients with early-stage HCC that are eligible for liver transplantation have contributed to the current situation.

‘Ultimately, this situation will only improve when newer therapies and more curative options for HCC become available’, said Dr Wang. ‘In the meantime, we need more research to help us understand the disparities identified in our study so that targeted interventions can be developed to ensure more equitable access to liver transplantation for all our HCC patients’.

‘This increase in the proportion of patients who are potential candidates for liver transplantation will be associated with an irremediable increase in the waiting time and of the drop-out due to tumour progression’, said Prof. Alejandro Forner from the Hospital Clinic Barcelona, Spain, and EASL Governing Board Member. ‘Efforts should be directed to design prioritising strategies to facilitate access to liver transplantation for patients affected by HCC, without harming the patients listed due to impaired liver function’.

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Since its foundation in 1966, this not-for-profit organization has grown to over 4,000 members from all over the world, including many of the leading hepatologists in Europe and beyond. EASL is the leading liver association in Europe, having evolved into a major European association with international influence, and with an impressive track record in promoting research in liver disease, supporting wider education and promoting changes in European liver policy.

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### **Onsite location reference**

Session title: Liver tumours: Clinical aspects except therapy

Time, date and location of session: 13. April 2018, 09:00 AM - 05:00 PM

Presenter: Jennifer Wang, USA

Abstract: While hepatocellular carcinoma (HCC) has become the leading indication for liver transplantation in the United States, the probability of receiving liver transplantation among adults with HCC has rapidly declined (1128)

### **Author disclosures**

Jennifer Wang: None reported.

Robert Gish: Dr. Gish has received Grants/Research Support from AbbVie, Benitec Biopharma, Gilead Sciences, and Merck & Co. Dr. Gish has performed as Consultant and/or Advisor to AbbVie, Akshaya Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Genentech, Gilead

Sciences, Hoffman-LaRoche, Ltd., Ionis Pharmaceuticals, Janssen, Merck & Co., Nanogen Biopharmaceutical, and Presidio Pharmaceuticals. Dr. Gish has current activity with the scientific or clinical advisory boards of AbbVie, AstraZeneca, Genentech, Gilead Sciences, Janssen, Merck & Co., and Nanogen Biopharmaceutical. Dr. Gish is a member of the Speakers Bureau for AbbVie, Bristol-Myers Squibb, Gilead Sciences, and Merck. Dr. Gish is a minor stock shareholder of Cocrystal Pharma.

Benny Liu: None reported.

Taft Bhuket: None reported.

Robert Wong: Dr. Wong receives research funding from Gilead Sciences and Abbvie, has served as a consultant and member of the advisory board for Gilead Sciences, and serves on the speaker's bureau for Gilead Sciences, Salix, and Bayer. Dr. Wong is also funded by an AASLD Foundational Clinical and Translational Research Award in Liver Diseases.

## References

1. Byam J, et al. Liver transplantation for hepatocellular carcinoma. *Hepatobiliary Surg Nutr.* 2013;2(1):22–30.
2. Maluccio M, et al. Survival in patients with hepatocellular carcinoma (HCC): A report of 1444 patients treated within a multidisciplinary program. *J Clin Oncol.* 2017;35(15\_suppl):e15652.
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4. Yang JD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol.* 2017;15(5):767–75.e3.

**PUBLIC RELEASE: 13 APRIL 2018**

## A web-based lifestyle intervention supports weight loss in patients with non-alcoholic fatty liver disease

*ILC 2018: Remote lifestyle modification intervention shown to be as effective as a face-to-face group programme for weight loss and improved liver health*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: Patients with non-alcoholic fatty liver disease (NAFLD) who participated in a web-based lifestyle modification intervention achieved similar levels of weight loss and more rapid normalization of their liver enzymes than patients who participated in an intensive, group-based programme. The results of this Italian study, which were presented today at The International Liver Congress™ 2018 in Paris, France, also suggested that the degree of weight loss achieved by some patients in both intervention groups was likely to have resulted in fibrosis regression.

‘We were impressed that more than one in 10 patients in both intervention groups achieved a weight loss target of 10%’, said Professor Giulio Marchesini from the University of Bologna, Italy, who presented the study findings. ‘This weight loss threshold has been associated with resolution of non-alcoholic steatohepatitis and regression of fibrosis in studies that have evaluated NAFLD histology’.<sup>1</sup>

NAFLD is the most common liver disease in Western countries and is characterized by excessive hepatic fat accumulation.<sup>2</sup> The global prevalence of NAFLD has been estimated to have reached 25% of adults,<sup>3</sup> and both genetic and lifestyle factors contribute to the pathogenesis of the disease.<sup>4</sup> Lifestyle modifications geared towards weight loss, increased physical activity and improved dietary habits are central to the management of NAFLD,<sup>2,4</sup> and structured intervention programmes are recommended in the guidelines.<sup>2</sup>

‘Lifestyle changes are mandatory for patients with NAFLD, but these are very difficult to achieve in busy clinical units’, explained Prof. Marchesini. ‘We wanted to develop a web-based programme to help them achieve these changes, and to compare its effects with a structured, face-to-face programme involving a multidisciplinary team. The participation of patients with NAFLD in structured lifestyle programmes may be jeopardized by job and other time constraints, and a web-based intervention may be better suited to young, busy patients’.

The study undertaken by Prof. Marchesini and colleagues included 716 patients with NAFLD. They either attended a 5-week intensive group-based lifestyle modification programme, created by a multidisciplinary team of physicians, dieticians and psychologists which encouraged a healthy diet and regular physical activity (n=438), or participated in a web-based intervention (n=278). The web-based programme included five modules, with interactive games, offline contact with the study centre, and questionnaires. Surrogate markers of NAFLD severity were tested at 6-, 12-, and 24-months of follow-up. The primary outcome measure for the study was the percentage of patients who achieved 10% weight loss.

According to Prof. Marchesini, body mass index decreased in both groups by almost 2 points, and the 10% weight loss target was achieved by 14% of all participants (12% of participants in the web-based intervention and 15% in the group-based intervention). All liver enzymes decreased significantly, irrespective of the intervention, but individuals in the web-based intervention were more likely than those in the group intervention to have a normal alanine aminotransferase (ALT) level at both 6 months (OR 2.34; 95% CI 1.27, 4.30) and 12 months (OR 2.22; 95% CI 1.33, 3.73). Surrogate markers of fibrosis decreased in both intervention groups, with statistically significant improvements from baseline observed in the Fibrosis-4 (FIB-4) index.

‘Our study has shown that a web-based lifestyle modification programme is a feasible and practical way of achieving a clinically meaningful level of weight loss in our NAFLD patients’, said Prof. Marchesini. ‘Ideally, we would now like to roll out the intervention to other liver units’.

‘Weight loss has long been recognized as an effective therapy for NAFLD, but the challenge has been creating the infrastructure to achieve it’, said Prof. Phil Newsome from the Queen Elizabeth Hospital and University of Birmingham, Birmingham, UK, and EASL Governing Board Member. ‘Most studies have used conventional resource-intensive regimens which are not widely available in most clinical practices. This study by Prof. Marchesini demonstrates the potential of web-based approaches to achieve this at scale. The challenge now will be to see if patients are able to sustain the weight loss for longer periods of time’.

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### **Onsite location reference**

Session title: NAFLD: Therapy

Time, date and location of session: 13 April 2018 17:45 - 18:00, Main plenary

Presenter: Giulio Marchesini, Italy

Abstract: Web-based counseling for NAFLD. Final results

### **Author disclosures**

Prof. Marchesini and co-authors declare no conflict of interests in relation to these data.

### **References**

5. Vilar-Gomez E, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology*. 2015;149(2):367–78.e5.
6. European Association for the Study of the Liver (EASL), et al. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol*. 2016;64(6):1388–402.
7. Younossi ZM. et al. Global epidemiology of nonalcoholic fatty liver disease — meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatol* 2016;64:73–84.

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**PUBLIC RELEASE: 13 APRIL 2018**

## Germany: compensated cirrhosis substantially increases comorbidities and healthcare costs for patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis

*ILC 2018: German patients with NAFLD/NASH who develop compensated cirrhosis have extensive comorbidities and are frequently hospitalized, adding to healthcare costs*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: An analysis of outcomes and costs for German patients with non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) who develop compensated cirrhosis was presented today at The International Liver Congress™ 2018 in Paris, France. Healthcare costs for this population spiked in the first year after compensated cirrhosis diagnosis. Comorbidities were common and one in five patients died within a year of cirrhosis diagnosis, highlighting the need for new treatment options to improve outcomes in these patients.

