3rd Global NASH Congress 2020
Metabolic Syndrome, Diabetes & NAFLD Symposium

London UK
10-11 February 2020

#NASHCongress

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Global Engage is pleased to announce the 3rd Global NASH Congress 2020, and co-located Metabolic Syndrome, Diabetes and NAFLD Symposium which will be taking place 10-11 February 2020 at the London Heathrow Marriott.

This established meeting featuring over 60 individual talks, panels and roundtable discussions has been purposely designed to facilitate collaboration and attract attendance from the multiple communities working on NASH, NAFLD, obesity, diabetes and metabolic syndrome. It has the USP of attracting multiple stakeholders including KOL, investigators, academia, pharma, providers and regulators, whose aim is to tackle the often overlooked NASH epidemic as well as overlapping areas and develop ground breaking and impactful treatments for patients.

The meeting will focus on several key themes:

- Regulatory Updates, Commercialization and Payor Perspective
- Optimising Preclinical & Translational Strategy / Models
- Non Invasive Biomarkers and Diagnostic Tools
- New targets for the treatment of NASH/ Fibrosis / NAFLD
- Recent updates in NASH Pathogenesis
- Emerging research and treatment areas - Novel targets and pathways, GLP-1 etc
- Clinical Development & Trial results / design / optimization
- Prevention and control / Nutrition and lifestyle
- Ties between obesity, diabetes and NAFLD
- Role of liver and NAFLD in insulin resistance and metabolic syndrome
- Organ communication between diseases

We look forward to welcoming you to the event.
Novel Biomarkers and Diagnostic Tools
- Advancing biomarkers for improved diagnosis, staging, changes and prognosis
  - Review of current and potential biomarkers for each stage
- Evaluation of diagnostic tools
  - Improving diagnostic accuracy for identification and clinical outcome
  - Patient identification
  - Selection of treatment
  - Where are new biomarkers coming from?
  - Liver biopsies
- Technology Focus - Imaging and other non-invasive technologies – overview, developments and methods
  - Quantitative analysis of samples
  - Improved disease measurement, tracking and monitoring
- Regulatory Updates, Commercialization and Payor Perspective
  - EMA / FDA – Current regulatory guidance, interaction and expectations for the future
  - Regulatory pathways for approval of products
  - Harmonizing clinical development and the regulatory landscape
  - Nash submission experiences in the EU and US
  - Payor perspective – Cost of treatment; Reimbursement; How will this work? Demonstration of patient benefit
  - Overcoming commercialisation challenges

Preclinical & Translational Strategy and New targets for treatment of NASH/ Fibrosis
- Pre-clinical development of NASH targets
- Target discovery and validation - New targets for treatment of NASH/ Fibrosis
- Preclinical & translational models – Predictive value
- Model consistency
- Marrying model identification with disease stage
- Integration of clinical data to validate existing and identify novel mechanisms and targets
- Successful compounds in the clinic – How did they perform in preclinical models

Recent updates in NASH Pathogenesis
Exploring factors for advances in treatment - such as:
- Genetic susceptibility
- Metabolic syndrome
- Mitochondrial dysfunction and apoptosis
- Insulin resistance
- Gut microbiome
- Combination therapies
- Gut immune system
- Prevention and treatment – Tackling the root cause by improving awareness
- Utilizing nutrition and lifestyle factors

Clinical Development & Clinical Trial Data
- Current NASH Drug Development case studies
- Improving patient recruitment and retention for clinical trials
- Novel clinical trial design – Uniformity and harmonization of trials
- Determining clinical endpoints
- Population screening
- Identifying correct treatment for stage
- What we learned from phase 3 clinical trials in 2019

Cross event roundtable discussions – Including:
Day 1
1. Clinical Trial Design
2. Liver biopsy; the gold standard
3. Collaborative projects: academia, healthcare providers, industry
4. Determining clinical endpoints
5. Insulin resistance and hyperinsulinemia
6. Use of non-invasive tests for liver fibrosis in the management of NASH/NAFLD

Day 2
1. Regulation of Inflammation and fibrosis
2. Influence of diet and lifestyle on NAFLD/ NASH
3. NAFLD & liver transplants
4. Prevention and control – influence of nutrition and lifestyle
5. Best practices for detecting, assessing and managing suspected drug-induced liver injury signals during NASH clinical trials

Metabolic Syndrome, Diabetes and NAFLD Symposium
- Links between obesity, diabetes and NAFLD
- Role of liver, & NAFLD in insulin resistance and metabolic syndrome
- Organ communication between diseases
- Non-invasive biomarkers, technology and diagnostic tools
- Emerging research and treatment areas - Novel targets and pathways, GLP-1 etc
- Mechanisms underlying the association between NAFLD, other diseases and CVD
- Effect of anti-diabetic drugs
- Diabetes management with end stage liver disease
- Prevention and control / Nutrition and lifestyle
- Clinical & Regulatory updates & pathways in NAFLD
- Clinical development & trial results / Design / Optimization
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VP, Musculoskeletal & Metabolic Imaging, BioTel Research

