



Best of ILC 2019

Metabolism, alcohol
and toxicity

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1. NAFLD: Clinical aspects except therapy

LB-01	Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension
GS-08	The prevalence of non-alcoholic fatty liver disease in young adults: An impending public health crisis?
PS-061	NAFLD/NASH patients with AdvLD have high comorbidity burden, HCRU and costs: results from Italian administrative databases
PS-203	Dietary risk factors for non-alcoholic fatty liver disease by cirrhosis status: The US multiethnic cohort
LBP-01	In NAFLD, alcohol drinking habits and genetics predict progression to advanced liver disease: Follow-up of population surveys

[Click here to skip to this section](#)

2. NAFLD: Therapy

GS-01	Efficacy, safety, and tolerability of lubiprostone for non-alcoholic fatty liver disease: The LUBIPRONE phase 2 study
GS-06	Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH
PS-105	Significant regression in fibrosis in paired liver biopsies following a 12-week aerobic exercise intervention in individuals with NAFLD
PS-112	Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes

[Click here to skip to this section](#)



3. NAFLD: Preclinical

PS-002	Persistence of hepatic and adipose tissue alterations in Th17, Treg and CD8+ cytotoxic T cells despite diet reversal in a mouse model of NAFLD
PS-129	The glucocorticoid antagonist ST-001 prevents fibrosis development and improves aspects of metabolic syndrome in the DIAMOND™ mouse model

[Click here to skip to this section](#)

4. Alcohol-related liver disease

GS-11	Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis
PS-171	Long-term survival in a 10-year prospective cohort of heavy drinkers: Liver stiffness is the best long-term prognostic parameter
PS-174	Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis

[Click here to skip to this section](#)

1. NAFLD: Clinical aspects except therapy

Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension



BACKGROUND & AIMS

- Severe PH is a key driver of decompensation and worse clinical outcomes
 - Lowering HVPG associated with clinical benefit
- **Aim:** To establish if emricasan reduces HVPG in cirrhosis patients with HVPG ≥ 12 mmHg (open-label study)

METHODS

- Patients with NASH cirrhosis and BL HVPG ≥ 12 mmHg randomized 1:1:1:1 to emricasan 5, 25, 50 mg or placebo orally twice daily for 48 wks
 - Primary endpoint: 1 follow-up HVPG at Wk 24
 - All HVPG tracings evaluated by central reader

RESULTS

- 263 subjects randomized (59 US/EU sites)
 - 13 discontinued prior to Wk 24
 - 7 had no/unevaluable Wk 24 HVPG
- Treatment groups were generally balanced

Population characteristics	%	Population characteristics	Mean (SD)
Sex, female	57	Age, years	60.8 (8.8)
Race, Caucasian	91	BMI, kg/m ²	35.3 (6.9)
Type 2 diabetes	84	MELD	9.0 (2.5)
Compensated	76	HVPG, mmHg	17.0 (3.6)
Early decompensated	24		

Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension



RESULTS (Cont.)

- HVPG was reduced in subsets of patients (*Table*)*
- TEAEs: 81.6% combined emricasan vs. 82.1% pbo
- SAEs: 17.9% emricasan vs. 11.9% pbo
- No imbalance in routine labs, vitals, ECGs

Least squares mean change [†] from baseline at Wk 24	Emricasan 5 mg N=65	Emricasan 25 mg N=65	Emricasan 50 mg N=66	Placebo N=67
HVPG (overall)	-0.6; p=0.96	-0.8; p=0.79	-1.0; p=0.65	-0.4
HVPG (compensated)	-0.8; p=0.10	-0.9; p=0.09	-0.5; p=0.27	+0.2
HVPG (compensated HVPG ≥16 mmHg) [‡]	-1.6; p=0.01	-1.7; p<0.01	-1.5; p=0.02	+0.5
Caspase 3/7	-4%; p=0.90	-31%; p<0.01	-37%; p<0.01	-4%
cCK18	-27%; p<0.01	-32%; p<0.01	-34%; p<0.01	-13%
ALT	-8; p<0.01	-8; p<0.01	-6; p=0.02	-3
AST	-6; p<0.01	-7; p<0.01	-3; p=0.18	-1

CONCLUSIONS Primary endpoint was not met. Data suggest that emricasan for 24 wks reduced portal pressure in compensated NASH cirrhosis patients with severe PH (especially higher BL HVPG). Decreases in transaminases suggest an intrahepatic effect with reduction of liver injury. Clinical outcomes and full safety data will be evaluated after the 48-wk study

*p-values (descriptive) for difference in least squares mean vs. placebo;

[†]Adjusting for baseline value, cirrhosis status, and/or NSBB use (multiple imputation for overall, observed case for rest);

[‡]Post-hoc.

The prevalence of non-alcoholic fatty liver disease in young adults: An impending public health crisis?



BACKGROUND & AIMS

- NAFLD has an estimated 20–25% worldwide prevalence
- A previous cross-sectional analysis¹ of the ALSPAC cohort in late teens (mean age 17.9 years) identified a NAFLD prevalence of 2.5% by ultrasound criteria
- This study aimed to identify the prevalence of NAFLD in this cohort, now young adults, using TE to measure fibrosis and steatosis with CAP

METHODS

- 4,021 participants had TE (FibroScan Echosens 502 Touch[®])
 - Exclusions: alcohol use disorder or excessive daily alcohol intake
 - Results with IQR/M >30% were excluded from fibrosis analysis, but not CAP
- Data were collated on Metavir F score, steatosis grade, BMI, and serology, including ALT, AST, and GGT
- Statistical analysis was performed using Stata MP 15.1

RESULTS

- Mean age was 24 years (± 0.8)
- 3,128 TE scans were eligible for fibrosis analysis
 - 76 (2.4%) had fibrosis; 8 (0.3%) had F4 fibrosis
 - ALT, AST, and GGT all associated with rising F score*

*ALT $p=0.0013$; AST $p<0.001$; GGT $p<0.001$.

1. Lawlor D, et al. J Clin Endocrinol Metab 2014;99:E410–E417.

Abeysekera K, et al. ILC 2019; GS-08

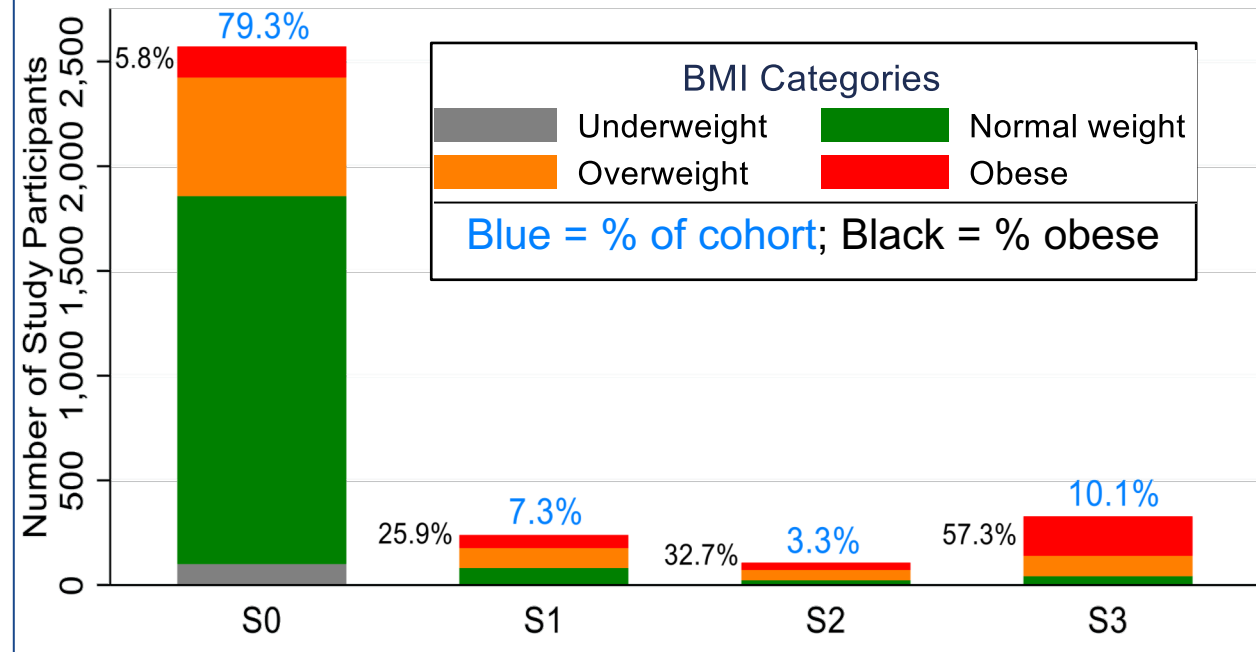
The prevalence of non-alcoholic fatty liver disease in young adults: An impending public health crisis?



RESULTS (Cont.)

- 3,277 eligible for steatosis analysis (*Figure*)
 - ALT, AST, and GGT all rose with CAP score*
- CAP score positively associated with F score*
- Cholesterol, triglyceride, and low-density lipoprotein levels rose with increasing steatosis grade* whilst high-density lipoprotein levels fell*
- BMI rose with rising F score and CAP score*

FIGURE Distribution of BMI categories across steatosis grade (derived by CAP measurement)



CONCLUSIONS This is the largest study to date to analyze fibrosis and steatosis in young adults with suspected NAFLD using TE. 1 in 5 had steatosis and 1 in 40 had fibrosis at 24 years, an increase on the previous estimate within the same cohort 6 years prior. These results suggest greater public health awareness of NAFLD is needed in young adults in the UK



BACKGROUND & AIMS

- NASH may progress to fibrosis, leading to AdvLD and further complications such as cirrhosis, LT and HCC, and is associated with a high rate of mortality
- **Aim:** Characterize epidemiology, demographics, comorbidity burden, HCRU, and costs among hospitalized NASH patients in Italian LHUs

METHODS

- Retrospective longitudinal cohort study using anonymized claims data from >9 million health-assisted patients
 - Inclusions: adult patients with ICD-9-CM hospitalization discharge codes for NAFLD/NASH between 01/2011–12/2017
 - Similar method to capture NAFLD/NASH-associated CC, DCC, LTx, or HCC index date
 - Exclusions: any defined liver disease