NAFLD is a major cause of liver disease worldwide with a global prevalence of 25% that is, alarmingly, thought to be rising, fueled by the global epidemic of obesity.<sup>9</sup> The progression from NAFLD to NASH to advanced fibrosis is well established.<sup>9</sup> For patients with NAFLD/NASH, increased morbidity and mortality is associated with increasing fibrosis.<sup>10</sup>

‘We know that compensated cirrhosis is often caused by NASH, but data on the associated morbidity, mortality, healthcare utilization and costs within the population of Germany are lacking’, explained Dr Ali Canbay from the University of Magdeburg Medical School in Germany, and lead author of the study. ‘We were able to extract these data from a large, anonymized billing database’.

The study presented by Dr Canbay obtained retrospective claims data for adult patients with a NAFLD/NASH diagnosis between 2011 and 2016 using the InGef FDB database (which contains anonymized billing data for about 6.3 million persons in about 60 health insurances in Germany).<sup>11,12</sup> A total of 800 patients who had a subsequent diagnosis of compensated cirrhosis were included in the analysis. Of these, 245 (30.6%) individuals progressed to end-stage liver diseases (ESLDs) (progressors) and 555 (69.4%) remained cirrhotic (non-progressors) within 1

year of follow-up after their cirrhosis index diagnosis. Comorbidities, all-cause mortality within 1 year of the cirrhosis index diagnosis, annual healthcare utilization, annual mean costs (1 year pre-index to 1 year post-index period) and cumulative mean costs (1 year to maximum 5 years pre-index and post-index period) were presented.

In the 1-year pre-index period, the most prevalent comorbidities were hypertension (78.8 %), type-2 diabetes mellitus (52.6%), cardiovascular diseases (48.8%) and hyperlipidaemia (47.5%). In the first year of the post-index period, 19.4% of the patients died. This percentage was significantly higher for progressors (46.1%) than non-progressors (7.6%) ( $p < 0.05$ ). Following the cirrhosis diagnosis, the mean annual number of all-cause hospitalizations and emergency room visits increased significantly by 91% and 106.8%, respectively ( $p < 0.05$ ).

During the 1-year pre-index period, the mean of annual all-cause healthcare cost was €6,146 per patient. In the first post-index year there was a substantial and significant increase (93%,  $p < 0.05$ ) in annual all-cause healthcare cost per patient to a mean of €11,877. The primary driver of healthcare costs was the inpatient setting, which accounted for 42.0% of pre-index costs and 68.4% of post-index costs. Cumulative mean costs for cirrhosis patients increased 143% over the 5-year period of the study ( $p < 0.05$ ).

'We demonstrated that German patients with NAFLD/NASH who develop compensated cirrhosis have a substantial burden of comorbidities and that their healthcare costs jump with the development of cirrhosis', said Dr Canbay. 'Novel treatment options are needed to improve patient outcomes'.

'This study highlights the burden of NASH cirrhosis on healthcare systems and reinforces the need for new therapies to tackle the epidemic currently affecting many European countries', said Prof. Phil Newsome from the Queen Elizabeth Hospital and University of Birmingham, UK, and EASL Governing Board Member.

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### **Onsite location reference**

Session title: Parallel session: Public health: General

Time, date and location of session: 12. April 2018, 04:00 PM - 04:15 PM, West 2

Presenter: Ali Canbay, Germany

Abstract: Substantial comorbidities and rising economic burden in real-world non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) patients with compensated cirrhosis (CC): A large German claims database study (2665)

### **Author disclosures**

- Ali Canbay disclosures: Shire, Alexion, Falk
- The analyses were performed in collaboration with Prof. Dr. Wolfgang Greiner and the Institut für angewandte Gesundheitsforschung (InGef)
- The study was financially supported by Gilead Sciences Europe, Ltd.

### **References**

9. Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease – meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64(1):73–84.
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**PUBLIC RELEASE: 13 APRIL 2018**

## Hepatitis C virus elimination programmes report encouraging results: is elimination within reach?

*ILC 2018: National programmes in Georgia and Iceland report high levels of engagement, treatment initiation, and cure, suggesting HCV elimination targets are achievable*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: Two nationwide programmes in Georgia and Iceland, which were designed to eliminate hepatitis C virus (HCV) at the population level, have reported encouraging results, suggesting that these countries could be on target to achieve their elimination goals. Although both programmes have adopted slightly different approaches, both have reported high levels of engagement, initiation of direct-acting antiviral agents (DAAs), and cure among patients chronically infected with HCV.

Worldwide, 71 million people are estimated to have chronic hepatitis C infection,<sup>1</sup> resulting in an estimated 700,000 deaths per year from hepatocellular carcinoma or cirrhosis.<sup>2</sup> The availability of oral, well-tolerated DAAs that can achieve cure rates of over 95% has led to the development of World Health Organization (WHO) elimination targets that propose a 90% reduction in HCV incidence and a 65% reduction in HCV-related mortality by 2030.<sup>1</sup>

### **Georgia programme: latest data**

The world's first hepatitis C elimination programme was initiated in Georgia in collaboration with the US Centers for Disease Control and Prevention (CDC), and with a commitment from Gilead Sciences to donate DAAs.<sup>15</sup> The programme was initiated in April 2015,<sup>3</sup> and the results from its first 2 years in action were presented today at The International Liver Congress™ 2018 in Paris, France.

'In Georgia, we have set out to achieve 90-95-95 targets by 2020, which means that we want to diagnose 90% of all HCV-infected individuals, we want to treat 95% of those diagnosed, and we want to cure 95% of those treated', explained Professor Tengiz Tsertsvadze from the Infectious Diseases, AIDS and Clinical Immunology Research Center in Tbilisi, Georgia. 'We had previously estimated that there were around 150,000 adults with HCV infection living in Georgia, which represents a prevalence in our population of 5.4%'.<sup>4</sup>

Hepatitis C screening programmes began in Georgia in 2015 and, by the end of April 2017, 43,989 individuals (29.3% of the estimated total population) had been diagnosed with HCV infection and registered with the elimination programme. A total of 33,673 individuals had initiated treatment with DAAs, and 24,273 individuals had achieved a sustained virological response (SVR), i.e. were cured.

‘In the first 2 years of this programme, we have diagnosed more than one-quarter of our HCV-infected adults in Georgia, we have treated 77% of those diagnosed, and cured over 95% of those completing treatment’, said Prof. Tsertsvadze. ‘Our priorities now are to develop innovative strategies to increase awareness, expand access to high-quality screening, and remove diagnostic and treatment barriers’.

### **Iceland programme: first results**

The Treatment as Prevention for Hepatitis C (TraP HepC) programme was initiated in Iceland in January 2016 with the aim of eliminating chronic HCV infection as a public health threat in Iceland.<sup>17</sup> The programme prioritizes treatment for people who inject drugs (PWID), patients with advanced liver disease, and prisoners, and treats patients who relapse or become reinfected promptly.<sup>17</sup> The study presented today assessed the impact of the TraP HepC programme on the prevalence of active HCV infection among PWID admitted to the Society of Alcoholism and other Addictions’ (SÁÁ’s) Vogur Hospital, Iceland’s largest addiction treatment centre, where more than 90% of PWID in the country are treated. During the first 15 months of the programme, 554 individuals with HCV infection were evaluated and DAAs were initiated in 518 individuals, with 473 (91.3%) completing treatment and 96% of these remaining HCV RNA negative at 12 weeks post-treatment, therefore cured of HCV infection. The prevalence of active HCV infection (viraemia) among PWID at Vogur Hospital showed a dramatic 72% reduction, from 43% in 2015, prior to initiation of the TraP HepC programme, to 12% in 2017.

‘Encouragingly, even in individuals with recent intravenous drug use, DAA treatment, although challenging, resulted in an 87% cure rate, including in those that did not complete the treatment regimen’, said Dr Valgerdur Rúnarsdóttir from Vogur Hospital in Reykjavík, Iceland. ‘People who inject drugs are key drivers of HCV infection in Iceland and this population should be a focus of treatment scale-up. We would like to emphasize and encourage collaboration between addiction treatment centres in both screening and treating HCV. This is key to success in reaching the population in focus’.

'There is no doubt that this is a challenging programme, but we believe it has been initiated successfully in Iceland and that we are well placed to achieve our elimination goal'.<sup>18</sup>

'These two HCV elimination programmes in two different settings show promising results', said Prof. Markus Cornberg from the Hannover Medical School, Germany, and EASL Governing Board Member. 'However, the programme in Iceland is unique and special because it is a defined (or better delimited) situation on an island with a defined target population. If elimination of HCV is possible without a vaccine, it will surely be possible in Iceland. The programme in Georgia still has a long way to go, as three quarters of patients are not yet diagnosed'.