SCOTT HARRIS  
Chief Medical Officer, Alimmune

SAM BLOM  
Application Manager, Aiforia Technologies

CHRIS BYRNE  
Professor Endocrinology & Metabolism, Human Development and Health Academic Unit, Faculty of Medicine, The Institute of Developmental Sciences (IDS), University of Southampton, UK
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Chief Scientific Officer, WCG – ACI Clinical

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Principal Investigator, Institute of Hepatology, UK

BREANN E ABERNATHY
PhD Candidate, University of Minnesota, USA

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Director, Pharmacology, Poxel

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Clinical and Academic Radiologist, UCL Centre for Medical Imaging

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Nutrition Biomedical Scientist Specialist, University of Southampton, UK

GAUTAM MEHTA (Chair)
Principal Investigator, Foundation for Liver Research

SANJEEV KHINDRI (Chair)
Acting Chief Medical Officer, Galecto Biotech AB

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CSO Cirius Therapeutics (Kalamazoo MI and San Diego CA, USA)

NEIL YOUNGSON (Chair)
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Research Director of Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa Italy & Professor of Medicine, UT Health Science Center San Antonio, TX, USA

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Associate Professor in clinical nutrition, Head of Clinical Research Unit, Uppsala University, Sweden

MELISSA PALMER
CEO Liver Consulting ; Former Head of Liver Disease Development, Takeda

CAREL LE ROUX
Professor of Experimental Pathology, Conway Institute, Diabetes Complications Research Centre, University College Dublin, Ireland

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Reader & Consultant in Hepatology, Barts Liver Centre, Queen Mary University of London, UK

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VENU INFORMATION

London Heathrow Marriott Hotel
Bath Road, Heathrow Airport Hayes, UB3 5AN, United Kingdom

Located less than half a mile away from the Heathrow Airport, this four-star deluxe hotel offers comfortable, noise-free accommodations and is near attractions such as Legoland and Windsor Castle. Modern and vibrant, discover the culinary delights and more in the London Heathrow Marriott.

3rd GLOBAL NASH CONGRESS 2020
Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide, and nonalcoholic steatohepatitis (NASH), its most aggressive form, can progress to fibrosis, cirrhosis, liver failure and HCC. Weight loss can lead to resolution of NASH and regression of fibrosis, but it is difficult to attain and particularly to maintain. There has been a dramatic increase in the number of compounds targeting different aspects of the pathogenesis of NASH. As of November 2019, in clinicaltrials.gov, there were 222 active studies in NASH – 19 Phase 1, 65 Phase 2 and 8 Phase 3 – either as monotherapy or in combination.
ANDREW BILLIN
Director Biomarker Sciences, Gilead Sciences

Utility of currently available non-invasive tests (NITs) for disease staging and prognosis in patients with NASH

- NITs are a critical tool for evaluating patients and for enrolling clinical trials. The talk will discuss:
  - NITs as useful tools to identify patients with advanced fibrosis due to NASH
  - Prognostic value of NITs and histology
  - Utility of NITs for monitoring treatment response

HENNING GRØNBÆK
Professor, Department Hepatology & Gastroenterology, Aarhus University Hospital

From single to multiomic blood biomarkers for diagnosis and staging of non-alcoholic fatty liver disease

- Non-alcoholic fatty liver disease (NAFLD), has been recognized as a clinical challenge for more than 20 years. However, there is still an unmet need for better biomarkers for diagnosis of NAFLD severity and treatment response.
- Due to the complexity of NASH pathogenesis, it is unlikely that a single biomarker will suffice to diagnose NASH with inflammation and fibrosis.
- The evidence of diagnostic blood biomarkers from single markers, clinical scores to multomics for diagnosis of NAFLD liver disease severity will be presented.

PATRICK VRILLANDT
Senior Clinical Assessor, Dutch Medicines Evaluation Board (CBG-MEB), The Netherlands

NASH is a cardiovascular disease

The primary endpoint for clinical trials in NASH is a matter of debate. Because hard clinical endpoints (like liver transplantation) occur only after many years, surrogate endpoints have been suggested instead. This talk will emphasize the importance of cardiovascular endpoints like Major Adverse Cardiovascular Events (MACE): cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke. From a regulatory perspective, it will not be acceptable to ignore MACE endpoints or consider these missing data. From a methodological point of view, MACE should probably be a component of the primary endpoint. In the trial, prevention of MACE should be optimized.