RESULTS

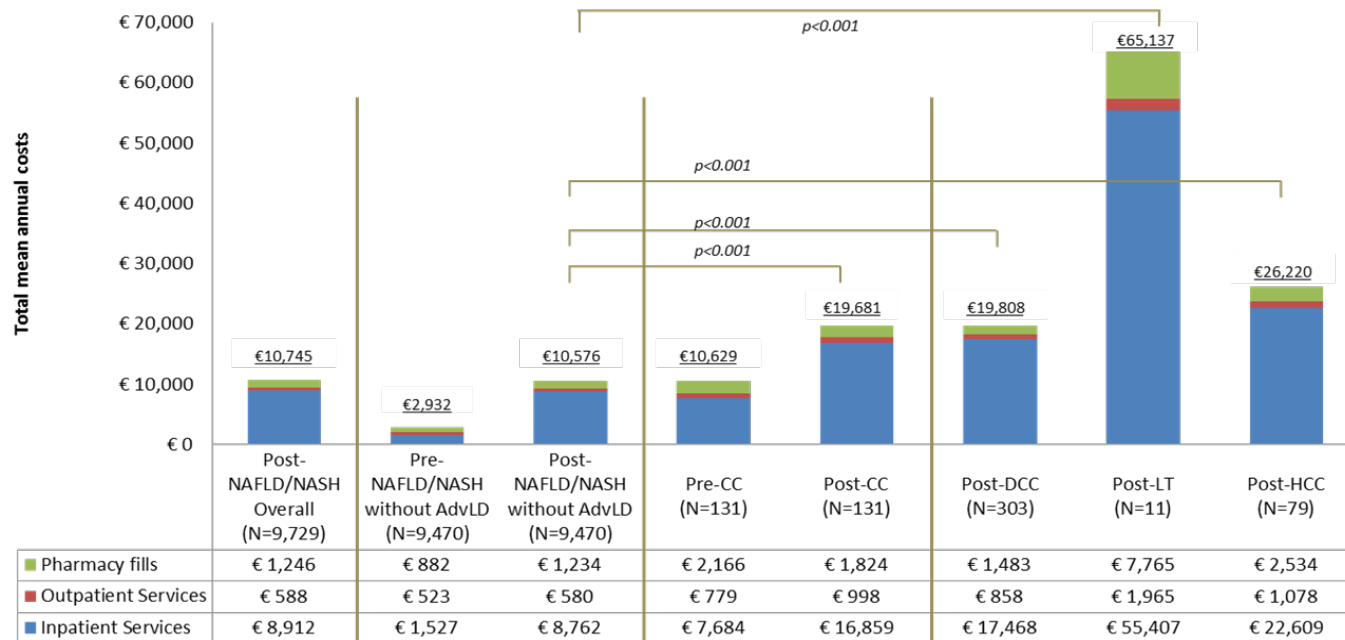
- N=9,729 with NAFLD/NASH (mean age 62 years)
 - 97% had no AdvLD, 1.3% had CC, 3.0% had DCC, 0.1% had LT, and 0.8% had HCC
 - High metabolic comorbidities in severity cohorts
 - T2DM 34–49%, renal impairment 41–91%, CVD 82–94%, and hypertension 35–47%
 - Significantly more patients with CC, DCC, or HCC had T2DM, renal impairment, and CVD combined, compared with patients without AdvLD*

NAFLD/NASH patients with AdvLD have high comorbidity burden, HCRU and costs: results from Italian administrative databases



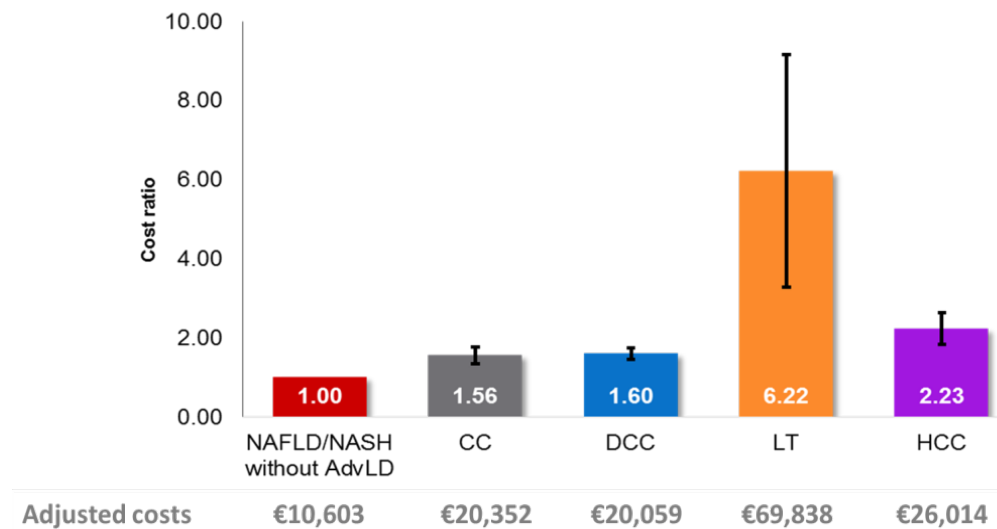
RESULTS (Cont.)

Mean annual all-cause healthcare costs by liver disease severity



- Post-index costs in patients with AdvLD >86% higher vs. patients without AdvLD*
 - Primarily driven by inpatient stays

Adjusted mean annual healthcare costs by liver disease severity†



CONCLUSIONS NAFLD/NASH patients in Italy have a high comorbidity burden; those with AdvLD have significantly higher costs, especially for inpatients. Early identification and effective management are needed to minimize disease progression and HCRU/costs



*p<0.001 for all; †Adjusted for baseline patient demographics and comorbidities (abdominal pain, anaemia, bariatric surgery, CVD, dyspepsia, hypertension, hyperlipidaemia, obesity, renal impairment, sleep apnoea, T2DM, thyroid disease, and vitamin D deficiency).



BACKGROUND & AIMS

- Epidemiological data on dietary risk factors for NAFLD from population-based studies are scarce
- **Aim:** Examine dietary factors in NAFLD by cirrhosis status in African Americans, Japanese Americans, Latinos, Native Hawaiians, and Whites from the US Multiethnic Cohort (MEC), a large prospective study with >215,000 participants in Hawaii and California

METHODS

- Nested case-control analysis was conducted within the MEC
- NAFLD cases identified between 1999–2015 using Medicare claims
- Controls selected among participants without liver disease and individually matched to cases (10:1) by birth year, sex, ethnicity, and length of Medicare enrolment
- Diet was assessed at baseline via a validated quantitative food frequency questionnaire
- Association between dietary factors and NAFLD by cirrhosis status quantified by ORs and 95% CIs using multivariable conditional logistic regression

Dietary risk factors for non-alcoholic fatty liver disease by cirrhosis status: The US multiethnic cohort



RESULTS

- 2,974 NAFLD cases (518 with cirrhosis; 2,456 non-cirrhotic) and 29,474 matched controls
- Red meat ($p=0.010$), processed red meat ($p=0.004$), poultry ($p=0.005$) and cholesterol ($p=0.005$) intake positively associated with NAFLD
 - Dietary fibre intake ($p=0.003$) inversely associated with risk
- NAFLD generally similar across racial/ethnic groups, except for poultry consumption (heterogeneity $p=0.004$)
- Stronger associations observed between red meat, cholesterol, and NAFLD with cirrhosis than without cirrhosis (heterogeneity $p=0.004$)

CONCLUSIONS Dietary factors including red meat, processed red meat, poultry, and cholesterol independently associate with risk of NAFLD in a multiethnic population, while dietary fibre is a protective factor. Red meat and cholesterol also associated with NAFLD-related cirrhosis



BACKGROUND & AIMS

- Less than 5% of NAFLD patients die from a liver-related cause, and risk factors for clinical liver outcomes remain poorly defined
- Current NAFLD criteria allow alcohol intake ≤ 30 g/day for men and ≤ 20 g/day for women
 - Unknown if these levels may be harmful in the context of pre-existing NAFLD
- **Aim:** Analyze risk factors for the development of advanced liver disease in the general population with NAFLD

METHODS

- Data from national health surveys: FINRISK 1992–2012 and Health 2000
- Exclusions: baseline clinical liver disease (n=288) or viral hepatitis (n=100)
- Linkage with national registers for hospitalization, death, and cancer using ICD codes reflecting liver cirrhosis, liver dysfunction, or liver cancer until 2013
 - NAFLD defined as a fatty liver index >30 + alcohol use ≤ 20 g/d (women)/ ≤ 30 g/d (men)
- Backward stepwise Cox regression with the following variables: age, sex, WHR, non-HDL, HDL, cholesterol, TGs, diabetes, hypertension, alcohol use, binge drinking, wine fraction, *PNPLA3*, *TM6SF2*, exercise, and smoking

In NAFLD, alcohol drinking habits and genetics predict progression to advanced liver disease: Follow-up of population surveys



RESULTS

- 6,462 NAFLD subjects with 70,401 person-years of follow-up
 - 58 liver events
- 43% rise in risk of liver events per each additional alcohol drink/day
- Potential misclassification from underreporting of alcohol use was negligible based on validation against CDT measurements in a subgroup of subjects

TABLE Independent predictors of incident advanced liver disease in the final multivariate model

	HR	95% CI	P-value
Age	1.05	1.02–1.07	<0.001
Waist–hip ratio (/1 SD)	1.80	1.32–2.44	<0.001
HDL cholesterol	2.09	1.08–4.04	0.03
Alcohol use (10 g/day)	1.43	1.12–1.82	0.004
Binge drinking			
Less often	Reference		
Monthly	2.69	1.27–5.69	0.01
Weekly	1.48	0.61–3.58	0.39
<i>TM6SF2</i> carrier	2.18	1.12–4.24	0.02
<i>PNPLA3</i> carrier	1.88	1.09–3.26	0.02

CONCLUSIONS Alcohol drinking habits and genetics are important co-factors in the progression of NAFLD, and abstinence should be recommended to persons with NAFLD. Our findings may help identify NAFLD patients at risk of complicated liver cirrhosis, in whom more intensive liver evaluation may be warranted



2. NAFLD: Therapy

Efficacy, safety, and tolerability of lubiprostone for non-alcoholic fatty liver disease: The LUBIPRONE phase 2 study