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### **Onsite location reference**

Session title: Parallel session: HCV: Striving towards elimination

Time, date and location of session: 13. April 2018, 05:30 PM - 05:45 PM, South 2

Presenters: Valgerdur Rúnarsdóttir, Iceland (1705) and Tengiz Tsertsvadze (4804)

Abstracts: Marked reduction in the prevalence of hepatitis C viremia among people who inject drugs (PWID) during 2<sup>nd</sup> year of the Treatment as Prevention (TraP HepC) program in Iceland (1705) and Hepatitis C care cascade in the country of Georgia after 2 years of starting national hepatitis C elimination program (4804)

### **Author disclosures**

None reported.

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**PUBLIC RELEASE: 13 APRIL 2018**

## Sustained virological response to oral hepatitis C virus treatment associated with reduced mortality in an Italian cohort

*ILC 2018: Large-scale, real-world data on the course of liver disease after clearance of HCV with direct-acting antiviral agents show reduced risk of death at all stages of disease*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: Patients with chronic hepatitis C virus (HCV) infection who achieve a sustained virological response (SVR) after direct-acting antiviral agent (DAA) treatment have lower all-cause mortality, according to a real-world study presented today at The International Liver Congress™ 2018 in Paris, France. The study, conducted in Italy, found that patients who achieved SVR were at reduced risk of death from both liver-related and other causes.

Chronic HCV infection affects an estimated 71 million people globally.<sup>19</sup> Left untreated, a significant number of those people will develop cirrhosis or liver cancer, which leads to the death of an estimated 700,000 people with HCV infection each year.<sup>20</sup> SVR, defined as undetectable HCV RNA 12 or 24 weeks after the end of therapy, equates to cure in >99% of patients.<sup>21</sup>

Although DAAs have proven highly effective at curing HCV, longer-term morbidity and mortality following DAA-induced SVR has not been well characterized.<sup>22</sup>

‘The long-term health benefits of an HCV cure, in terms of survival, need to be evaluated in long-term, real-world settings’, explained Dr Vincenza Calvaruso from the University of Palermo in Italy, and lead author of the study. ‘We were able to prospectively follow almost 5,000 patients from when they started DAA treatment and look at the impact of achieving SVR on their survival prospects, particularly in patients with Child–Pugh A compensated cirrhosis’.

The study evaluated data from the prospective RESIST-HCV (Rete Sicilia Selezione Terapia - HCV) cohort which collates data for all HCV cases at Sicilian liver centres.<sup>23</sup> Patients who started DAA treatment in 22 centres between March 2015 and December 2016 (4,926 patients, mean age 65.9 ± 11.6 years, 57.6% male) were observed for a median of 65 weeks (range 1–199). The patients were at different stages of disease; 1,158 (23.5%) were non-cirrhotic, 3,326 (67.5%) had compensated cirrhosis, and 442 (9%) had decompensated cirrhosis. Following DAA treatment, more than 90% of patients achieved SVR.

Fifty-three patients (1.1%) died after the antiviral therapy, 23 from liver-related causes and 30 from unrelated causes such as cardiovascular disease and sepsis. Patients who failed to achieve SVR were almost 30 times more likely to die from any cause than those who did achieve SVR (HR 28.9; 95% CI 16.5, 50.8;  $p < 0.001$ ). Both liver-related and non-liver related mortality were predicted by lack of SVR (HR 14.9, 95% CI 6.3, 35.1;  $p < 0.001$  and HR 41.77, 95% CI 17.3, 100.9;  $p < 0.001$ , respectively) and by presence of decompensated cirrhosis (Child–Pugh B; HR 29.4, 95% CI 3.8, 223.9;  $p < 0.001$  and HR 3.0, 95% CI 1.4, 6.2;  $p = 0.006$ , respectively). Body mass index and the presence of diabetes were also found to be predictors of non-liver-related mortality.

‘We found that in this real-world setting with patients using a variety of DAA regimens, achieving SVR reduced mortality from both liver-related and unrelated causes at all stages of disease’, said Dr Calvaruso. ‘An interesting finding that deserves further investigation was a reduced risk of cardiovascular mortality for patients achieving SVR’.

‘DAA therapy results in the achievement of SVR, which is a cure of HCV infection in more than 90% of patients’, said Prof. Markus Cornberg from the Hannover Medical School, Germany, and EASL Governing Board Member. ‘However, a recent Cochrane analysis has challenged whether or not DAA therapy will have an impact on mortality rates. These data are therefore important in documenting that achievement of SVR is beneficial and associated with reduced mortality’.

###

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### **Onsite location reference**

Session title: Parallel Session: Parallel session: Clinical impact of HCV cure

Time, date and location of session: 14. April 2018, 08:00 AM - 08:15 AM, Main Plenary

Presenter: Dr Vincenza Calvaruso, Italy

Abstract: Disease outcomes after DAA-induced SVR: data from the RESIST-HCV cohort (4253)

### **Author disclosures**

None reported in relation to this study.

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**PUBLIC RELEASE: 13 APRIL 2018**

## **Budesonide add-on therapy improves markers of disease activity but fails to improve histology in patients with primary biliary cholangitis**

*ILC 2018: Randomized, placebo-controlled study reports that budesonide add-on therapy improves biochemical markers of disease activity but not histology in high-risk patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: The addition of budesonide is associated with clinically meaningful improvements in biochemical markers of disease activity but no improvement in liver histology in high-risk patients with primary biliary cholangitis (PBC) experiencing a sub-optimal response to ursodeoxycholic acid (UDCA), according to the results of a study presented today. The placebo-controlled study, which randomized 62 patients with PBC, was terminated early because of slow recruitment and as a result, insufficient power to detect a significant histological difference between treatment groups.

PBC is an autoimmune liver disease that is characterized by the progressive destruction of the small bile ducts, resulting in intrahepatic cholestasis, parenchymal injury, and, ultimately, end-stage liver disease.<sup>1,2</sup> The condition typically occurs in middle-aged women, with features frequently including fatigue, pruritis, jaundice, xanthomas, osteoporosis, and dyslipidaemia.<sup>3,3</sup> Ursodeoxycholic acid is the first-line therapy for PBC; however, up to 40% of patients have an insufficient response to this therapy.<sup>1,5</sup> Second-line licensed therapy is with obeticholic acid.<sup>1</sup> Previous studies evaluating the combination of budesonide and UDCA in patients with PBC reported promising results,<sup>6</sup> although relevant budesonide toxicity was reported in patients with late-stage disease.<sup>7</sup>

The study presented today at The International Liver Congress™ 2018 in Paris, France, represents an important, long-awaited, placebo-controlled trial evaluating patients with PBC at high risk of progression. Patients were required to have histologically confirmed PBC and inflammatory activity according to the Ishak score, failure to achieve serum alkaline phosphatase

(ALP)  $<1.5 \times$  the upper limit of normal after at least 6 months of UDCA therapy, and a high risk of disease progression. Patients were randomized to receive either budesonide 9 mg/day or placebo in addition to UDCA for the duration of the study, with the possibility to taper budesonide down to 6 mg/day upon normalization of aspartate aminotransferase (AST). The primary efficacy endpoint was improvement in liver histology with respect to inflammation (an improvement of at least 3 points in the Ishak score or no inflammatory activity) and no progression of fibrosis.

After a mean treatment duration of 25.3 months, the primary histological endpoint in an intention-to-treat analysis was not met, with 11/26 patients (42.3%) in the budesonide group and 5/17 patients (29.4%) in the placebo group having an improvement in liver histology ( $p=0.225$ ). However, normalization of serum ALP occurred in 14/40 patients (35.0%) in the budesonide group and in 2/22 patients (9.1%) in the placebo group ( $p=0.023$ ). Serious adverse events occurred in 10 and seven patients in the budesonide and placebo groups, respectively. Similar numbers of patients reported adverse events in each treatment group; adverse drug reactions were reported for 24 patients (60%) in the budesonide group and eight patients (36%) in the placebo group.

‘Our study found that add-on budesonide produced clinically meaningful improvements in biochemical markers of disease activity that, unfortunately, did not translate into improved liver histology’, said Professor Gideon Hirschfield from the University of Birmingham in the UK. ‘The overall safety and tolerability of long-term budesonide treatment in this population was acceptable and in keeping with clinical experience’.

Professor Hirschfield believes that the recruitment challenges that led to a lack of statistical power for the primary histological endpoint in this study are relevant for future studies in PBC. ‘Nevertheless’, he says, ‘the observation that liver biochemical improvements were seen with add-on budesonide is consistent with prior trial data and treatment goals’.

‘Study recruitment inevitably pre-dated second-line licensed therapy with obeticholic acid’, he noted. ‘However, our results suggest that after licensed therapy has been offered to patients, there may be individuals in whom there is a high risk of progression and for whom the addition of budesonide to anti-cholestatic therapy will produce biochemical improvements in disease activity’.