ELI GAJRAJ
Principal Technical Adviser, NICE Scientific Advice

HTA perspective on evidence generation

The talk will briefly touch upon NICE’s purpose, methods and decision-making. The talk will focus on the design of clinical trials and outcome measures to generate evidence that will facilitate a NICE appraisal. This will include patient-relevant outcomes, health-related quality of life measures and long-term outcomes. A HTA perspective on issues relating to the development of diagnostics and the use of surrogate outcomes in trials will be outlines

CLAUD KREMOSER
Chief Executive Officer, Phenex AG

NASH is more than just steatosis: LXR inverse agonist PX665 inhibits liver DNL but shows potent insulin sensitizing and beta cell preserving and antifibrotic effects in relevant rodent models.

LXR (Liver X Receptor) is the master regulator of de novo lipogenesis (DNL) in the liver and of triglyceride (TG) resynthesis in the intestine. Inhibiting the LXR pathway through the potent synthetic LXR inverse agonist PX665 reduces DNL in the liver but also intestinal lipid absorption resulting in potent plasma TG and liver fat lowering. Moreover, inhibiting LXR seems to have specific effects on the production and excretion of lipotoxic lipid mediators. Reducing such lipotoxic lipid species has substantial effects on beta cell preservation in islets as well as on improving overall insulin sensitivity, specifically in oxidative skeletal muscle. Thus, the LXR inverse agonist PX665 seems to be an ideal candidate for the treatment of NASH by not only ameliorating the metabolic situation in the liver but by improving the hallmarks of metabolic syndrome and type 2 diabetes systemically.

AMALIA GASTALDELLI
Research Director of Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Pisa Italy &Professor of Medicine, UT Health Science Center San Antonio, TX, USA

Pancreas liver cross talk in diabetes and NAFLD

NAFLD is a major risk factor for type 2 diabetes (T2D) due to the impairment of many metabolic pathways, including decreased hepatic insulin sensitivity and insulin secretion. Conversely, patients with T2D have a higher prevalence of steatohepatitis, liver fibrosis and end-stage liver disease. The two major hormones secreted by the pancreas, i.e., insulin and glucagon, have a major effect on hepatic glucose and lipid metabolism. Moreover, the liver clears the majority of insulin secreted by the pancreas, thus modulating peripheral insulin concentrations. The talk will focus on the cross talk between pancreas and liver and its impact on NAFLD and related risk of T2D.
**HANNES HAGSTRÖM**  
Associate Professor, Consultant in Hepatology,  
Unit of Hepatology, Karolinska University Hospital, Sweden  
**Identifying patients with risk of adverse outcomes – where should we look more closely?**  
Progression of fibrosis is slow in NAFLD, and only a minority of patients develop clinically significant liver disease. The talk will focus on how to identify those with the highest risk of fibrosis progression, development of cirrhosis and liver-related death.

**TONI VIDAL-PUIG**  
Professor of Molecular Nutrition and Metabolism,  
University of Cambridge; Associate Director MRC Metabolic Disease Unit; Honorary Consultant in Metabolic Medicine Addenbrooke’s Hospital;  
Scientific Director Cambridge Phenomics Centre; Associate Faculty Sanger Institute  
**Adipose tissue expandability, lipotoxicity and fatty liver**  
Our main hypothesis is that the link between obesity and metabolic complications such as NAFLD is the ectopic accumulation of lipids. Based on this the intellectual framework of our approaches include strategies to improve adipose tissue storage capacity, promote energy dissipation and modulation of lipid networks to prevent toxic lipid formation. More specifically we will focus on the early stages of NAFLD and the transition to NASH. Also I will provide information about current efforts to identify preclinical models to study NAFLD/NASH suitable for translation.

**CAREL LE ROUX**  
Professor of Experimental Pathology, Conway Institute, Diabetes Complications Research Centre, University College Dublin, Ireland  
**How the gut talks to the brain to impact the liver**  
- Obesity is a disease of the subcortical areas of the brain.  
- The best way to reduce the symptoms of obesity is to enhance satiety signals from the gut to the brain.  
- At least 10% weight loss is required to impact complications of obesity such as NAFLD and NASH.