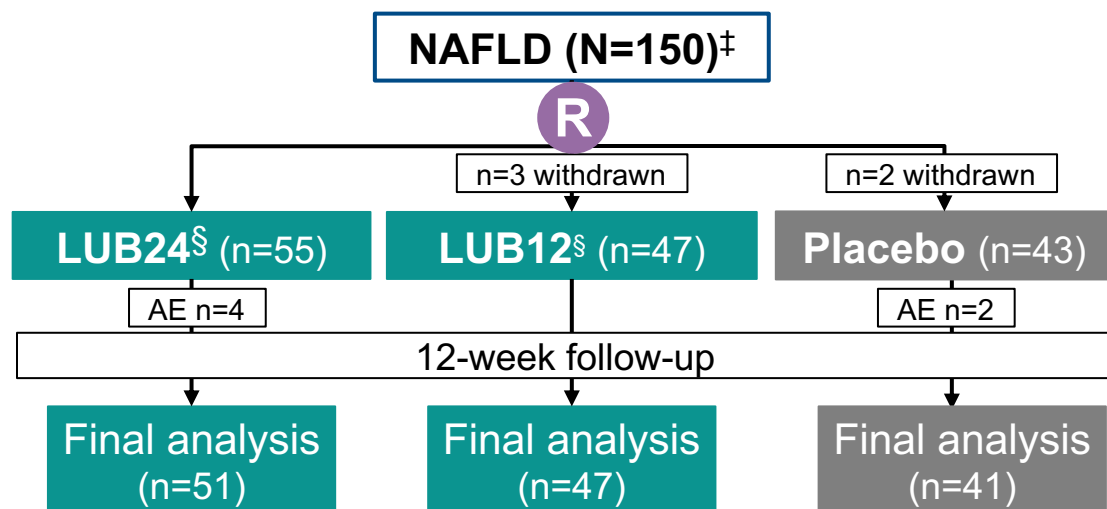


BACKGROUND & AIMS

- Progression of NAFLD is associated with increased gut permeability
- **Aim:** Double-blind, placebo-controlled, randomized, phase 2 trial to determine whether lubiprostone (LUB) improves gut permeability in NAFLD patients, resulting in reduction of ALT

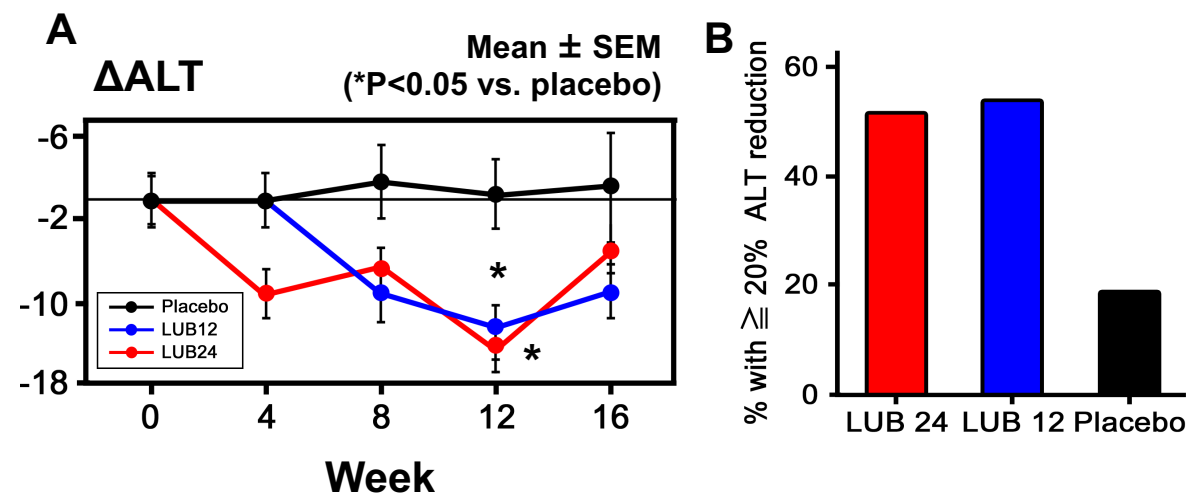
METHODS

- Primary endpoint: ALT reduction at Week 12
- Secondary endpoints: improvement in LMR,[†] blood EAA, MRI-PDFF, liver stiffness



RESULTS

- ALT significantly improved with LUB (*Figure A, B*)



Efficacy, safety, and tolerability of lubiprostone for non-alcoholic fatty liver disease: The LUBIPRONE phase 2 study



RESULTS (Cont.)

- LMR and blood EAA were significantly lower in LUB vs. placebo (*Table*)
- $\geq 15\%$ MRI-PDFF reduction significantly higher in LUB vs. placebo (*Figure C*)
- ALT reduction significantly greater in LMR responders vs. non-responders (*Figure D*)
- No statistically significant differences between LUB12 and LUB24
- LUB24 had a higher rate of AEs (33%) vs. placebo (7%, $p=0.0025$)[†] and LUB12 (7%)

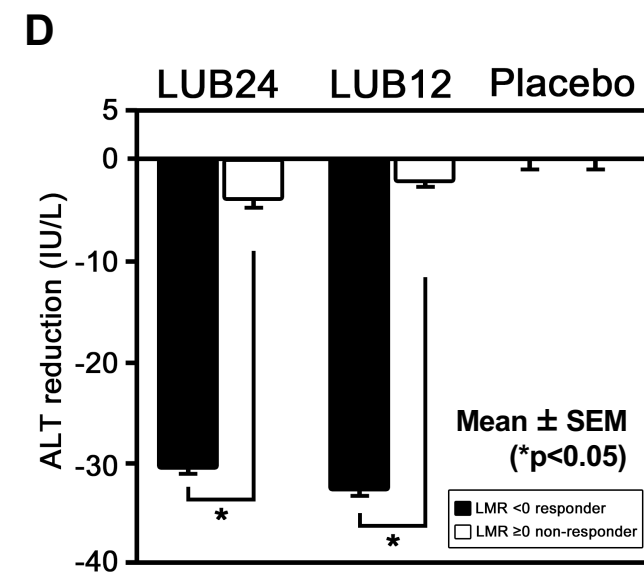
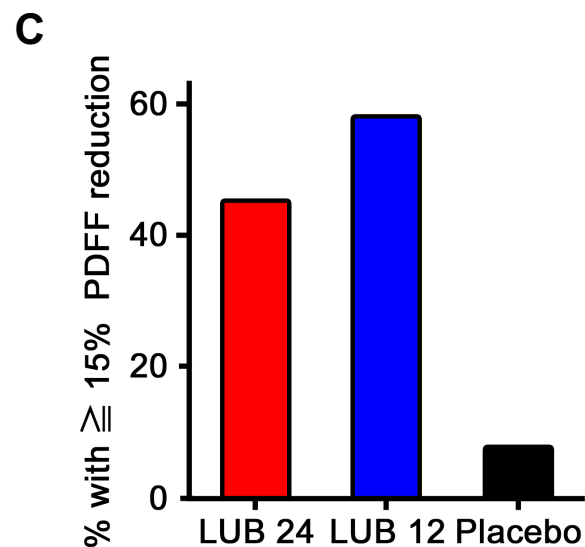


TABLE Change from baseline in measures of gut permeability

Variables	Mean (SD) change from baseline to 12 weeks			P-value	
	LUB24	LUB12	Placebo	LUB24 vs. placebo	LUB12 vs. placebo
LMR ($\times 10^3$)	-5 (13)	-4 (12)	5 (19)	0.001	0.008
EAA ($\times 10^2$)	-2 (9)	-1 (7)	0.5 (11)	0.002	0.0008

CONCLUSIONS LUB12 showed favourable efficacy and tolerability; manipulating gut permeability may be a promising novel approach in NAFLD



[†]Especially diarrhoea.
Kessoku T, et al. ILC 2019; GS-01

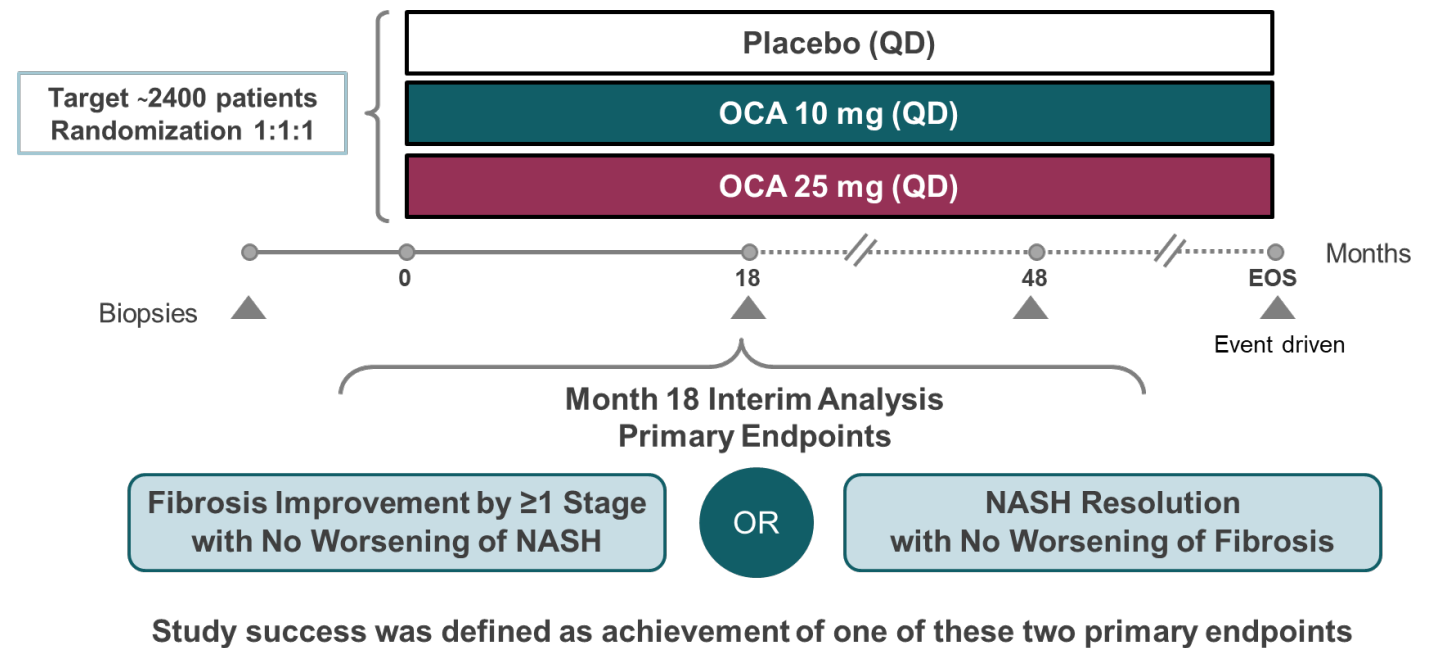
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH



BACKGROUND & AIMS

- OCA is a potent FXR agonist shown in preclinical models to have a direct antifibrotic effect in the liver¹
- In the phase 2b FLINT study, OCA 25 mg for 72 weeks improved fibrosis and other histological features of NASH²
- OCA is the only investigational drug to have received Breakthrough Therapy designation by the US FDA for the treatment of NASH patients with liver fibrosis
- This Month 18 interim analysis of REGENERATE evaluated OCA on liver histology in NASH patients with F2/F3 fibrosis

METHODS



1. Albanis A, et al. AASLD 2005 (Hepatology 2005;42:1040A);

2. Neuschwander-Tetri BA, et al. Lancet 2015;385:956–65.

Younossi Z, et al. ILC 2019; GS-06

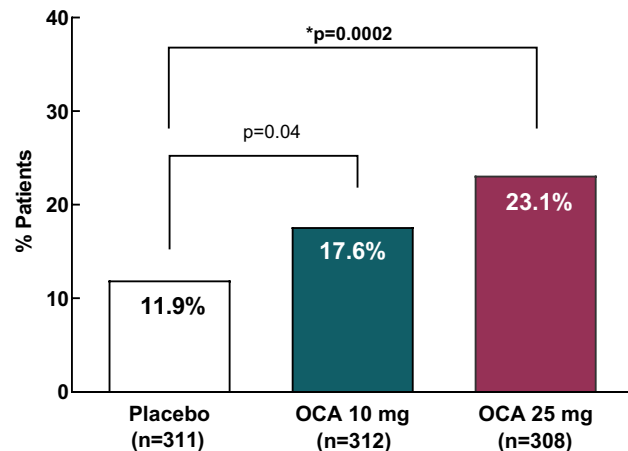
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH



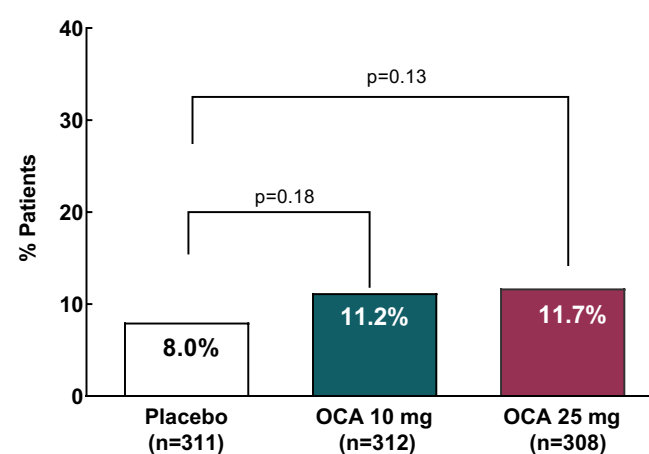
RESULTS

- OCA 25 mg QD met the primary endpoint of improvement in liver fibrosis with no worsening of NASH ($p=0.0002^*$ vs. placebo)
 - The antifibrotic effect of OCA was dose dependent and consistent across endpoints and key subgroups
- Although the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met, OCA improved NASH disease activity based on key histological parameters including NAFLD activity score, hepatocyte ballooning and lobular inflammation

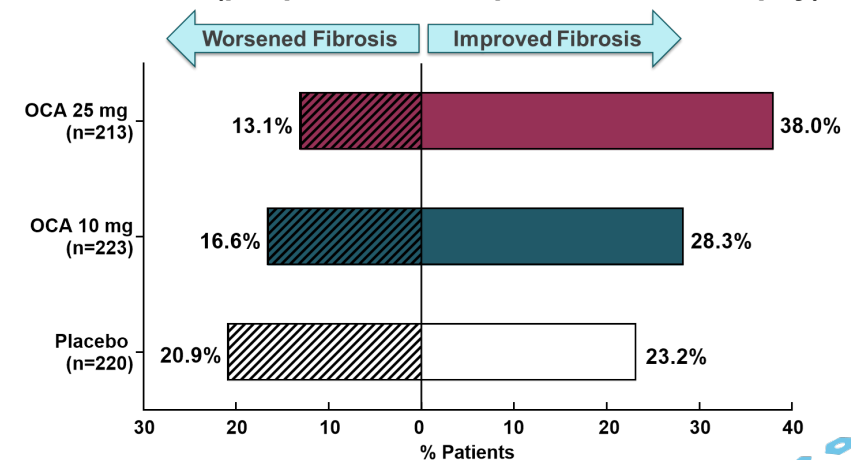
Primary endpoint (ITT): fibrosis improvement by ≥ 1 stage with no worsening of NASH



Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



Fibrosis improvement or worsening by ≥ 1 stage (per protocol with post-baseline biopsy)



*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

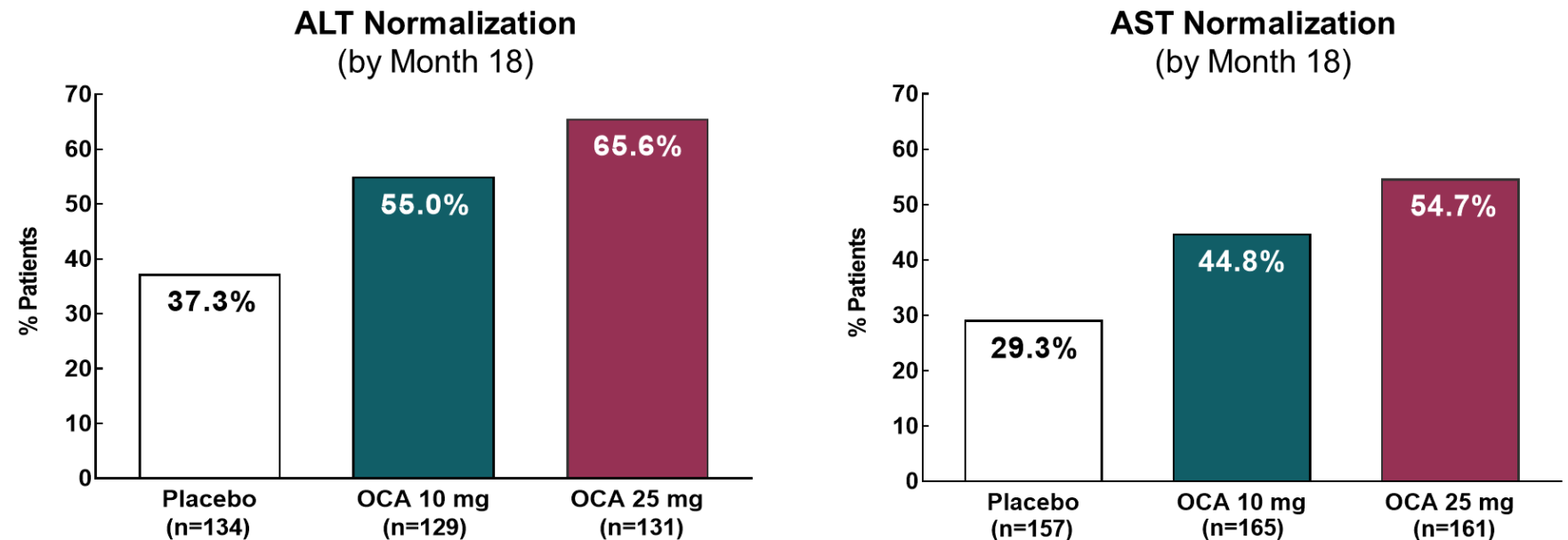
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH



RESULTS (Cont.)

- OCA rapidly decreased ALT, AST and GGT levels, which are routinely monitored by clinicians
- AEs were mostly mild to moderate in severity and the most common were consistent with the known profile of OCA

Normalization of aminotransferases in patients with elevated baseline levels



CONCLUSION REGENERATE is the first successful phase 3 study in NASH. These results are highly relevant because fibrosis is a strong predictor of liver-related morbidity and mortality in NASH.¹ The REGENERATE study is ongoing to confirm benefit on clinical outcomes

Significant regression in fibrosis in paired liver biopsies following a 12-week aerobic exercise intervention in individuals with NAFLD



BACKGROUND & AIMS

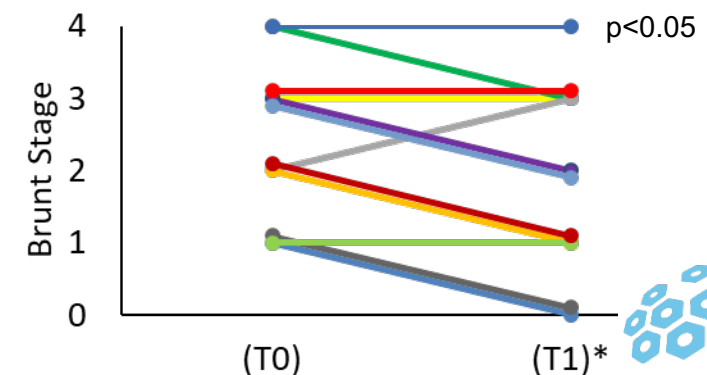
- Lifestyle modifications targeting 7–10% weight loss is the current recommended treatment for histological improvement of NAFLD
- The effects of exercise therapy on NAFLD using histological assessment remain unknown
- **Aim:** Investigate the effects of a 12-week exercise intervention (EI) on hepatic fibrosis in individuals with biopsy-proven NAFLD and examine the sustainability of the EI 12 weeks after completion

METHODS

- Assessments at baseline (T0), after EI (T1), and 12 weeks after T1 (T2)*
 - Liver biopsy, transient elastography, cardiorespiratory fitness (VO_{2max}), physical activity levels, and anthropometry
- EI group: 2 supervised and ≤ 3 unsupervised sessions per week, increasing intensity (45–75% heart rate reserve) and duration (24–45 minutes), for 12 weeks
- Control group: 3 physical assessments

RESULTS

Figure 1. Significant regression in hepatic fibrosis stage in the EI group (n=12) at T1 in the absence of clinically significant weight loss ($p < 0.05$)