‘Clinical research to improve the therapeutic options available for primary biliary cholangitis is key, and studies such as these are important to help understand the measures needed to individualize treatment protocols by identifying the hallmark clinical features of response’, said

Prof. Marco Marzioni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. 'This study also highlights the complexity of research focusing on cholangiopathies, and how this is impacted by the small pool of patients that are eligible to enter clinical trials. Yet, hepatologists do not leave those patients behind, and continue to work on developing more effective clinical management options'.

###

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### **Onsite location reference**

Session title: General session II and award ceremony I

Time, date and location of session: 13. April 2018, 10:00 AM - 10:15 AM , Main Plenary

Presenter: Gideon Hirschfield, UK

Abstract: Results of a randomised controlled trial of budesonide add-on therapy in patients with primary biliary cholangitis and an incomplete response to ursodeoxycholic acid (2095)

### Author disclosures

Author disclosures are as declared in the ILC 2018 programme. The clinical trial sponsor is Dr Falk Pharma GmbH. Roland Greinwald and Markus Proels are employees of Dr Falk Pharma.

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**PUBLIC RELEASE: 13 APRIL 2018**

## Long-term obeticholic acid treatment leads to reversal or stabilization of fibrosis/cirrhosis in patients with PBC

*ILC 2018: After 3 years of treatment with obeticholic acid, 85% of patients with PBC and an incomplete response to UDCA experienced stabilization or regression of fibrosis/cirrhosis in the POISE biopsy sub-study*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL FRIDAY 13 APRIL 2018 07:00**

13 April 2018, Paris, France: The first results from the POISE biopsy sub-study have today confirmed that long-term treatment with obeticholic acid (OCA) leads to the reversal or stabilization of fibrosis/cirrhosis in patients with primary biliary cholangitis (PBC) who have had an incomplete response to ursodeoxycholic acid (UDCA). These results provide the first evidence that improvements in biochemical markers of PBC observed in previous studies are accompanied by anti-fibrotic effects in line with those observed in pre-clinical trials.

‘There is strong evidence from clinical trials that OCA leads to significant reductions in alkaline phosphatase (ALP) that are predicted to improve clinical outcomes of patients with PBC who do not respond adequately to or do not tolerate UDCA’,<sup>1</sup> said Dr Christopher Bowlus from the University of California, Davis in the USA, who presented the results today at The International Liver Congress™ 2018 in Paris, France. ‘This study offers the first evidence from paired liver biopsies that OCA is indeed a disease-modifying therapy’.

Primary biliary cholangitis is a rare autoimmune liver disease characterized by biliary destruction, progressive cholestasis, and, ultimately, the development of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).<sup>1,3</sup> The primary medical treatment for PBC is UDCA, however, up to 40% of patients have an insufficient response to this treatment, putting them at risk of potentially life-threatening complications.<sup>1,3</sup>

Obeticholic acid is a potent agonist of the farnesoid X receptor (FXR), which regulates bile acid synthesis and transport.<sup>1</sup> Two previously reported Phase 2 studies<sup>4,5</sup> and a pivotal Phase 3 study (POISE)<sup>6</sup> confirmed that OCA, primarily in combination with UDCA, leads to significant reductions in serum ALP and improvements in other biochemical liver markers, leading to the recent approval of the treatment by the US Food and Drug Administration (FDA).<sup>3</sup>

The biopsy sub-study of POISE involved patients undergoing liver biopsies prior to, and after 3 years of, treatment with OCA. Biopsies were centrally read and assessed using a six-tier staging system (from no fibrosis to cirrhosis). Thirteen patients – all receiving treatment with UDCA at baseline – had paired biopsies that were adequate for analysis.

At baseline, nine of the 13 patients (69%) presented with pre-cirrhotic fibrosis and four (31%) with cirrhosis. At the last visit before the final biopsy, serum ALP was reduced and direct bilirubin levels were comparable to baseline (median changes from baseline: -99 U/L and 0.0 µmol/L, respectively). After 3 years of OCA treatment, the majority of patients improved (n=6; 46%) or maintained (n=5; 38%) their histological stage, while two patients (15%) deteriorated. Of the four patients with baseline cirrhosis, three (75%) improved to fibrosis without cirrhosis while receiving OCA treatment.

‘Eighty-five percent of the patients with PBC in this study with an incomplete response to UDCA had regression or no worsening of their fibrosis or cirrhosis after 3 years of OCA treatment – a period of time during which we would have expected some degree of fibrosis progression’, said Dr Bowlus. ‘OCA represents the first new treatment approved for PBC in decades, and these results support the potential of OCA to slow disease progression in this group of patients who have the greatest need for new treatments. The results of the ongoing COBALT study will determine if the biochemical improvements of the POISE study and the histological results reported here translate to improved clinical outcomes’ (NCT02308111).

‘Relevant changes are on the way for the management of patients with PBC, for which ursodeoxycholic acid has been the only treatment option for a long time’, said Prof. Marco Marzoni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. ‘Now new medicines are coming and the first of these to be available, obeticholic acid, has been shown to ameliorate surrogate markers of disease progression. The current study, however, reports the first evidence that OCA is also able to halt the deposition of collagen tissue in the liver, a significant outcome for the natural history of PBC’.

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### **Onsite location reference**

Session title: Poster Late Breakers

Time, date and location of session: 12. April 2018, 09:00 AM - 14. April 2018, 05:00 PM, Poster Area

Presenter: Christopher Bowlus, USA

Abstract: Long-term obeticholic acid (OCA) treatment associated with reversal or stabilization of fibrosis/cirrhosis in patients with primary biliary cholangitis (PBC) (5662)

### **Author disclosures**

Christopher L Bowlus has received grant support from Intercept, CymaBay, Gilead, BMS, GSK, Takeda, and Genkyotex; and has served as an Advisor to Contaus, Patara, Intercept, and GSK. Alberto Pares Darnacullea has participated in advisory boards and lectures for Intercept Pharma. Paul Pockros has received consultancy and speaker honoraria from Intercept and research funding from Scripps Health. Pierre Bedossa has received funding from Intercept. Richard Pencek, Leigh MacConell, David Shapiro, Elizabeth Malecha, and Uchenna Iloeje own stock in and are employees of Intercept. Joost PH Drenth has served on advisory boards for AbbVie, Gilead, and Intercept, and his department receives research funding from AbbVie, Ipsen

and Gilead – all reimbursements received go to the Radboudumc. Andreas Kremer has served as a consultant or advisor for Beiersdorf, Elsevier, GSK, Intercept, Janssen, MSD, and has received speaker honoraria from BMS, Falk, Intercept, Janssen, MSD. Lisa Forman and Stephen Ryder report no conflicts of interest.

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**PUBLIC RELEASE: 13 APRIL 2018**

## Selective internal radiation therapy (SIRT) fails to extend survival in the SORAMIC study palliative cohort

*ILC 2018: The addition of SIRT to sorafenib in patients with advanced hepatocellular carcinoma was associated with no overall survival benefits compared with sorafenib alone, but may offer benefits in some subgroups of patients*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL 13 APRIL 2018 07:00 CET**

13 April 2018, Paris, France: The final results of the palliative cohort of the SORAMIC study in patients with unresectable, locally advanced primary liver cancer have confirmed no clinical advantage to adding selective internal radiation therapy (SIRT) to standard sorafenib treatment compared with using sorafenib alone. However, although the overall survival rates in the total patient population did not differ significantly between treatment groups, subgroup analyses suggested possible survival benefits with adding SIRT to sorafenib in some patient groups.

‘SORAMIC is the first large, randomized controlled trial to compare the efficacy and safety of combining liver-directed SIRT and sorafenib with using sorafenib alone’, explained study director, Prof. Dr Jens Ricke from the Ludwig-Maximilians-University in Munich, Germany, who presented the results today at The International Liver Congress™ 2018 in Paris, France.

‘Although we were disappointed to find no overall survival benefit of adding SIRT to sorafenib across the entire study population, we did observe a survival benefit in younger patients, those with a non-alcoholic aetiology of the cirrhosis, and those with no cirrhosis at all’.