**DANIEL SIKKEMA**  
Vice President, Quanterix  
**Metabolic changes and biomarkers preceding and associated with NASH**  
- Proglucagon peptides, Diabetes type 2  
- Obesity and inflammation  
- Technologies to non-invasively measure biomarkers in an ultrasensitive manner

**KANITA SALIC**  
Scientist, Study Director  
Preclinical, Metabolic Health Research, TNO, The Netherlands  
**Preclinical translational strategies in models of NAFLD/NASH and fibrosis**  
Translational strategies often focus on histology and often models are used in which disease inducers are not translational. In this talk the relevance of a broader preclinical translational strategy, including human diet-based disease inducers and molecular profiling analyses to study the overlap of molecular disease signatures between NASH patients and preclinical disease models will be presented. Several examples will be given using, among others, Ldlr-/-.Leiden mice in which NASH and fibrosis can be induced without cholesterol supplementation. The mice show features of human pathology on histological and biochemical level and recapitulate molecular transcriptomics and metabolomics signatures of NASH patients. Intriguingly, the models presented allow the study of organ cross talk along the gut-brain axis and development of cardiovascular disease in NASH.

**JONATHAN RIEK**  
VP, Musculoskeletal & Metabolic Imaging, BioTel Research  
**Practical considerations for imaging in NASH**  
There are many ways to look at imaging for NASH. One of the current trends is to try to replace the biopsy with noninvasive techniques to replicate the histopathological measurements. Proton-density fat fraction (PDFF) is an MRI technique that quantifies the percent of visible hydrogen protons in the liver that come from fat. This has been demonstrated to be both accurate and precise. Magnetic Resonance Elastography (MRE) can measure the stiffness of liver tissue with good reproducibility as well. Iron-corrected T1 may also be a useful measurement, but has several limitations. The question this talk hopes to answer is how to integrate these imaging techniques into a NASH clinical trial, and what are the limitations of each.
With the increasing prevalence of NAFLD worldwide, there is an urgent clinical need for reliable methods to diagnose and stage liver pathology. Liver biopsy, the current gold standard, is invasive and limited by sampling and observer dependent variability. Magnetic resonance protocols for liver tissue characterisation have been developed and evaluated in a variety of clinical settings. Multiparametric MRI has shown excellent diagnostic performance against liver biopsy for the staging of liver fibrosis and quantification of fat and iron, and good prognostic performance for the prediction of adverse clinical outcomes. Furthermore, MR based techniques show promise as tools for monitoring the effects of therapy picking up early improvements. Lastly, MRI techniques have shown superior reproducibility compared to alternatives and have been used to study liver fat and liver iron in population level studies. Collectively, the emerging evidence suggests that liver multiparametric MR techniques can be powerful tools for the assessment of patients with NAFLD, as they allow for the quantification of multiple parameters and can be applied in a variety of contexts of use.

**Biomarkers in Non-Alcoholic Fatty Liver Diseases**

- Use of imaging biomarkers to stratify patients with NAFLD
- Novel methods in MRI
- Application of metabolic imaging in NAFLD

**Integration of NAFLD Screening into secondary and tertiary care**

- NAFLD screening is currently not recommended in the general population, though 20-30% are affected
- NAFLD diagnostic algorithms include non-invasive scores and elastometry as primary and advanced tools
- Automated screening tools in primary care as well as platforms for secondary NAFLD diagnostics are urgently needed

**Current and future landscape of clinical and regulatory pathways in NAFLD**

- NAFLD screening is not recommended for the general population, but can it be justified for T2DM and/or obesity?
- What screening tools can be effectively utilized for these populations and how should they be applied?
Recent evidences have highlighted the role of microRNAs as novel biomarkers and diagnostic tools. miRNAs as novel biomarkers and diagnostic tools

Recent evidences have highlighted the role of microRNAs as key molecular triggers of NAFLD, by participating in the development of adipose tissue dysfunction and insulin resistance, up to their pathological role on the different liver cell types, during disease progression. Several current basic and clinical investigations have pinpointed the capacity of miRNAs to act as accurate non-invasive diagnostic and prognostic biomarkers for NAFLD, particularly those circulating within extracellular vesicles, as an alternative to the limitations posed by liver biopsy-based findings. Finally, different molecules targeting key miRNAs participating in NAFLD pathogenesis have shown promise in preclinical development, inspiring new efforts in achieving its safe, successful translation into the clinic.

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions, thus becoming one of the leading causes of chronic liver disease worldwide. Liver biopsy remains the gold standard to stage NAFLD and to monitor response to various pharmacological treatments of NAFLD. However, liver biopsy has some limitations, and is not preferred by patients due to its invasiveness. Currently, there are no acceptable sensitive or specific non-invasive surrogates of liver biopsy for monitoring pharmacological treatments of NAFLD. However, recent studies have shown that the metabolism of 13C-liver metabolic probes within the hepatic mitochondria have good correlation with both histological stages and markers of liver inflammation and fibrosis. Thus, the use of these metabolic probes could be promising non-invasive surrogates of liver biopsy in patients with NAFLD.
CONGRESS SCHEDULE