*Except liver biopsy at T2.
O’Gorman P, et al. ILC 2019; PS-105

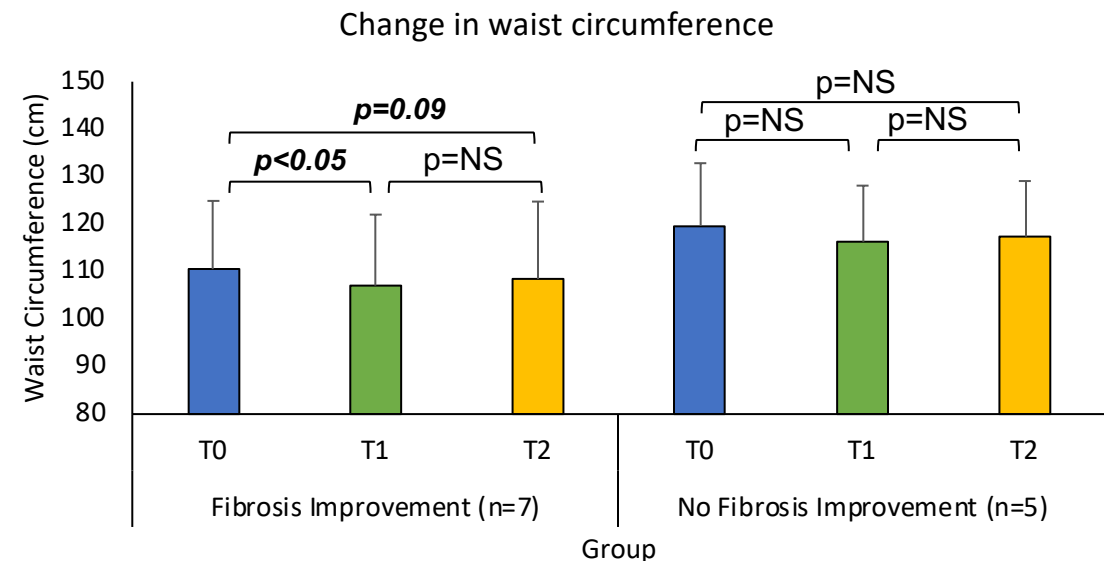
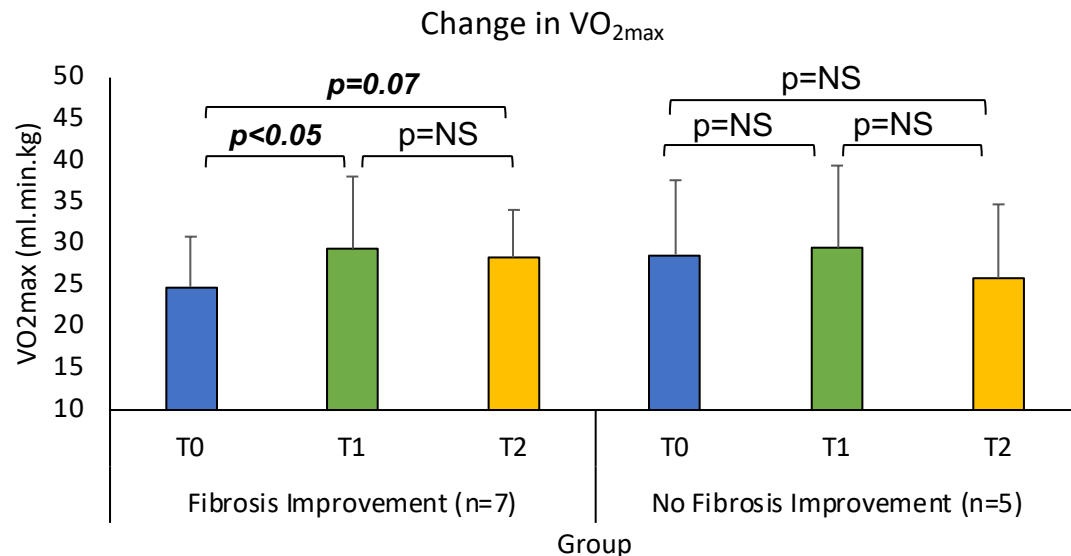
Significant regression in fibrosis in paired liver biopsies following a 12-week aerobic exercise intervention in individuals with NAFLD



RESULTS (Cont.)

Figure 2. Significant improvement in VO_{2max} in individuals in EI group who demonstrated fibrosis improvement at T1 ($p<0.05$), that tended to be sustained at T2 ($p=0.07$)

Figure 3. Significant improvement in waist circumference in individuals in EI group who demonstrated fibrosis improvement at T1 ($p<0.05$) that tended to be sustained at T2 ($p=0.09$)



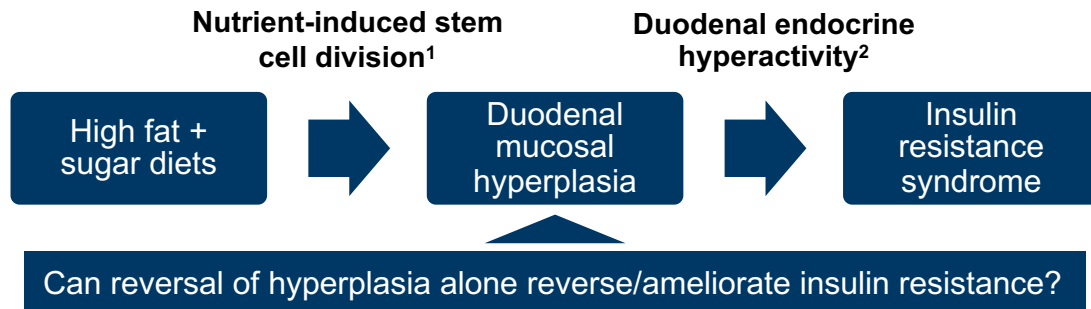
CONCLUSIONS 58% of individuals demonstrated fibrosis regression at T1, despite only 3/12 achieving $\geq 5\%$ weight loss. Future studies should aim to integrate exercise into the community setting to promote lifelong adherence to exercise therapy

Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes



BACKGROUND & AIMS

Putative role of duodenal mucosal hyperplasia in metabolic disease

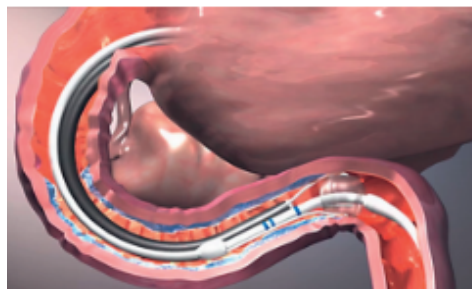


Aim: Evaluate effect of DMR on glycaemia, hepatic fat, and mechanistic endpoints

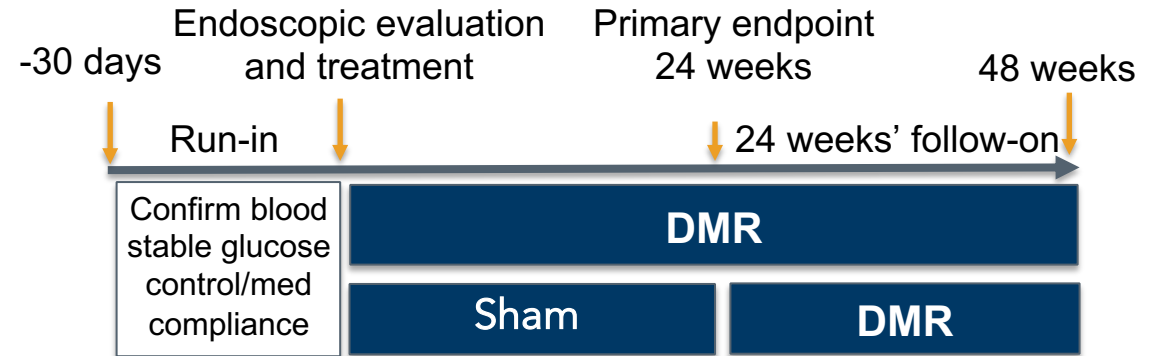
DMR: REVITA single catheter



Schematic of DMR



METHODS



- Revita-2 (NCT02879383): multicentre study with early open-label cohort (training purposes, n=24) and randomized double-blind cohort (n=108)
 - 17/20 (85%) open-label subjects with MRI-PDFF data had excess baseline liver fat (>5%)
- Inclusion criteria: HbA1c 7.5–10%; $24 \leq \text{BMI} \leq 40$; ≥ 1 oral medications
- DMR procedure: single catheter

Endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycaemic and lipid profiles in type 2 diabetes

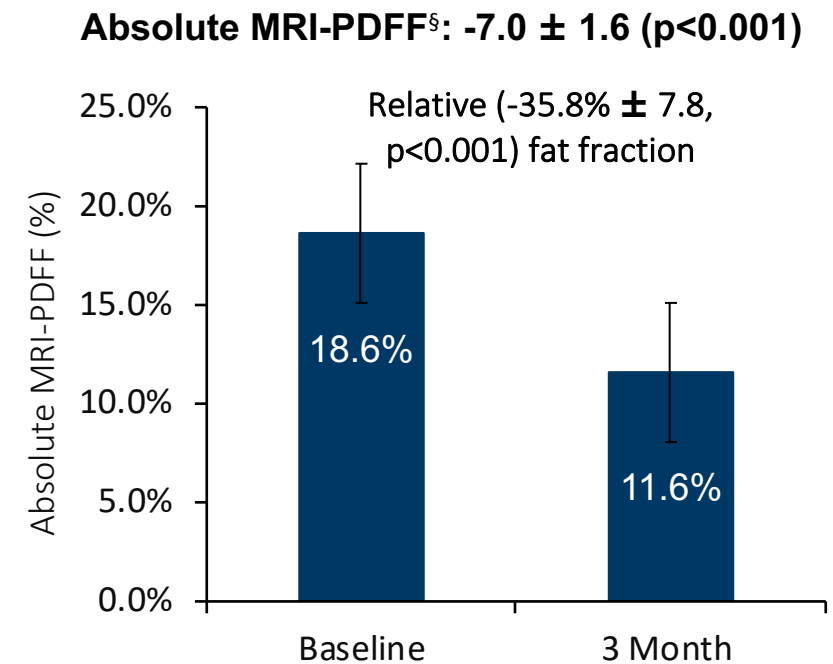
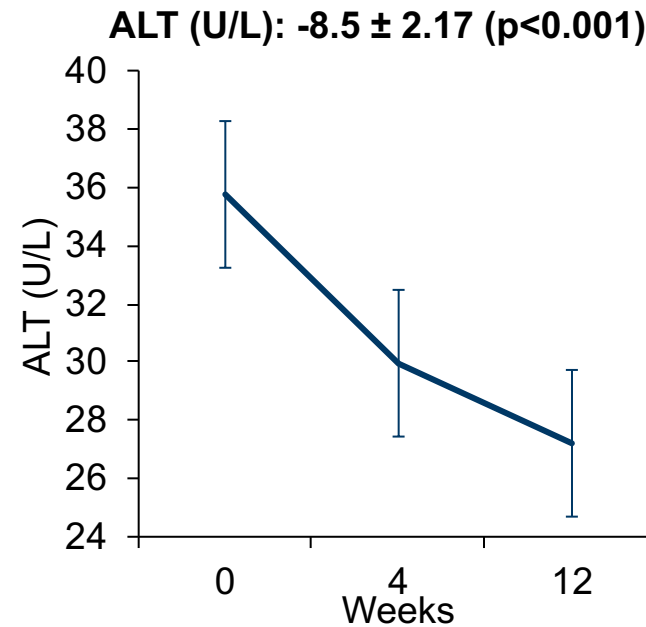