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and the second most common cause of cancer-related death.<sup>1,2</sup> HCC can be treated surgically by resection or transplantation, however, many patients are not candidates for surgical interventions and, for these patients, the prognosis remains poor.<sup>1</sup> Sorafenib is the standard, first-line systemic therapy for individuals with advanced HCC,<sup>1</sup> with the SHARP study demonstrating an increased median overall survival from 7.9 months to 10.7 months with sorafenib treatment compared with placebo in this population.<sup>3</sup>

The SORAMIC (SORAfenib in combination with local MICro-therapy guided by gadolinium-EOB-DTPA-enhanced MRI; NCT01126645) study was initiated in February 2010 and comprises three separate diagnostic, local ablation, and palliative sub-studies.<sup>4</sup> The palliative sub-study

presented today randomized 424 patients with inoperable HCC who were not candidates for transarterial chemoembolization (TACE) to receive treatment with either SIRT with yttrium-90 resin microspheres (SIR-Spheres®) plus sorafenib (target dose 400 mg bid) or sorafenib alone. The primary endpoint of the study was overall survival (OS) in the intention-to-treat population.

As Prof. Dr Ricke reported, the median OS was 12.1 months (95% CI: 10.6, 14.6) in the SIRT + sorafenib arm (n=216) and 11.5 months (95% CI: 9.8, 13.9) in the sorafenib arm (n=208) (HR: 1.01; 95% CI: 0.82, 1.25; p=0.93). In the per-protocol group, the median OS was 14.1 months (95% CI: 10.9, 16.4) in the SIRT + sorafenib arm (n=114) and 11.1 months (95% CI: 9.7, 13.9) in the sorafenib arm (n=174) (HR: 0.86; 95% CI: 0.67, 1.11; p=0.25).

A subgroup analysis of the per-protocol population in this study revealed a survival benefit of SIRT + sorafenib for patients ≤65 years of age (HR: 0.652), those with a non-alcoholic aetiology of the cirrhosis (HR: 0.632), and those with no cirrhosis (HR: 0.465). Adverse events grade 3 or higher were reported in 115/159 (72.3%) patients in the SIRT + sorafenib arm and in 135/197 (68.5%) patients in the sorafenib arm.

‘There remains a significant unmet need for new treatment approaches in patients with unresectable HCC, and SIRT had shown promising results in previous, non-randomized studies’,<sup>5,6</sup> said Prof. Dr Ricke. ‘We believe our results have generated some very interesting new hypotheses in terms of the types of HCC patients that might benefit from combination therapy of SIRT and sorafenib, and we hope to explore these further in the future’.

‘The SORAMIC trial is the first reported randomized controlled trial evaluating the survival benefit of adding SIRT to sorafenib in unresectable, locally advanced HCC not suitable for TACE’, said Prof. Alejandro Forner from the Hospital Clinic Barcelona, Spain, and EASL Governing Board Member. ‘Regrettably, the study failed to meet the primary endpoint and the addition of SIRT to sorafenib did not show an overall survival that was superior to sorafenib alone. Further studies are needed to identify which specific population might benefit from this treatment approach’.

###

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### **Onsite location reference**

Session title: Late breaker session

Time, date and location of session: 14. April 2018, 05:00 PM - 05:15 PM, Main Plenary

Presenter: Jens Ricke, Germany

Abstract: The impact of combining selective internal radiation therapy (SIRT) with sorafenib on overall survival in patients with advanced hepatocellular carcinoma: The SORAMIC trial palliative cohort (5449)

### **Author disclosures**

None reported.

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**PUBLIC RELEASE: 13 APRIL 2018**

## HCV-related liver transplantation and post-transplant survival rates in Europe have improved rapidly in the era of direct-acting antiviral drugs

*ILC 2018: Since 2014, the percentage of liver transplants performed as a result of HCV infection has declined rapidly and post-transplant survival rates are improving*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2018, Paris, France: HCV-related liver transplantation rates in Europe have declined dramatically since the availability of direct-acting antiviral (DAA) drugs and survival rates after transplantation have reached an all-time high. A study presented today at The International Liver Congress™ 2018 in Paris, France, has found that the percentage of liver transplants performed as a result of hepatitis C virus (HCV) infection has more than halved since the availability of DAA drugs, and that post-transplant survival rates among those with HCV infection are now similar to those reported in patients with hepatitis B virus (HBV) infection.

‘Direct-acting antiviral drugs have revolutionized the treatment of HCV-infected individuals – even those with advanced liver disease’,<sup>1</sup> explained Dr Giovanni Perricone from the ASST Great Metropolitan Hospital Niguarda in Milan, Italy, who presented the study findings today. ‘Unlike the older HCV treatment regimens involving ribavirin and pegylated interferon, these newer agents are highly effective and well tolerated across genotypes, and we have shown previously that the remarkable clinical improvements that can be achieved using these agents can lead to the delisting of some individuals waiting for liver transplantation’.<sup>2</sup>

In the latest research conducted by Dr Perricone and colleagues, data from the European Liver Transplant Registry from between January 2007 and June 2017 were reviewed, involving a total of 36,382 adults who underwent liver transplantation as a result of HCV, HBV, alcoholic liver disease or non-alcoholic steatohepatitis (NASH). To assess the impact of DAAs on liver transplantation rates, data were analyzed in separate treatment eras: the interferon (IFN) era from 2007 to 2010, the protease inhibitor (PI) era from 2011 to 2013, and the second-generation DAA era from 2014 to June 2017.

The percentage of liver transplants conducted as a result of HCV infection decreased from 22.8% during the IFN era to 10.6% during the DAA era. In contrast, the percentage of transplants conducted as a result of NASH increased from 1.1% to 6.2%. Within the DAA era, the percentage of liver transplants due to HCV decreased from 21.1% during the first half of 2014 to 10.6% during the first half of 2017.

According to Dr Perricone, the decreased requirement for liver transplantation during the DAA era was more pronounced in patients with HCV related to decompensated liver disease (-68.8%) than in those with HCV-related hepatocellular carcinoma (-34.0%). The 3-year survival of liver transplant recipients with HCV infection has also improved from 65.1% in the IFN era to 76.9% in the DAA era – a survival rate that is now comparable to that of patients with HBV infection (78.0%) ( $p=0.38$ ).

‘Our study provides clear evidence that DAAs are changing the epidemiology of liver transplantation, at least in countries like Italy where the prevalence of HCV infection is high’,<sup>3</sup> said Dr Perricone. ‘We anticipate that rates of HCV-related transplantation will continue to decline as more patients gain access to these highly effective treatments’.

‘For the first time in many years, we have also seen improved survival in liver transplant recipients with HCV infection, and this can be attributed directly to the availability of DAA drugs’.

‘These are very important data that emphasize the effectiveness of DAA therapies against HCV’, said Prof. Markus Cornberg from the Hannover Medical School, Germany, and EASL Governing Board Member. ‘These data are important, especially as a recent Cochrane report has concluded that there is not sufficient evidence to understand how sustained virological response affects long-term clinical outcomes’.

###

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**Onsite location reference**

Session title: Poster Late Breakers

Time, date and location of session: 12. April 2018, 09:00 AM - 05:00 PM, Poster Area

Presenter: Giovanni Perricone

Abstract: The percentage of patients with HCV infection in need of a liver transplant is rapidly declining while survival after transplantation is improving: A study based on European Liver Transplant Registry (5412)

**Author disclosures**

None reported.

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**PUBLIC RELEASE: 13 APRIL 2018**

## **NGM282 – an engineered analogue of FGF19 – shows promise in patients with primary sclerosing cholangitis**

*ILC 2018: Phase 2, randomized, double-blind, placebo-controlled study reports significant improvements in markers of disease activity and fibrosis with subcutaneous NGM282 in patients with primary sclerosing cholangitis*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL 13 APRIL 2018 07:00CET**

13 April 2018, Paris, France: The fibroblast growth factor 19 (FGF19) engineered analogue, NGM282, inhibits bile acid synthesis, decreases markers of hepatic inflammation, and significantly improves markers of fibrosis in patients with primary sclerosing cholangitis (PSC), according to the results of a Phase 2, multicentre, randomized, double-blind, placebo-controlled study reported today. The study, which involved 62 patients with PSC diagnosed according to EASL criteria,<sup>7</sup> offers hope of a new medical treatment for a condition in which effective drug therapies are currently limited.<sup>8</sup>

‘Primary sclerosing cholangitis is a rare, inflammatory, cholestatic liver disease that is characterized by progressive fibrosis of the bile ducts and liver, and causes progressive liver dysfunction’, explained Prof. Gideon Hirschfield from the University of Birmingham in the UK, who presented the results today at The International Liver Congress™ 2018 in Paris, France. ‘Liver transplantation is effective for advanced disease, but there are currently no medical treatments that have been shown to prolong transplant-free survival’.<sup>8</sup>

NGM282 is a non-tumourigenic engineered analogue of FGF19, an endocrine gastrointestinal hormone that regulates bile acid, carbohydrate and energy homeostasis.<sup>9,10</sup> In an animal model, NGM282 was shown to suppress the classic pathway of bile acid production, and to inhibit fatty acid synthesis and *de novo* lipogenesis.<sup>11</sup> NGM282 was well tolerated in a healthy volunteer study,<sup>12</sup> and the molecule has recently shown potential as a treatment for non-alcoholic steatohepatitis (NASH).<sup>13</sup>

The study presented today by Prof. Hirschfield randomized 62 patients with PSC and an elevated alkaline phosphatase (ALP) level ( $\geq 1.5$ x the upper limit of normal) to receive either a daily subcutaneous injection of NGM282 at a dose of 1 mg or 3 mg, or placebo. The primary endpoint was the change in ALP from baseline to Week 12.