DAY 1 MONDAY 10TH FEBRUARY 2020

BEVIN GANGADHARAN
Research Associate, Oxford University
**Novel serum biomarkers for NAFLD Identified using proteomics**
Several biomarkers identified using proteomics which successfully track disease progression including ones which can discriminate healthy individuals from NAFLD, NAFL from NASH and the stages of lobular inflammation. We have developed the first antibody-free serum protein biomarker assay and are currently looking into developing a rapid point-of-care test (POCT) which would work with a single drop of finger pricked capillary blood. We are the first to publish a novel method which uses a universal calibration mix which can be used for any protein biomarker and up to six different biomarkers in a single acquisition. We are the only group who have been successful in using this novel method which has the potential to improve biomarker detection and quantitation in the clinic.

DEVANAND SARKAR
Professor, Virginia Commonwealth University, USA
**RNAi strategy for the treatment of NASH: focus on astrocyte elevated Gene-1 (AEG-1)**
AEG-1 is overexpressed in NASH patients. A hepatocyte-specific AEG-1 transgenic mouse develops spontaneous NASH and a hepatocyte-specific conditional AEG-1 knockout mouse shows resistance to high fat diet (HFD)-induced NASH.
- AEG-1 induces NASH by inhibiting PPARα, thus fatty acid β-oxidation, by increasing translation of fatty acid synthesizing enzymes, and by activating NF-κB, a master regulator of pro-inflammatory cytokines.
- Treatment with hepatocyte-targeted nanoparticles delivering AEG-1 siRNA prevented development of NASH in mice fed HFD.

ANJA GEERTS
Professor, Department of Gastroenterology and Hepatology, University of Ghent, Belgium
**The pitfalls of bariatric surgery in NAFLD patients**
Bariatric surgery is often presented as a therapy for NAFLD. However, the risk of alcohol addiction is a major problem in this population. Development of rapid progressive liver failure is the danger that we will be increasingly confronted with.

SVEN FRANCQUE
Chairman, Division of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium
**The adipose tissue-liver axis in NAFLD: implications for therapy**
Adipose tissue dysfunction and inflammation is considered an important aetiological factor in the pathogenesis of NAFLD. Not only substrates released or insufficiently buffered by the adipose tissue, but also adipokines, inflammatory cytokines and immune cells originating from the adipose tissue impact on the liver. Hepatokines exert reciprocal influences. The adipose tissue-liver crosstalk is not only important in understanding NAFLD pathophysiology, but also in understanding the extra-hepatic consequences associated with NAFLD. This concept is also relevant in the treatment of NAFLD, which requires a systemic approach. Several drugs that impact on adiposity or adipocyte function, such as glucagon-like peptide 1 receptor agonists or peroxisome proliferator-activated receptor gamma agonists used for the treatment of obesity and/or diabetes, could therefore also be considered for the treatment of NAFLD. Liraglutide and pioglitazone have already been tested in that context. Interestingly, several of the new drugs in the pipeline for NAFLD build further on this concept and hold promise. The presentation will summarize current data on the adipose tissue-liver axis in NAFLD and discuss its potential therapeutic relevance.

18:25-18:25 Chair’s Closing Remarks / End of Day One
18:25-19:25 Networking Drinks Reception
**TABLE 1: Clinical Trial Design**

**SVEN FRANCQUE**  
Chairman, Division of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium

Although a lot of progress has been made in defining target population as well as efficacy endpoints, several issues remain debated. Liver biopsy is still the gold standard and a prerequisite in Phase 3. The role of non-invasive tools in patient selection and treatment response is increasing, but their exact value needs further validation, especially in how to define treatment response. The relation of non-invasive as well as histological endpoints with ultimate clinical outcomes also still needs to be established. How cardiovascular disease can be integrated in clinical trials remains unclear. Life style modification and treatment of co-morbidities might impact on disease natural history and influence trial results, but their standardisation in trials is challenging. All these aspects will be discussed.

**TABLE 2: Liver biopsy; the gold standard**

**ANDREW FOWELL**  
Consultant Hepatologist, Queen Alexandra Hospital

- Liver biopsy; still the ‘gold standard’?
- What are the best non-invasive alternatives for diagnosing NASH and related fibrosis?
- Monitoring fibrosis progression and regression in NAFLD.

