

## ORAL PRESENTATIONS

was found in 373 (29.9%) patients; severe fibrosis (F3-4) was found at liver biopsy in 272 (21.8%) patients. NASH was diagnosed in 756 (60.6%) cases and was similarly distributed between those with normal and high ferritin levels. Serum ferritin  $>2 \times \text{ULN}$  (32.2% of the total population with hyperferritinemia), significantly associated with F3-4 (OR = 2.10 [95% CI 1.40–3.14],  $p < 0.001$ ). After a median follow-up of 90 months, 24 patients (2.3%) died, while 57 (4.8%) and 18 (1.5%) developed liver-related events and HCC. At univariate analysis, the incidence of liver-related events and mortality varied significantly according to serum ferritin values  $>2 \times \text{ULN}$  (log-rank test:  $p = 0.004$  and  $p = 0.001$ , respectively). However, at multivariate Cox regression analysis adjusted for age, body mass index, diabetes and fibrosis, ferritin levels  $>2 \times \text{ULN}$  independently predicted mortality (HR = 3.04 [95% CI 1.16–7.93],  $p = 0.023$ ) but not liver-related events (HR = 1.67 [95% CI 0.90–3.11],  $p = 0.105$ ).

**Conclusion:** Ferritin levels higher than  $2 \times \text{ULN}$  are associated with severe liver fibrosis in NAFLD patients and are able to predict long-term mortality.

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### OS-1611

#### AI-based histologic measurement of NASH (AIM-NASH): A drug development tool for assessing clinical trial end points

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**Background and aims:** Limitations of manual pathology may confound results of NASH clinical trials. Our aim was to develop an AI-based drug development tool (AIM-NASH) that reproducibly calculates NASH Clinical Research Network (CRN) scores.

**Method:** AIM-NASH machine learning (ML) models were developed using 5923 biopsies from six phase 2b or 3 trials in NASH subjects with F1-F4 fibrosis. Models were trained to identify NASH histologic features and predict ordinal CRN scores using  $>100k$  annotations from expert pathologists. Analytic performance was tested in a held-out dataset of 639 HandE- and 633 trichrome-stained biopsy images (NCT02784444; EMINENCE). Agreement between AIM-NASH scores and the consensus of 3 expert hepatopathologists was evaluated using linearly-weighted Kappa ( $\kappa$ ) statistics. Histologic end points were retrospectively assessed by AIM-NASH and central reader scores from a separate phase 2b trial (NCT03449446; ATLAS). Comparisons of treatment responses between groups were made using the Mantel-Haenszel test, stratified by diabetes and cirrhosis status.

**Results:** Agreement between AIM-NASH and consensus reads was higher than that among pathologists [AIM-NASH steatosis  $\kappa = 0.71$  (95% CI 0.67–0.74) vs mean pairwise inter-pathologist steatosis  $\kappa = 0.60$  (0.56–0.63); lobular inflammation  $\kappa = 0.50$  (0.45–0.55) vs 0.33 (0.29–0.37); ballooning  $\kappa = 0.58$  (0.53–0.63) vs 0.48 (0.44–0.52); fibrosis  $\kappa = 0.58$  (0.54–0.62) vs 0.50 (0.47–0.53)]. In ATLAS, AIM-NASH identified more responders vs the central reader in subjects treated with cilofexor and firsocostat for  $\geq 1$ -stage fibrosis improvement

without NASH worsening (26% vs 21%), NASH resolution without fibrosis worsening (16% vs 5%), and  $\geq 2$ -point reduction in NAS (68% vs 38%), and greater improvements in treated subjects vs placebo (Table).

Table: AIM-NASH and Central Reader Assessments of Treatment Response in ATLAS (F3-F4).

End points*	AIM-NASH			Central Reader		
	CILO+FIR	Placebo	P value	CILO+FIR	Placebo	P value
Fibrosis improvement without NASH worsening	26% (16/61)	13% (4/32)	0.142	21% (13/63)	11% (4/38)	0.190
NASH resolution without fibrosis worsening	16% (9/55)	7% (2/27)	0.212	5% (3/63)	0% (0/38)	0.332
$\geq 2$ -pt reduction in NAS	68% (40/59)	27% (8/30)	<b>&lt;0.001</b>	38% (24/64)	11% (4/38)	<b>0.001</b>

\* Sample size for each end point varies due to data availability. CILO, cilofexor; FIR, firsocostat; NAS, NAFLD Activity Score.

**Conclusion:** AIM-NASH enables automated, and sensitive ML-based CRN scoring, and generates reproducible assessments of disease activity from biopsy samples. AIM-NASH may potentially support standardized evaluation of histologic end points in NASH clinical trials.

### OS-1780

#### Incidence rates of select outcomes among patients with non-alcoholic steatohepatitis (NASH) and evidence of fibrosis or cirrhosis

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**Background and aims:** There are limited epidemiologic data available characterizing patients with NASH using longitudinal data, and rates of rare events require a large patient sample. Electronic health record (EHR) databases represent useful real-world data sources for studying the epidemiology of NASH. This study aimed to systematically estimate incidence rates (IRs) of over 40 a priori outcomes within a cohort of patients with NASH.

**Method:** Patients with NASH were identified between 2016 and 2019 within Optum's EHR Research Database by structured (diagnosis codes, procedure codes, labs) and natural language processing (NLP) data. Patients with NASH were classified as having cirrhosis or fibrosis using information from the baseline period (the year prior to and including cohort entry). Outcomes were identified in the time following cohort entry using International Classification of Diseases, 10<sup>th</sup> revision diagnosis codes and lab values. Outcome IRs were estimated among the subset of patients at risk for that particular outcome at the beginning of follow-up (after excluding those with a prior history).

**Results:** Among 93,204 patients identified as having NASH, 44,685 (48%) had evidence of fibrosis and 29,770 (32%) had evidence of cirrhosis. Patients with NASH were an average of 58 years old, 60% were female, and 81% were white. Estimated IRs of select outcomes are summarized in Table. IRs were highest for NASH patients with cirrhosis. IRs of kidney and cardiovascular outcomes were up to ~2-fold higher for patients with cirrhosis compared to those with fibrosis, and IRs of liver outcomes were several-fold higher.