Although there were no significant reductions in serum ALP levels in either active treatment group compared with placebo, at Week 12 significant reductions in serum levels of alanine aminotransferase (ALT) (-40 U/L) and aspartate aminotransferase (AST) (-23 U/L) in the NGM282 3 mg/day treatment group were observed ( $p < 0.01$  vs. placebo). Serum levels of 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4), which reflects bile acid synthesis, and total bile acid, were also significantly reduced in both NGM282 treatment groups at Week 12 compared with placebo.

'We also saw significant reductions in surrogate markers of fibrogenesis in the patients who received NGM282, with reductions especially pronounced in patients with higher-risk disease (Enhanced Liver Fibrosis Score  $> 9.8$  at baseline)', said Prof. Hirschfield. 'These changes are consistent with those observed in patients with non-alcoholic steatohepatitis which were also presented at ILC this year'.

NGM282 was well tolerated in this study, with no differences in PSC-related clinical events between the NGM282 treatment groups and the placebo group. No drug-induced pruritus was observed and no neutralizing anti-drug antibodies were detected during or after treatment with NGM282. The most frequently reported adverse events amongst the NGM282-treated patients were diarrhoea, frequent stools and injection site reactions, the majority of which were mild and resolved while on treatment.

'This study provides good evidence of relevant clinical activity for NGM282 in individuals with PSC and highlights the need to explore NGM282's impact on liver fibrosis in larger studies of a longer duration', said Prof. Hirschfield. 'NGM282 seems to be a promising treatment for patients with PSC, for whom very few medical options currently exist'.

'Studies like this one are key, since they investigate possible novel treatments for PSC, a disease that currently has no effective therapies', said Prof. Marco Marzoni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. 'Although this trial did not achieve fully positive results in terms of reduction of markers of disease progression, it certainly indicates that the manipulation of key molecules involved in the pathophysiology of PSC is the route to cure for our patients'.

###

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### **Onsite location reference**

Session title: Late Breaker Session, General Hepatology

Time, date and location of session: 14. April 2018, 04:15 PM - 04:30 PM, Main Plenary

Presenter: Gideon Hirschfield, UK

Abstract: NGM282, an engineered analogue of FGF19, significantly improves markers of bile acid synthesis, hepatic injury and fibrosis in PSC patients: Results of a phase 2, multicenter, randomized, double-blind, placebo-controlled trial (5580)

### **Author disclosures**

None reported.

### **References**

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**PUBLIC RELEASE: 13 APRIL 2018**

## Automated analysis of biopsy samples enables rapid and reproducible quantification of NASH disease activity

*ILC 2018: New deep-learning approach to pattern recognition in liver biopsy samples enables automated scoring of ballooning and inflammation in a pre-clinical model of NASH*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL 13 APRIL 2018 07:00CET**

13 April 2018, Paris, France: Deep-learning approaches to pattern recognition in liver biopsy samples have moved one step closer to clinical application, with a new study reporting a good correlation between an automated image analysis system and an expert reviewer for the identification of key markers of disease activity in a pre-clinical model of non-alcoholic steatohepatitis (NASH). The study reported today at The International Liver Congress™ 2018 in Paris, France, found that deep-learning algorithms applied using open-source pathology software (QuPath<sup>1</sup>) could accurately identify cell histology patterns consistent with lobular inflammation and hepatocellular ballooning – markers of disease activity that are essential to establish the diagnosis and severity of NASH.<sup>2</sup>

Non-alcoholic steatohepatitis is the progressive form of non-alcoholic fatty liver disease (NAFLD), in which excessive fat accumulates in the liver of individuals who do not have a history of alcohol abuse.<sup>2,3</sup> NAFLD is regarded as a hepatic manifestation of metabolic syndrome, with the number of individuals with NAFLD/NASH increasing rapidly worldwide, in parallel with the increasing prevalence of obesity.<sup>3</sup> Although clinical algorithms based on blood test results are being developed to identify patients with progressive NASH,<sup>4-6</sup> liver biopsy remains essential to establish both the diagnosis of NASH and the severity of the disease.<sup>2</sup>

‘The histological evaluation of NASH by microscopy is time consuming and limited by inter- and intra-observer variability’, explained Mr John Brozek from the French biotechnology company, GENFIT, which is developing the deep-learning system. ‘We have been working to eliminate the subjectivity associated with interpreting histological images and have recently used deep-learning technologies to quantify histological patterns associated with NASH in an animal model’.<sup>7,8</sup>

In the study presented today by Mr Brozek, animal models (rats or mice fed a choline-deficient, L-amino-acid-defined diet supplemented with cholesterol) were used to evaluate hepatocellular ballooning and lobular inflammation in liver biopsy samples. An expert histopathologist determined the ballooning and inflammation scores for all the animals included in the study, and deep-learning models were constructed to detect and analyze these histological features. An initial training set (n=31) was used to calibrate ballooning and inflammation for subsequent prediction of these histological features in four independent cohorts (n=271).

According to Mr Brozek, the deep-learning system was able to predict cell histological patterns relating to ballooning and inflammation with accuracies of 98% and 91%, respectively. Excellent agreement was observed between the expert and fully automated scores of ballooning at a cellular level for each of the cohorts ( $k=0.84$  and  $k=0.81$ ). An excellent correlation was also observed with the full tissue samples ( $k=0.71$ ), and between whole slide imaging-based automatic scoring of inflammation on the training cohort ( $Rho=0.907$ ).

‘Deep-learning-based scoring systems allow an exhaustive and reproducible analysis of all cells in a biopsy sample, and they can analyze specific regions of cells that can be difficult to interpret manually, even if you are an expert’, said Mr Brozek. ‘Our automated scoring system for ballooning and inflammation showed a high correlation with expert evaluation and it is ready to be used for high-throughput activity scoring in pre-clinical studies or, in the near future, as a companion diagnostic tool for clinical application’.

‘There are key challenges in the consistency of liver biopsy interpretation and machine learning offers the promise of a more standardized, objective approach that allows for the analysis of biopsies in clinical trials’, said Prof. Phil Newsome from the Queen Elizabeth Hospital and University of Birmingham, UK, and EASL Governing Board Member.

###

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### Onsite location reference

Session title: Poster Late Breakers

Time, date and location of session: 09.00–17.00, 12 April 2018, Poster Area

Presenter: John Brozek

Abstract: A deep-learning approach for pattern recognition allows rapid and reproducible quantification of histological NASH parameters: integration into the QuPath platform (5737)

### Author disclosures

John Brozek is an employee of GENFIT.

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**PUBLIC RELEASE: 13 APRIL 2018**

## Phase 2 studies of two novel treatments for primary biliary cholangitis report encouraging results

*ILC 2018: Ongoing Phase 2 studies of tropifexor and seladelpar report promising preliminary efficacy, safety and tolerability results, paving the way for longer-term studies in patients with primary biliary cholangitis*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL 13 APRIL 2018 07:00CET**

13 April 2018, Paris, France: Preliminary results from two ongoing Phase 2 studies of novel agents under investigation for the treatment of primary biliary cholangitis (PBC) have suggested promising efficacy, safety and tolerability profiles in patients not responding to current standard of care, potentially paving the way for longer-term studies. In the first study presented this week at The International Liver Congress™ 2018 in Paris, France, the non-bile acid farnesoid X receptor (FXR) agonist, tropifexor, demonstrated dose-dependent activity on markers of cholestasis and hepatocellular damage over 4 weeks, with no apparent increase in itching. The second study evaluated 12–26 weeks of treatment with the selective peroxisome proliferator-activated receptor-delta (PPAR- $\delta$ ), seladelpar, at doses of 2, 5, and 10 mg/day, and reported potent and sustained anti-cholestatic and anti-inflammatory activity without an increase in pruritus.