**TABLE 3: Regulation of Inflammation and fibrosis**

**VINOOD PATEL**  
Reader, University of Westminster, UK

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver disease worldwide and is also an emerging risk factor for liver cirrhosis leading to hepatocellular carcinoma. NAFLD is also a metabolic condition that etiologically parallels with obesity, type 2 diabetes, and the metabolic syndrome, however the precise mechanisms leading to disease progression are still evolving. There are several classical key events occurring during the overlapping transition from NAFL to NASH which include, lipotoxicity, mitochondrial dysfunction, oxidative stress and toll-like receptor signalling. More recently other factors also play a pivotal trigger in the progression of NAFLD including, hepatic innate immune response; dysregulated microbiota and the role of bile acids; genetic variants (PNPLA3); dietary factors (high fructose/omega 6 fatty acids). Many of these pathways also act as initiators for hepatic stellate cell activation leading to fibrosis, indicating the complexity of identifying a single treatment for fibrosis prevention/reversal.

**TABLE 4: Insulin resistance and hyperinsulinemia**

**AMALIA GASTALDELLI**  
Head of Cardiometabolic Risk Lab, Italian National Research Council, Italy

**JERRY COLCA**  
CSO, Cirius Therapeutics

Patients with NAFLD/NASH (with or without type 2 diabetes) are at high risk for adverse cardiometabolic issues. One of the predisposing factors may hyperinsulinemia that results from increased insulin secretion in response to insulin resistance and inappropriately reduced hepatic clearance of insulin. We propose to discuss the following topics:
- What is the impact of increased insulin resistance and dysfunctional insulin secretion on NAFLD?
- What are the ways that insulin secretion and clearance can be measured in the clinical setting?
- What is the evidence of reduced hepatic clearance of insulin in NAFLD/NASH subjects with and without diabetes?
- What are the implications of reduced insulin clearance on hepatic metabolism?
- What are the implications of this pathophysiology to drug development?

**TABLE 5: Use of non-invasive tests for liver fibrosis in the management of NASH/NAFLD**

**WILLIAM ROSENBERG**  
Peter Scheuer Chair in Liver Diseases, Deputy Director, UCL Institute for Liver and Digestive Health
KEYNOTE ADDRESS: LIAT HAYARDENY
Chief Scientific Officer, Galmed Pharmaceutical Ltd
Aramchol, a stearoyl CoA desaturase modulator, from scientific rationale to clinical phase 3 (ARMOR)
Aramchol (arachidyl amido cholanic acid) is an orally active, liver target, fatty acid-bile acid conjugate, that reduces liver fat content in NAFLD patients. In a one-year Phase 2b study, Aramchol reduced liver fat, promoted NASH resolution and improved liver biochemistries and fibrosis, of interest was also the reduction in HbA1c. Aramchol exerts its effects in a dose response manner where 600mg was better than 400mg and placebo in all clinical end points. Aramchol has an excellent safety and tolerability profiles. Aramchol is presently being evaluated in Phase 3 study for NASH. The mechanism by which Aramchol exerts its clinical activity is down regulation of SCD1. SCD 1, a key enzyme, catalyzes the rate limiting step in the biosynthesis of monounsaturated fatty acid, involves in triglyceride biosynthesis whose loss enhances fatty acid β-oxidation. Down regulation of SCD1 also targets the proliferation and collagen production from hepatic stellate cells and directly affect fibrosis.

NIKOLAI NAOUMOV
Executive Director, Hepatology Science and Innovation, Novartis, Switzerland
Progress in developing combination therapies – Novartis’ approach
• 2019 is an important milestone in NASH drug development with results and learnings from the first Phase 3 trials and several large Phase 2 trials becoming available.
• Recognizing the complex pathophysiology of NASH and patients’ heterogeneity, Novartis’ approach has been focused on developing Tropifexor - a highly potent, multi-modal, non-steroid FXR agonist - as monotherapy, as well as a therapy-backbone of several combinations, with both internal compounds and through inter-company collaborations to optimally serve the spectrum of NASH patients.

SVEN FRANCQUE
Chairman, Division of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium
NAFLD as a risk factor for cardiovascular disease
The primary cause of death in patients with NAFLD is cardiovascular disease (CVD) and NAFLD patients seem to be at increased risk compared to a matched control population, pointing towards an independent contribution of NAFLD to the development of cardiovascular morbidity and mortality. The close intertanglement of NAFLD and the metabolic syndrome make it difficult to compile hard clinical evidence to substantiate the latter statement, although a lot of clinical data are supportive and many pre-clinical and clinical data give insight into the potential mechanistics underlying the association between NAFLD and CVD. With the emerging treatments for NAFLD, some of which also impact on metabolic factors that also impact CVD, the issue becomes particularly relevant, as NAFLD pharmacotherapy must not only be safe, but some might have a beneficial effect on CVD outcomes, which might represent an additional benefit beyond the hepatological endpoints and play a role in their indication and positioning. The presentation will summarize the current knowledge and its potential implications for the overall clinical care of patients with NAFLD.
the cardiovascular space that can also be applied to the hepatic endpoint. This presentation will discuss adjudication rationale and history, current best practices, and examples.