RESULTS

Baseline and 12-week metabolic and glycaemic values*

Indices	Baseline	12 weeks	P-value
HbA1c (%)	8.4 ± 0.2	7.4 ± 0.2	0.001
Fasting plasma insulin† (uU/ml)	13.6 ± 1.8	9.8 ± 1.1	<0.05
Fasting C-peptide (ng/ml)	3.2 ± 0.3	2.7 ± 0.2	0.01
Fasting TGs (mg/dl)	209.0 ± 32.0	150.0 ± 20.0	<0.01
Fasting HDL (mg/dl)	45.7 ± 2.8	49.2 ± 3.2	<0.05
Ferritin‡ (ng/ml)	90.8 ± 16.6	69.4 ± 15.5	<0.01
ALT (U/L)	35.8 ± 4.1	27.2 ± 2.4	<0.01
HOMA-IR†	6.0 ± 0.7	4.1 ± 0.6	0.01
Body weight (kg)	89.7 ± 1.9	86.6 ± 2.0	<0.01

Revita-2 open-label cohort: change over 12 weeks in ALT and liver MRI-PDFF*



CONCLUSIONS DMR was successfully implemented in T2D subjects with a favourable safety/ tolerability profile (median procedure time = 45 minutes), and is a promising potential treatment for T2D and NAFLD/NASH. Randomized cohort data will follow later this year



*Values are all mean (± SEM); n=24 unless indicated; †n=22; ‡n=23; §Subset of 17 subjects with excess baseline liver fat by MRI-PDFF.

3. NAFLD: Preclinical

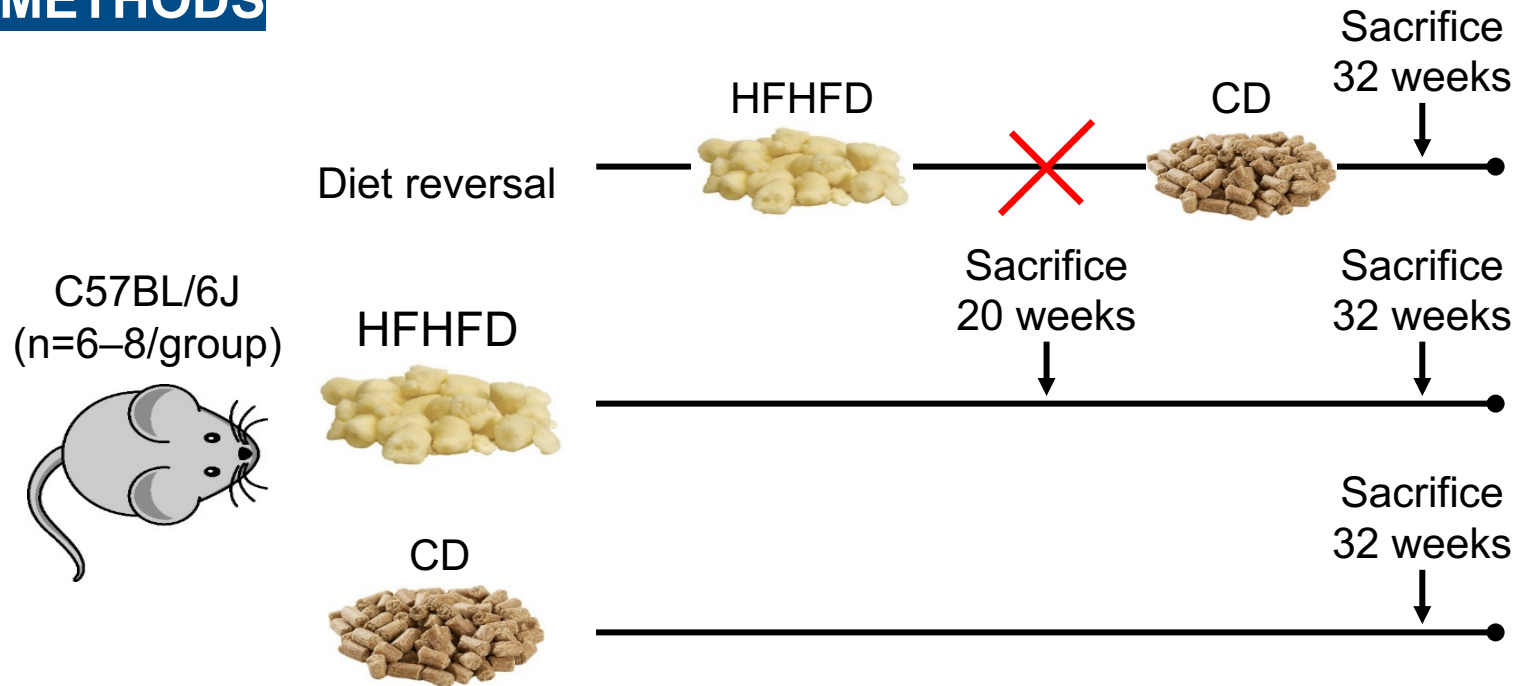
Persistence of hepatic and adipose tissue alterations in Th17, Treg and CD8+ cytotoxic T cells despite diet reversal in a mouse model of NAFLD



BACKGROUND & AIMS

- Adipose tissue is involved in NASH pathogenesis
- Mice with severe NAFLD exhibit elevated hepatic Th17 cells, an abundance of visceral adipose tissue (VAT) CD8+ Tc cells and a reduction of VAT Treg cells
- **Aim:** Investigate the potential reversibility of these alterations upon diet reversal

METHODS

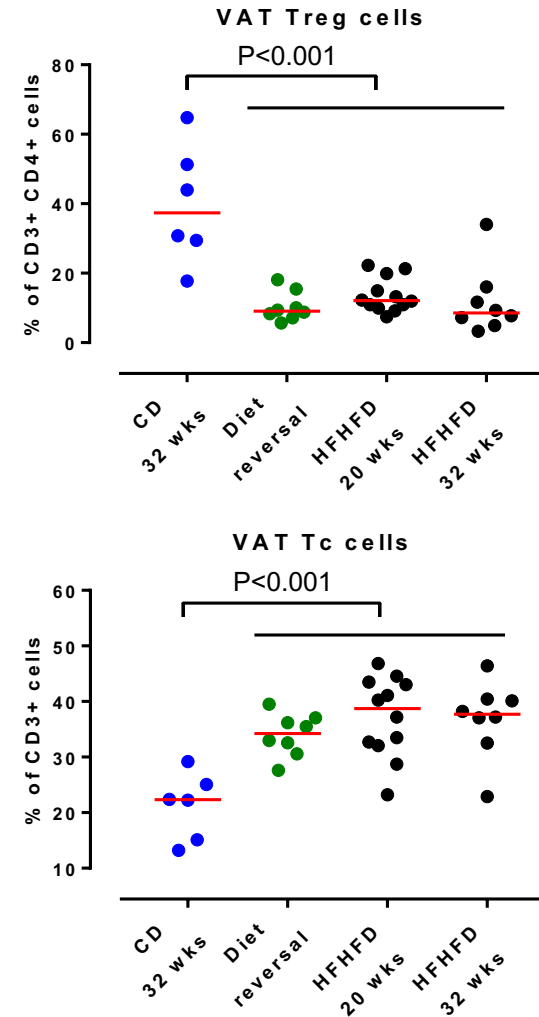
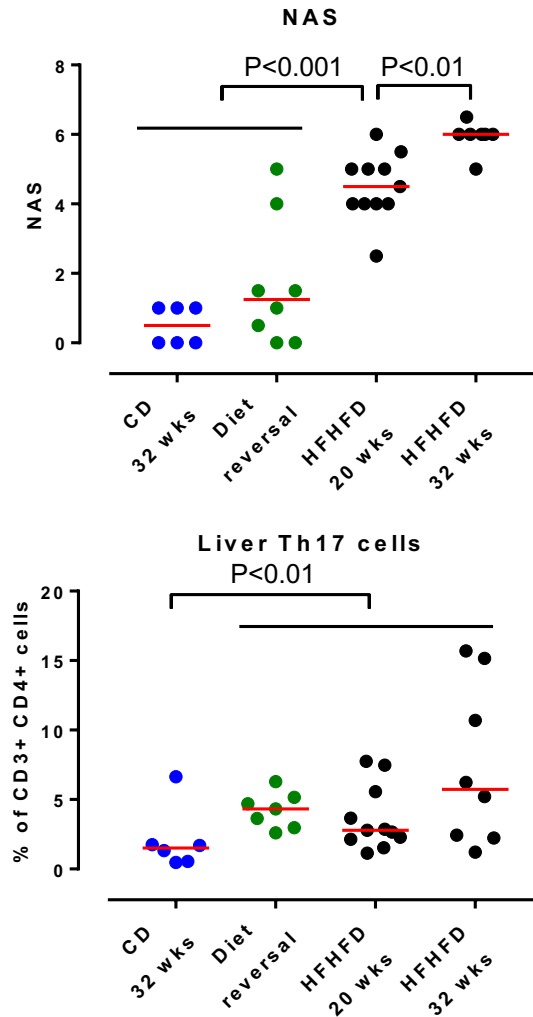
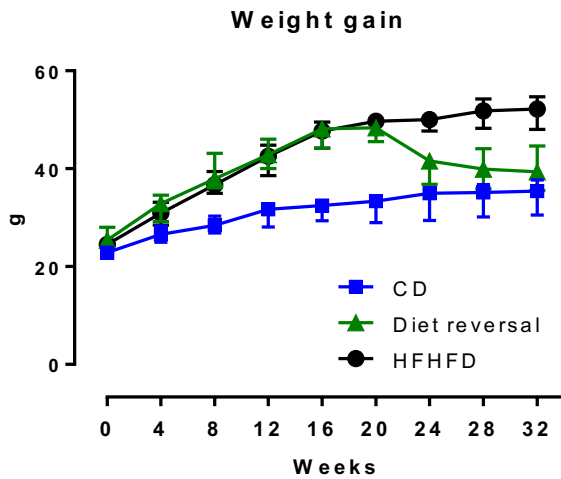