Primary biliary cholangitis is a progressive cholestatic liver disease characterized by an immune-mediated destruction of intrahepatic bile ducts.<sup>1,10</sup> Ursodeoxycholic acid (UDCA) has been the mainstay of treatment for PBC for more than 20 years, however, up to 40% of patients receiving UDCA have persistent elevations of alkaline phosphatase (ALP) or bilirubin, and a further 3–5% of patients are unable to tolerate treatment.<sup>1,11</sup> The bile acid FXR agonist obeticholic acid (OCA) is approved as an add-on therapy in patients with PBC, or for those intolerant of UDCA;<sup>1</sup> however, approximately 50% of patients in the Phase 3 study of added OCA did not meet the trial's pre-specified dichotomous biochemical efficacy endpoint.<sup>12</sup>

Tropifexor is a novel, selective, non-bile acid FXR agonist that reduced cholestasis and hepatocellular damage in rodent models.<sup>13</sup> The ongoing Phase 2 study reported this week enrolled PBC patients with an inadequate response to UDCA (ALP  $\geq 1.67 \times$  ULN or bilirubin  $>$ ULN), who were randomized to receive tropifexor 30  $\mu$ g, 60  $\mu$ g, or 90  $\mu$ g once daily or a

matching placebo for 4 weeks. The primary endpoint was change from baseline in gamma-glutamyltransferase (GGT).

Dose-dependent decreases in GGT, ALP, bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed and, by Day 28, a 72% reduction in GGT and a 41% reduction in ALT were reported in the highest tropifexor dosing group (90 µg/day;  $p < 0.001$  vs. placebo). Tropifexor was reported to be generally safe and well tolerated at the doses tested.

‘The dose-dependent activity of tropifexor on markers of cholestasis and hepatocellular damage indicates the potential benefit of FXR agonism in patients with PBC’, said Prof. Dr Christoph Schramm from the University Medical Centre in Hamburg, Germany, who presented the study results. ‘The absence of a discernible increase in itch could be a major advantage of this FXR agonist, with a resulting impact on patient quality of life’.

In the second study presented in Paris, patients with an inadequate response to UDCA or intolerance to treatment were randomized to receive one of three doses of the selective PPAR- $\delta$  agonist, seladelpar, 2 mg, 5 mg, or 10 mg/day. The primary efficacy outcome was change from baseline in ALP. At 12 weeks, changes in ALP were reported to be -21%, -33%, and -45% in the 2 mg/day (n=6), 5 mg/day (n=25), and 10 mg/day (n=22) treatment groups, respectively. At 26 weeks, 69%, 67%, and 79% of patients had an ALP  $< 1.67 \times$  ULN in the 5 mg/day (n=13), 5–10 mg/day (n=6), and 10 mg/day (n=19) treatment groups, respectively, with similar reductions in ALP observed in each group (-43% to -45%). Overall, 29% of patients had normal ALP at 26 weeks.

According to the investigators, seladelpar was generally well tolerated, with no aminotransferase safety signal observed. ‘Seladelpar continues to demonstrate an impressive level of activity that is now sustained over 26 weeks of treatment. In the absence of a transaminase safety signal,<sup>14</sup> the doses of 5 and 10 mg/day appear to represent an appropriate risk/benefit profile,’ said Professor Gideon Hirschfield from the University of Birmingham, UK. ‘Moreover, in our study seladelpar treatment was not associated with an increase in pruritus, indeed a substantial decrease was observed in some treatment groups at Week 26, suggesting anti-pruritic activity’.

‘Clinical research in PBC is very active at present and these two studies indicate how much scientists are engaged in designing studies aimed at providing patients with effective treatments’, said Prof. Marco Marzioni from the University Hospital of Ancona, Italy, and EASL Governing Board Member.

###

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### **Onsite location reference**

Session title: Late Breaker Session

Time, date and location of session: 14. April 2018, 05:30 PM - 05:45 PM, Main Plenary

Presenter: Christoph Schramm, Germany

Abstract: Early assessment of safety and efficacy of tropifexor, a potent non bile-acid FXR agonist, in patients with primary biliary cholangitis: An interim analysis of an ongoing phase 2 study (5581)

Session title: Poster Late Breakers

Time, date and location of session: 12. April 2018, 09:00 AM - 14. April 2018, 05:00 PM, Poster Area

Presenter: Gideon Hirschfield, UK

Abstract: Treatment efficacy and safety of seladelpar, a selective peroxisome proliferator-activated receptor delta agonist, in primary biliary cholangitis patients: 12- and 26-week analysis from an ongoing international, randomized, dose ranging phase 2 study (5588)

### Author disclosures

Gideon Hirschfield and co-authors: as stated in the ILC 2018 programme.

Christoph Schramm and co-authors: none reported.

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**PUBLIC RELEASE: 14 APRIL 2018**

## Updates on new therapies in development for rare liver diseases

*ILC 2018: Long-term data with sebelipase alfa for lysosomal acid lipase deficiency and preliminary data for investigational RNAi therapeutics for acute intermittent porphyria and alpha-1 antitrypsin deficiency add continued hope for the future management of metabolic and rare liver diseases*

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

**UNDER EMBARGO UNTIL SATURDAY 14 APRIL 2018 07:00**

14 April 2018, Paris, France: Promising results for three drugs for the treatment of three rare liver diseases were presented today at The International Liver Congress™ 2018 in Paris, France. Sebelipase alfa, approved for treatment of lysosomal acid lipase (LAL) deficiency in 2015,<sup>24</sup> showed sustained improvements and long-term tolerability in a diverse patient population. Preliminary findings with two investigational RNA interference (RNAi) therapeutics were also positive; givosiran substantially reduced the annualized attack rate in patients with acute intermittent porphyria (AIP), and ARO-AAT demonstrated positive preclinical safety and efficacy in alpha-1 antitrypsin (AAT) deficiency – pointing to the developing potential of this new therapeutic strategy in patients with few treatment options. LAL deficiency, an underappreciated cause of cirrhosis and severe dyslipidaemia, is a rare autosomal recessive disorder characterized by accumulation of cholesteryl esters and triglycerides in the liver.<sup>25</sup> The age at onset and rate of progression vary greatly.<sup>25</sup> Sebelipase alfa is a recombinant human LAL enzyme indicated for the treatment of LAL deficiency which was approved in 2015 following successful Phase 2/3 trials.<sup>26,27</sup>

‘It is exciting to see clinical benefits and good tolerability confirmed in this long-term follow-up across a diverse population of adult and paediatric patients with LAL deficiency’, said Dr Florian Abel from Alexion Pharmaceuticals, Inc., New Haven, CT, USA. ‘This population included patients who would have been ineligible to participate in previous clinical studies because of their age or prior transplant status’.

Data were presented today for 31 patients who were enrolled in a multicentre, open-label study of sebelipase alfa 1 mg/kg by intravenous (IV) infusion every other week for up to 96 weeks. Permitted dose escalation/reduction was from a maximum of 3 mg/kg weekly to a minimum of 0.35 mg/kg every other week.

There were marked reductions from baseline in alanine aminotransferase (ALT; -44.4%) and aspartate aminotransferase (AST; -38.4%). There were also reductions from baseline in liver volume (-17.6%), liver fat content (-14.9%), and spleen volume (-16.5%). In the 7/13 patients with data available, liver fibrosis improved or did not progress. Most adverse events were mild to moderate in severity, three patients experienced infusion-associated reactions. Two patients were positive for anti-drug antibodies, on one occasion each, but neither developed neutralizing antibodies.

'We were pleased to see that long-term treatment with sebelipase alfa was well tolerated and that improvements in markers of liver injury were sustained', said Dr Abel.

AIP is the most common form of acute hepatic porphyrias (AHPs), a family of rare, inherited metabolic diseases resulting in deficiencies in the liver enzymes responsible for haem biosynthesis.<sup>28</sup> Central to the pathophysiology of all AHPs is the induction of aminolevulinic acid synthase 1 (ALAS1), which can lead to accumulation of the neurotoxic haem intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), which are causal for potentially life-threatening disease manifestations.<sup>29</sup> RNAi is a naturally occurring cellular mechanism mediated by small interfering RNA (siRNA) that allows for the inhibition of protein synthesis through the cleavage and degradation of a specific mRNA.<sup>30</sup> Givosiran is an investigational, subcutaneously administered RNAi therapeutic targeting liver ALAS1 to reduce ALA and PBG accumulation in patients with AHPs.

A Phase 1, multinational, randomized, placebo-controlled study of givosiran has been conducted in three parts; Part A: single ascending dose, Part B: multiple ascending dose and Part C: multiple dose (four cohorts of four to five patients each), to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran in patients with AIP (ClinicalTrials.gov Identifier: NCT02452372). The study has now been completed and givosiran was generally well tolerated, with no serious adverse events or clinically significant laboratory abnormalities related to the study drug.