...our targeted messaging and outreach campaigns. Qualified subjects are referred to our global site network for trial enrollment. Our Dedicated Research Sites (DRSs) have the capacity and resource to achieve high volume pre-screening. Combining fibroscan and blood tests AES can successfully identify those patients most likely to have NASH thereby accelerating recruitment to NASH trials.

...NAFLD real world cohort: Experience from Germany

Real life cohorts may help to better understand the natural history of NAFLD and to identify individuals who may benefit from future therapies. Here we present the first data from a German NAFLD real world cohort and discuss how follow up data can be used to capture clinical end points and pharmacovigilance.

...Anti-inflammatory/anti-fibrotic mechanisms for the treatment of NASH

...Brief overview of anti-inflammatory/antifibrotic MOA for the treatment of NASH
...Clinical vs preclinical data
...Are preclinical models predictive at all for these MOA?

...the role of lysosomal acid lipase activity in NAFLD/NASH pathogenesis

NASH pathogenesis is multifactorial and not completely clear. Lysosomal acid lipase (LAL) is an enzyme that hydrolyzes triglycerides and cholesterol esters in several cells including...
hepatocytes, Kupffer cells, bone marrow-derived monocyte-macrophages and platelets. Recent data suggest that transcriptional or post-transcriptional reductions of LAL activity in blood have relevance for the pathogenesis of NASH.
Continued

haptic steatosis. Bisphenol A (BPA) is a weak estrogen and reproductive, developmental, and systemic toxicant in animals that is present in polycarbonate plastics. Concerns for BPA exposure are centered around endocrine disruption and early in life exposure. Our studies indicate that developmental BPA exposure induced hepatic steatosis in mice in adulthood, which was associated with alterations in gene expression. A second example is Per and polyfluoroalkyl substances (PFASs), which are a group of man-made chemicals that can be found in food packaging, stain repellent fabrics, and non-stick products. PFOS, PFOA, PFNA, and PFHxS are known to have multiple adverse liver effects in rodents and have been detected in human liver biopsy samples. Our presentation will summarize the findings of several studies we have conducted with various diet combinations and human hepatocyte models to understand the lipogenic potential of PFASs for human liver.

**HAROLD H. SHLEVIN**
President and Chief Executive Officer, Galactin Therapeutics Inc.
**Clinical development of belapectin (GR-MD-02), a galectin-3 inhibitor, in treatment of NASH cirrhosis**
Galectin-3 inhibition has been shown to be central to the fibrotic process. NASH related cirrhosis represents an area of high unmet medical need and is rapidly becoming the number one reason for liver transplants. Belapectin (GR-MD-02), a galectin-3 inhibitor, has been demonstrated to decrease hepatic venous pressure gradient in compensated NASH cirrhotic patients without varices at baseline. We will discuss how results of our Phase 2 study have helped to inform the design of a phase 3 trial.

**HUBERT CHEN**
Chief Medical Officer, Metacrine
**Sustained FXR agonist as optimized, best-in-class treatment for NASH**
Activating farnesoid X receptor (FXR) has been clinically validated to improve non-alcoholic steatohepatitis (NASH) and fibrosis, although common drawbacks include increased low-density lipoprotein cholesterol (LDL-C) and moderate/severe pruritus within the therapeutic dose range. Recently, transient non-bile acid FXR agonists have shown limited efficacy with once-daily dosing, likely due to suboptimal target engagement. Sustained FXR agonist with a novel non-bile acid structure and enhanced potency, such as new target for NASH drug development

**MICHAEL FUCHS**
Professor of Medicine, Virginia Commonwealth University and Chief of Hepatology & Liver Transplantation, McGuire VA Medical Center, USA
**Novel serum biomarkers mirroring the transition from steatosis to steatohepatitis**
- Linking oxysterols to insulin resistance and inflammasome activation
- Identification of new NASH serum biomarkers and Cyp7b1 as new target for NASH drug development

**MELISSA PALMER**
CEO Liver Consulting; Former Head of Liver Disease Development, Takeda
**Best practices for detecting, assessing and managing suspected drug-induced liver injury signals during NASH clinical trials**
- The last decade has seen a rapid growth in the number of clinical trials enrolling patients with NAFLD and NASH. Patients with NASH often require different approaches to the assessment and management of suspected drug induced liver injury (DILI) compared to patients with healthy livers.
- Currently no regulatory guidelines or position papers

**RUI CASTRO**
Assistant Professor, Department of Biochemistry and Human Biology, Faculty of Pharmacy, University of Lisbon, Portugal
**Inter-organ crosstalk in NAFLD**
NAFLD highly associates with components of the metabolic syndrome, such as obesity and type II diabetes, two of the best characterized NAFLD risk factors. In fact, NAFLD is a complex and multifactorial disease, and its pathogenesis also involves the adipose tissue, skeletal muscle and gut, in a bilateral crosstalk. As such, NAFLD triggering and progression remains incompletely understood, particularly regarding the signaling mechanisms responsible for disruption of extra-hepatic homeostasis.