- T-cell subsets characterized in liver and VAT via flow cytometry
 - CD8+ Tc cells expressed as a percentage of CD45+/CD3+ cells
 - Treg (CD25+/Foxp3+) and Th17 (ROR γ t+) cells expressed as a percentage of CD3+/CD4+ cells

Persistence of hepatic and adipose tissue alterations in Th17, Treg and CD8+ cytotoxic T cells despite diet reversal in a mouse model of NAFLD



RESULTS



CONCLUSIONS

Although diet reversal induced metabolic and histological normalization in HFHFD-fed mice, these induced alterations in hepatic Th17, VAT Tc, and VAT Treg cells were not reversed within 12 weeks. This finding challenges our current understanding of reversibility of NAFLD-related inflammation upon lifestyle modification



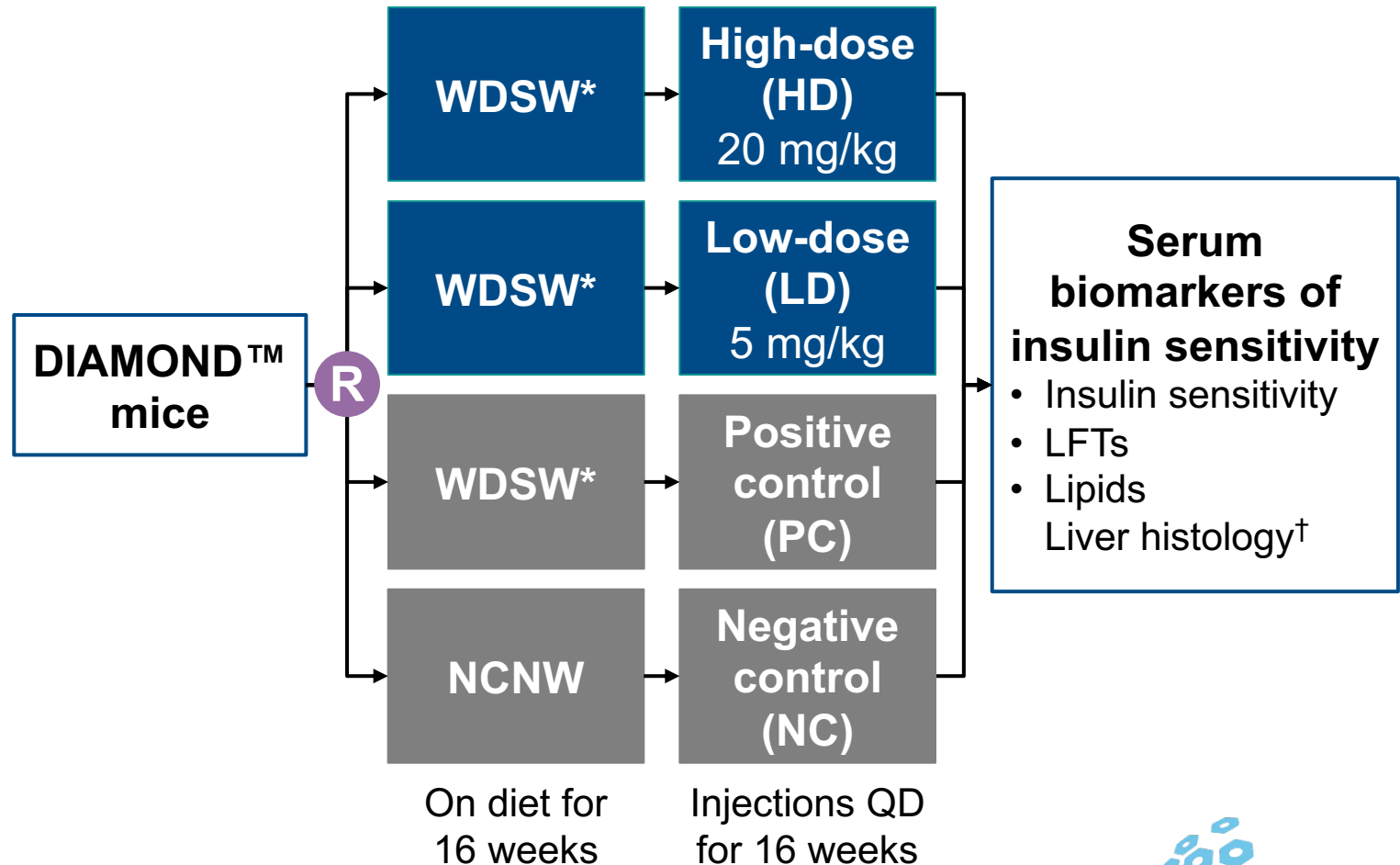
The glucocorticoid antagonist ST-001 prevents fibrosis development and improves aspects of metabolic syndrome in the DIAMOND™ mouse model



BACKGROUND & AIMS

- ST-001 (fluasterone) has a dual anti-glucocorticoid and anti-inflammatory/fibrotic MoA relevant to NASH and metabolic syndrome
 - Effective in reducing plasma glucose in a diabetic mouse model
 - Potent G6PD inhibitor, reducing NOx and limiting inflammation leading to fibrosis/cirrhosis
- **Aim:** Determine if ST-001 could prevent development of NASH in the DIAMOND™ mouse model

METHODS



The glucocorticoid antagonist ST-001 prevents fibrosis development and improves aspects of metabolic syndrome in the DIAMOND™ mouse model



RESULTS

- Body weight/liver weight of the HD group were significantly lower than the PC and LD groups
- Steatosis percentage was higher in the HD/LD groups, but steatosis grade did not differ
- Fasting blood glucose was higher in HD/LD groups, but ketones and serum TGs were lower
- Serum LFTs and cholesterol did not differ between the PC and treatment groups
- 66% of PC mice progressed to NASH, but none of the HD/LD mice progressed beyond simple steatosis ($p \leq 0.001$)
- ST-001 eliminated ballooning in the HD/LD groups compared with PC ($p \leq 0.0001$)

Mouse	Fibrosis (NASH CRN)	Perisinusoidal fibrosis (0–2)	NAS	SAF activity score
Positive control	0.67	1.00	4.56	1.78
High-dose	0.00 $p=0.0006$	0.10 $p=0.0069$	4.10	1.1
Low-dose	0.00 $p=0.0010$	0.11 $p=0.0110$	4.00	1.00

CONCLUSIONS While ST-001's effect on NASH development is inconclusive, improvements in measures of fibrosis and NAFLD were demonstrated. As a potent G6PD inhibitor, ST-001's inhibition of NOX reactive oxygen formation may be fundamental to fibrosis prevention

4. Alcohol-related liver disease



BACKGROUND & AIMS

- Neutrophil-to-lymphocyte ratio (NLR) has been shown to reflect sepsis and inflammation
- This study assessed the role of the NLR in the prognosis of alcoholic hepatitis

METHODS

- NLR calculated from 789 patients in the STOPAH trial
- Patients were randomized to prednisolone treated or no prednisolone treatment groups
- Prevalent infections treated prior to randomization; infections developing after inclusion were recorded
- Prevalent AKI was defined by initial creatinine $\geq 133 \mu\text{mol/L}$. Incident AKI was defined as an increase of serum creatinine by $26.5 \mu\text{mol/L}$, or by 50% by Day 7 in those without baseline AKI
- OR and t-tests were used for comparative analysis

RESULTS

- Higher NLR found in patients with prevalent AKI (11.1 vs. 6.0; $p=0.001$ [2.6, 7.6]) and with prevalent infection (7.8 vs. 6.3; $p=0.02$ [0.2, 2.8]) vs those without such features
- Higher NLR values were seen in those patients with incident AKI and in those who developed infection (*Table*)
- If $\text{NLR} \geq 5$, a favourable Lille score was more likely with prednisolone treatment (*Figure*)

Baseline neutrophil-to-lymphocyte ratio indicates infection and acute kidney injury, and is related to corticosteroid Lille response in alcoholic hepatitis



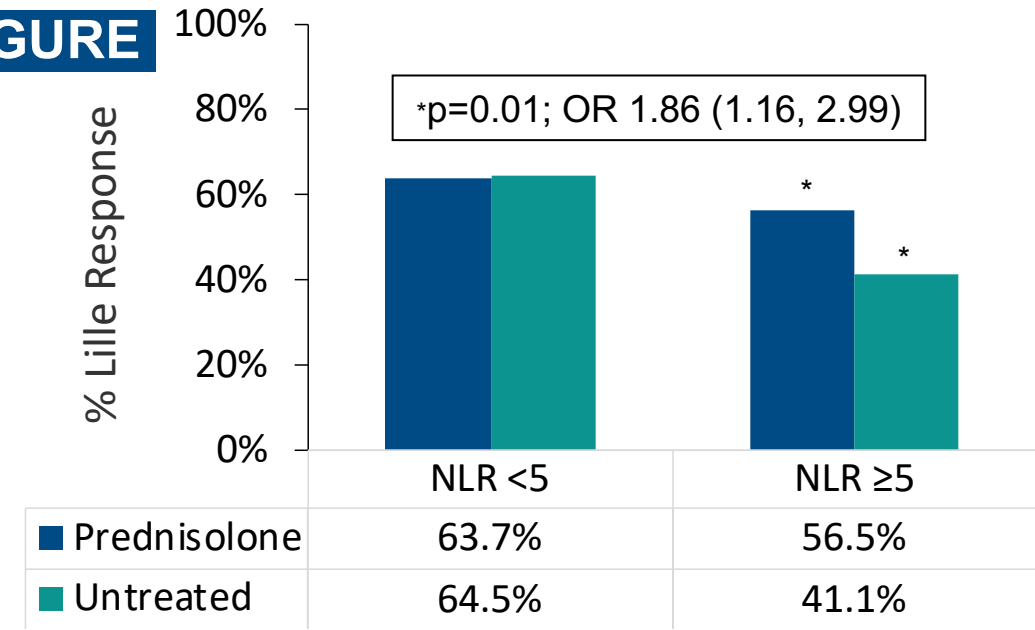
RESULTS (Cont.)