Monthly dosing of givosiran led to rapid, dose-dependent, and durable silencing of induced ALAS1 mRNA of approximately 60%, with concomitant lowering of ALA and PBG by >80% in

patients with recurrent attacks. Patients treated with a monthly dose of 2.5 mg/kg of givosiran had an 83% mean decrease in the annualized attack rate (requiring hospitalization, urgent care, or haemin) compared with placebo, and an 88% decrease in the number of haemin doses. Patients completing the Phase 1 study were eligible to enrol in an open-label extension study (NCT02949830). As of February 2018, the safety profile in patients in the open-label extension (n=16) was consistent with that observed in Part C. Patients that had received givosiran in Part C (n=12) had further reductions in annualized attack rate of 93%, relative to the 3-month run-in period.

‘Givosiran has the potential to significantly lower liver ALAS1 levels in a sustained manner and to thereby decrease the accumulation of neurotoxic intermediates that potentially lead to severe or life-threatening neurovisceral attacks. We’re very encouraged by our results, as treatment was associated with marked reductions in both annualized attack rate and haemin use’, said Dr Eliane Sardh from the Karolinska University Hospital, Stockholm, Sweden. ‘These results suggest that givosiran, which is currently being studied in a Phase 3 trial, has the potential to become a transformative treatment option for patients with hepatic porphyrias, a debilitating and potentially life-threatening disease’. (NCT03338816).

AAT deficiency is an autosomal, co-dominant genetic disorder in which the PiZ mutation results in the misfolded protein (Z-AAT) that accumulates in hepatocytes and can lead to fibrosis, cirrhosis and hepatocellular carcinoma.<sup>31</sup> The only current treatment option for AAT deficiency-related liver disease is liver transplant.<sup>31</sup> ARO-AAT is a second-generation, subcutaneously administered RNAi therapeutic that replaces ARC-AAT, a first-generation intravenously administered RNAi therapeutic that previously demonstrated proof of concept in the PiZ mouse model expressing human Z-AAT, and achieved deep knockdown in healthy volunteers and patients.<sup>32,33</sup>

‘ARO-AAT is a liver-targeted RNAi therapeutic that durably reduced Z-AAT liver mRNA and serum protein in PiZ mice. The degree of mRNA reduction correlated with the amount of siRNA in the liver’, said Dr Christine Wooddell of Arrowhead Pharmaceuticals, Madison, WI, USA. ‘We have also assessed the pharmacokinetics and biodistribution of ARO-AAT in rats, efficacy in PiZ mice, and pharmacological activity in non-human primates’.

In the studies presented today, ARO-AAT in rats demonstrated high tissue distribution, with the highest exposure in the liver through Day 16, peaking at 4 hours. Repeat dosing (4 mg/kg once every 2 weeks, four times) of young PiZ mice reduced Z-AAT liver mRNA by 95%, plasma Z-

AAT by 96%, monomeric liver Z-AAT by 98%, and polymeric Z-AAT by 41%. ARO-AAT prevented increases of Z-AAT polymer globules that were observed in untreated controls of the same age, with a 2.6-fold increase in number, an 8-fold increase in affected liver area, and a 3.3-fold increase in globule size. Non-human primates had a mean reduction of serum AAT of 89–91% that was sustained for more than 7 weeks after the second dose received, following administration of two doses of 3 mg/kg, 4 weeks apart. These results are supportive of monthly or less frequent dosing for ARO-AAT.

‘We believe that the results from these studies strongly support advancement of ARO-AAT into the clinic’, said Dr Wooddell. ‘A Phase 1 single- and multiple-ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and effect of ARO-AAT on serum alpha-1 antitrypsin levels in healthy adult volunteers started administering doses to subjects on 12 March 2018’.

‘Rare diseases are a greater challenge than you might expect, as apart from the difficulties in reaching a full diagnosis, there are often no effective treatments available’, said Prof. Marco Marzoni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. ‘For instance, the study investigating a treatment for LAL deficiency is important, as this is a disease that we only recently learned to identify’.

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## Onsite location reference

Session title: Parallel session: Clinical developments in metabolic and rare disease

Time, date and location of session: 14. April 2018, 08:30 AM - 08:45 AM, West 3

Presenter: Florian Abel, USA

Abstract: Effect of sebelipase alfa on liver parameters over 96 weeks in a diverse population of children and adults with lysosomal acid lipase deficiency (1515)

Session title: General session III and award ceremony II

Presenter: Eliane Sardh, Sweden

Abstract: A phase 1/2, randomized, placebo controlled and open label extension studies of givosiran, an investigational RNA interference (RNAi) therapeutic, in patients with acute intermittent porphyria (2456)

Session title: Parallel session: Clinical developments in metabolic and rare disease

Presenter: Christine Wooddell, USA

Abstract: ARO-AAT, a subcutaneous RNAi-based therapeutic for alpha-1 antitrypsin-related liver disease, demonstrates liver exposure-response and efficacy in preclinical studies (2636)

## Author disclosures

C. Wooddell, H. Chen, J. Griffin, R. Zhu, Q. Chu, H. Hamilton, J. Hegge, D. Christianson, Z. Li and B. Given: employed at Arrowhead Pharmaceuticals.

J. Teckman: Grant: Alnylam, Arrowhead Pharmaceuticals, Alpha-1 Foundation, Gilead;  
Consultant: Dicerna, Ionis Pharmaceuticals, Genkyotex, The Alpha-1 Project, RxCellerate, Editas, Intelia, AstraZeneca.

K. Blomenkamp: none reported.

E. Sardh and co-authors: none reported.

F. Abel and co-authors: none reported.

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**Embargoed until 15:00, Friday, 13 April 2018 (Paris/Geneva time)**

**Source: [www.who.int/hepatitis/](http://www.who.int/hepatitis/)**

## **Hepatitis C: simplified curative treatments can drive global scale-up**

13 April 2018, Paris – Access to hepatitis C curative therapy is increasing, with simplified and more affordable treatments becoming more readily available to save lives and accelerate global scale-up.

According to a WHO progress report, an estimated 1.5 million people started direct-acting antiviral (DAA) treatment in 2016, compared to around 1 million in 2015.<sup>1</sup> Behind the impressive scale-up seen in 2016, a diverse set of countries have been leading the action.

Egypt and Pakistan, two countries with the heaviest burdens of hepatitis C virus infection (HCV) in the world, accounted for half the number of people receiving HCV cure. Other countries to report progress included Australia, Brazil, China, France, Georgia, Mongolia, Morocco, Rwanda and Spain.

Despite significant progress, the overall number of people receiving HCV cure is still only around 3 million – out of a total 71 million people who require it.

"We appeal to global and national leaders to seize the incredible opportunities now available to cure all people of chronic hepatitis C and save lives," said Dr Gottfried Hirnschall, Director of the WHO Department of HIV and Global Hepatitis Programme. "Champion countries are rapidly scaling up, showing that the elimination of hepatitis C is not a pipe dream – it can and has to be done."

Major simplification of HCV treatment and its delivery to support global scale-up is now possible, according to new evidence gathered for WHO's updated treatment guidelines in development.

New, highly effective treatments, which can cure all 6 major subtypes of HCV with a success rate of over 90%, are now available.

Treatment delivery can now be simplified with the use of one-pill-a-day, fixed-dose combination drugs, which remove the need for genotyping. Previously, patients needed an expensive genotyping test before treatment, to determine which of the several different regimens could cure them.

Use of such pan-genotypic regimens can also make it easier for countries to manage procurement and supply of DAAs to accelerate scale-up efforts.

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<sup>1</sup> Progress report on access to hepatitis C treatment. WHO: March 2018 (<http://www.who.int/hepatitis/news-events/hep-c-access-report-2018/en/>)

New evidence suggests that all people aged 12 or above diagnosed with chronic HCV (with the exception of pregnant women) should be offered treatment.

"Starting curative treatment earlier in all people with hepatitis C, regardless of their disease stage, can be highly beneficial," said Dr Marc Bulterys, Team Lead for the Global Hepatitis Programme. "This means they will be cured swiftly, significantly reducing the risk of liver cancer and other diseases."

Globally, around 400 000 people die of cirrhosis and liver cancer caused by untreated HCV infections every year. Cure leads to reductions of at least 87% in liver-related deaths and 80% in the risk of liver cancer due to HCV. Cure can also reduce common comorbidities among people with HCV, such as depression, diabetes and chronic renal disease.

A vast majority--an estimated 62%--of people in need of HCV curative therapy live in low- and middle-income countries that have voluntary licenses for DAAs and therefore could procure low-cost generic medicines.

WHO is reviewing this body of evidence for simplified treatment for all people living with HCV for inclusion in its upcoming HCV treatment guidelines, to be released soon.

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**Editor's note:** WHO is organizing a [symposium, "Meeting the 2030 elimination goals of the WHO viral hepatitis strategy"](#), on 14 April 2018 at 14:00 at the International Liver Congress. The symposium will cover progress, challenges in access to HCV treatment, and new directions for the upcoming guidelines.

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