**CHRIS BYRNE**
Professor Endocrinology & Metabolism, Human Development and Health Academic Unit, Faculty of Medicine, The Institute of Developmental Sciences (IDS), University of Southampton, UK
**Diabetes and NAFLD: a vicious spiral affecting both diseases**
- Risk of diabetes with NAFLD
- Worsening insulin resistance and glycaemic control with NAFLD affecting diabetes treatments
- Diabetes management with end stage liver disease.

**MICHAEL FUCHS**
Professor of Medicine, Virginia Commonwealth University and Chief of Hepatology & Liver Transplantation, McGuire VA Medical Center, USA
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as Metacrine’s MET409, has demonstrated prolonged FXR engagement and an encouraging safety and tolerability profile— including a lack of adverse impact on LDL-C levels — in early clinical trials. These results demonstrate the potential of sustained FXR agonism to deliver a differentiated, best-in-class profile.

...systematically address best practices pertaining to DILI in NASH clinical trials.

- Recommended best practices pertaining to hepatic inclusion and exclusion criteria, monitoring of liver tests, DILI detection, approach to a suspected DILI signal, causality assessment and hepatic discontinuation rules will be discussed.

As such, researchers should focus on particular aspects of the disease and, accordingly, choose the most appropriate model. Still, and to concur with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) criteria, minimum requirements for models of NASH should be set. But which are these requirements? Should the focus be put solely on the liver? How does the translational value of genetic and dietary animal models compare? Could it be advantageous to use more than one model? These are some of the aspects that will be discussed.

**TABLE 3: NAFLD & Liver Transplantation**

MICHAEL FUCHS
Professor of Medicine, Virginia Commonwealth University and Chief of Hepatology & Liver Transplantation, McGuire VA Medical Center, USA

Nonalcoholic steatohepatitis (NASH) is the fastest-growing indication for liver transplantation and a leading cause of hepatocellular carcinoma among patients listed for liver transplantation in the United States. NASH poses a significant challenge in both pre- and post-transplant period due to its association with metabolic syndrome as well as cardiovascular and chronic kidney disease. In the absence of FDA-approved pharmacotherapy, life-style interventions and optimizing of risk factors remains the mainstay of therapy. Some of the many challenges in the field include:

**Pre-Transplant:**
- What is the optimal strategy to assess cardiovascular risk?
- Should treatment of risk factors for NASH be different in patients on the transplant wait list?

**Post-transplant:**
- What is a reasonable strategy to identify NASH recurrence or de novo NASH?
- What is the role of immunosuppressive drugs in post-transplant NASH?
- What is the optimal strategy to address weight gain?
- Are FDA-approved drugs for NASH in the pre-transplant setting also suitable after transplant?
- Should a different regulatory pathway for NASH drugs apply in the post-transplant setting?

**TABLE 4: Influence of diet and lifestyle on NAFLD/NASH**

JOANNA DOWMAN
Consultant Hepatologist, Queen Alexandra Hospital, UK

- Optimal dietary recommendations for patients with NASH
- What are the hepatic and extra-hepatic benefits of physical activity in NASH, and what exercise should we recommend?
- Barriers to lifestyle modification from both the HCP and patient perspective, and how can we enhance patient motivation and engagement?
- In the approaching era of licensed drug therapies for NASH, how can medication be promoted as complimentary to, rather than a replacement for, lifestyle modification?

**TABLE 5: Best practices for detecting, assessing and managing suspected drug-induced liver injury signals during NASH clinical trials**

MELISSA PALMER
CEO Liver Consulting ; Former Head of Liver Disease Development, TakedaContinued

The last decade has seen a rapid growth in the number of clinical trials evaluating novel molecules with a variety of mechanisms of action targeted to treat NASH. Due to the underlying chronic liver disease, patients with NASH require different approaches to the assessment and management of the new onset of elevated liver-related blood tests and suspected drug-induced liver injury (DILI) compared to patients with healthy livers. Topics for discussion will include:

- Are patients with NASH at increased risk for DILI?
- Hepatic eligibility criteria
- Monitoring if liver tests during NASH clinical trials
- Assessment of DILI risk during NASH drug development
- Hepatic discontinuation rules
- Monitoring and assessment of DILI during clinical trials of compensated and decompensated cirrhotic patients with NASH
- Seladelpar histology results– What does this mean for NASH clinical development?
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