- Risk of developing infection and incident AKI after prednisolone treatment greater if NLR >8 vs ≤8:
 - Infection by Day 7: 17.3% vs 7.4%: p=0.006; OR 2.60
 - Infection by Day 28: 30.6% vs 20.0%: p=0.031; OR 1.76
 - Incident AKI: 20.8% vs 7.0%: p=0.008; OR 3.46

TABLE

		NLR	
Incident AKI	Present (n=67)	7.5 (6.4, 8.7)	p=0.0056
	Absent (n=403)	6.0 (5.6, 6.4)	
Infection by Day 7	Present (n=94)	7.8 (6.3, 9.2)	p=0.035
	Absent (n=695)	6.1 (5.8, 6.5)	
Infection by Day 28	Present (n=185)	7.1 (6.3, 8.0)	p=0.025
	Absent (n=604)	6.1 (5.6, 6.5)	

FIGURE



CONCLUSIONS

High NLR associates with prevalent AKI and infection in alcoholic hepatitis. A Lille response to prednisolone is more likely if NLR ≥5, but development of infection or AKI after prednisolone treatment is greater if NLR >8

Long-term survival in a 10-year prospective cohort of heavy drinkers: Liver stiffness is the best long-term prognostic parameter



BACKGROUND & AIMS

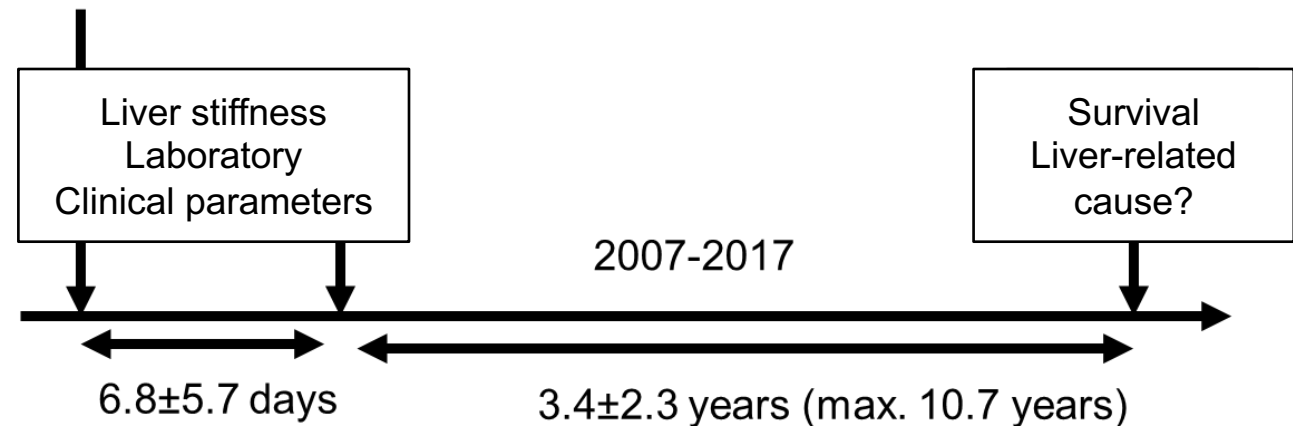
- Liver stiffness (LS) measurement by TE is well established for early fibrosis but no prospective long-term data on survival in ALD exist
 - LS is elevated by fibrosis and other pathological confounders such as inflammation, cholestasis or pressure
- **Aim:** Establish long-term survival data in a 10-year prospective cohort of heavy Caucasian drinkers primarily presenting for alcohol detoxification

METHODS

- Heavy drinkers (n=675) admitted for alcohol detoxification with initial LS measurement (FibroScan)
 - Mean alcohol consumption 186.5 g/d
 - Mean duration of heavy drinking was 14.3 years
- 106 patients (15.7%) died during the observation period

Alcohol detoxification

Endpoints

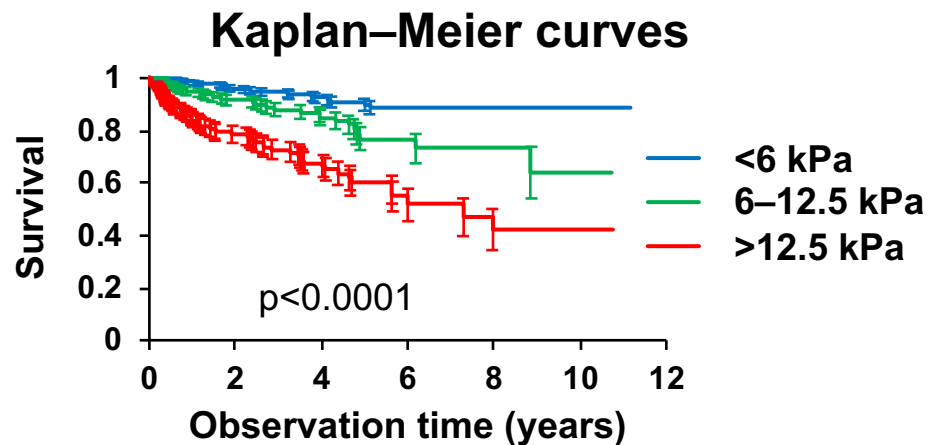


Long-term survival in a 10-year prospective cohort of heavy drinkers: Liver stiffness is the best long-term prognostic parameter



RESULTS

- LS was the best univariate parameter associated with survival ($r=0.296$, $p<0.0001$)
 - LS remained (next to age, ALP, and albumin) an independent predictor of death in multivariate analysis



	<6 kPa	6–12.5 kPa	>12.5 kPa
3-year survival rate	94%	88%	74%
5-year survival rate	90%	78%	64%

TABLE ROC analysis for overall and 1–5-year mortality

Parameter	Overall	1 year	2 year	3 year	4 year	5 year
Age	0.67	0.70	0.68	0.67	0.67	0.68
ALP	0.69	0.75	0.74	0.74	0.70	0.70
Bilirubin total	0.66	0.75	0.71	0.69	0.67	0.65
INR	0.62	0.71	0.66	0.64	0.60	0.60
Urea	0.49	0.56	0.53	0.50	0.50	0.47
Creatinine	0.44	0.51	0.46	0.44	0.44	0.43
Haemoglobin	0.66	0.73	0.70	0.67	0.68	0.67
Leucocytes	0.52	0.54	0.53	0.51	0.48	0.51
Albumin	0.68	0.81	0.74	0.73	0.71	0.67
Liver stiffness	0.72	0.76	0.75	0.74	0.72	0.73
LS cut-off (kPa)	14.0	26.3	23.4	14.0	14.0	6.4

CONCLUSIONS LS is the best independent predictor of long-term survival in heavy drinkers. LS monitoring should be mandatory for surveillance of drinkers



Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis



BACKGROUND & AIMS

- Accurate diagnosis of severe alcoholic hepatitis (SAH) is important in determining therapy
- However, surveys suggest only a minority of patients undergo liver biopsy due to high cost and potential complications
- **Aim:** Determine a new non-invasive diagnostic test for steatohepatitis that would distinguish SAH from its most common differential, acute decompensation (DC) of alcohol-related cirrhosis

METHODS

- SAH patients had biopsy-proven steatohepatitis with MDF ≥ 32
- Serum BAs measured by mass spectrometry in two cohorts

	Exploratory cohort		Validation cohort	
	SAH	DC	SAH	DC
N=	68	21	65	40
Mean age (years)	49	54	47	51
Median MELD	23	26	25	30
Mean bilirubin ($\mu\text{mol/L}$)	378	246	323	261
Median MDF	54	65	56	79

- Analyzed by OPLS-DA and AUROC

Serum bile acid profiles distinguish severe alcoholic hepatitis from decompensated alcohol-related cirrhosis

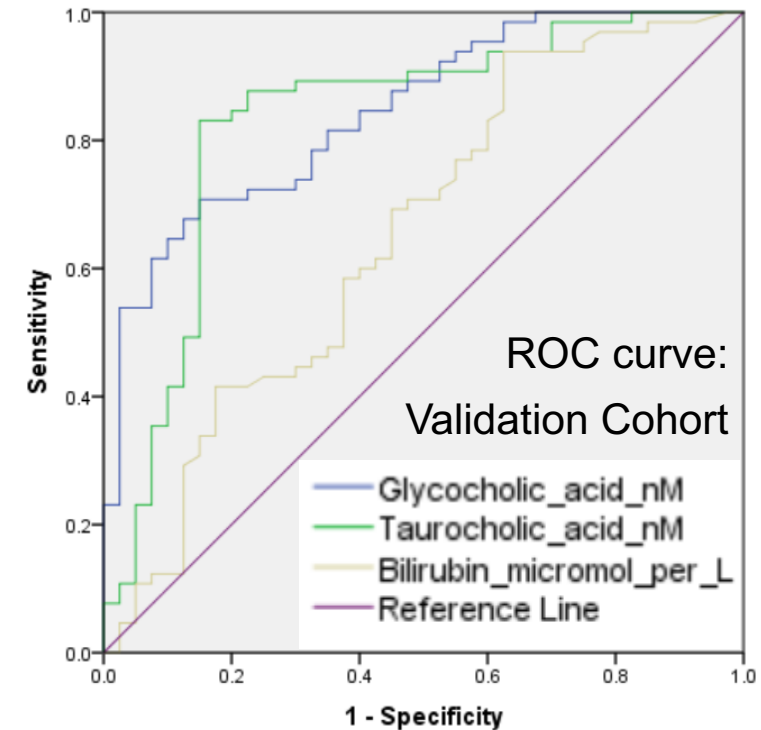


RESULTS

- OPLS-DA accurately discriminated AH from DC in both cohorts:
 - GCA and TCA acid were the dominant metabolites

	Full BA profile	GCA	TCA	Bilirubin
Exploratory cohort				
AUROC	0.93	0.90	0.87	0.79
95% CI	0.87–0.99	0.83–0.97	0.77–0.97	0.67–0.91
Validation cohort				
AUROC	0.93	0.85	0.83	0.65
95% CI	0.88–0.98	0.77–0.92	0.74–0.92	0.54–0.76

AUROC analyses for serum BAs and bilirubin



CONCLUSIONS SAH has a serum BA profile distinct from patients with DC and similar liver dysfunction. The entire BA profile and individual BAs of GCA and TCA are promising non-invasive biomarkers for SAH, and may reduce the need for liver biopsy