# Artificial intelligence-powered digital pathology model supports that fibrosis is reduced by semaglutide in patents with NASH

**Stephen A. Harrison** (stephenharrison87@gmail.com)[1], Sven Francque[2], Vanja Cejvanovic[3], Helena Cortez-Pinto[4], Niels Krarup[3], Quang Le[5], Anne-Sophie Sejling[3], Vlad Ratziu[6]

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# AI-assessed continuous fibrosis score shows significant reduction in fibrosis with semaglutide 0.4 mg versus placebo

AI-assessed change in continuous fibrosis score

P=0.0099

| Placebo | Semaglutide 0.4 mg |
|---|---|
| 0 | –0.27 |

## Aim

- Pathologist assessment of liver biopsy is the gold standard for diagnosis of non-alcoholic steatohepatitis (NASH), but manual examination is complex, and includes a degree of subjectivity and intra- and inter-observer variability.[1–3]
- Artificial intelligence (AI) could support clinical decision-making by identifying changes not quantifiable by manual evaluation, reducing variability, and providing continuous measurements rather than ordinal classification.
- Using liver biopsy samples from a phase 2 trial that compared the effect of three different doses of the glucagon-like peptide-1 receptor agonist semaglutide (0.1, 0.2 and 0.4 mg once daily) with placebo in patients with NASH,[4] this study aimed to compare key histological features of NASH as assessed by pathologists and machine learning models and evaluate inter-agreement variability between methods.

## Methods

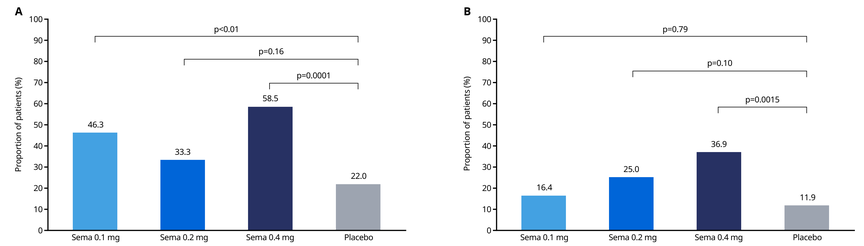
- All biopsies at baseline (N=320) and week 72 were each manually assessed by two independent pathologists who were blinded to the patient, treatment and each other's assessment. During trial conduct, digitalization of liver biopsies was initiated and 251 subjects had their baseline biopsy digitalized.
- The PATH AI models were developed using 5,923 biopsies of subjects with NASH and stage F0-F4 fibrosis.
- The AI models were trained to identify and segment NASH histologic features, generate NASH Clinical Research Network (CRN) scores, and detect and quantitate the proportion of fibrosis patterns consistent with stage F0–4 fibrosis architecture.
- Endpoints assessed by the AI model included change from baseline to week 72 in AI-based fibrosis stage (0–4).
- Inter-agreement variability between the AI model and pathologist results was also assessed.

## Key results

- By pathologist assessment, NASH resolution without fibrosis worsening was achieved by significantly more patients receiving semaglutide 0.4 mg vs placebo (p<0.0001) (**Figure 1A**).
- The AI model determined that fewer patients achieved the primary endpoint compared with the pathologists' evaluation in the semaglutide groups as well as the placebo group.
- However, as with pathologist assessment, achievement of NASH resolution was dose-dependent and the difference between semaglutide 0.4 mg and placebo remained statistically significant (p=0.0015) (**Figure 1B**).

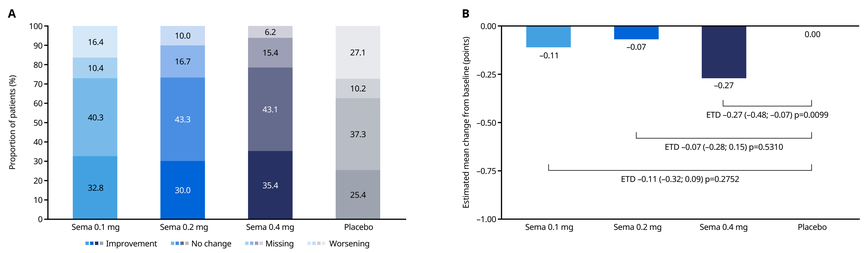
## Key results

**Figure 1:** Proportion of patients with NASH resolution without fibrosis worsening as evaluated by (A) pathologists (N=320) and (B) AI at week 72 (N=251)




A and B: p-values are two-sided and taken from a Cochran-Mantel-Haenszel test stratified by baseline diabetes status and baseline fibrosis stage. Patients with missing outcomes were imputed as non-responders.

**Figure 2:** AI-assessed change in (A) categorical CRN fibrosis stage and (B) continuous fibrosis stage from baseline to week 72 (N=251)




A: Analysis updated to include all subjects with a baseline digitalized biopsy. Cochran-Mantel-Haenszel test stratified by fibrosis and diabetes status, both at baseline. Patients with missing endpoint were imputed as non-improvers; B. Mean changes from baseline estimated from an ANCOVA, with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline body weight and baseline value of the analyzed parameter as covariates. Missing data were imputed from observed data in the placebo group using the same ANCOVA method but without treatment as factor.

AI, artificial intelligence; ANCOVA, analysis of covariance; CRN, Clinical Research Network; ETD, estimated treatment difference; NASH, non-alcoholic steatohepatitis; sema, semaglutide.

## Key results (cont.)

- Using categorical AI-assessed change, a numerically higher but non-significant proportion of patients achieved an improvement in fibrosis stage with semaglutide 0.4 mg compared with placebo (p=0.328) (**Figure 2A**).
- There was a dose-dependent reduction in the proportion of patients with fibrosis worsening with semaglutide vs placebo (p=0.003 for semaglutide 0.4 mg) (**Figure 2A**).
- By continuous AI-assessed fibrosis score, there was a treatment difference of –0.27 between semaglutide 0.4 mg and placebo (p=0.0099) (**Figure 2B**).
- There was a low-to-moderate agreement between pathologists' assessment and AI learning in baseline scoring across fibrosis stage and change from baseline in categorical fibrosis stage (data not shown).

## Conclusions

- Both pathologist and AI evaluation of biopsies indicated a difference between treatments for the primary endpoint favoring semaglutide vs placebo.
- AI-assessed continuous fibrosis scores showed fibrosis was significantly reduced with semaglutide 0.4 mg vs placebo, despite the absence of difference using categorical fibrosis staging.
- An AI-based approach can provide additional value to the interpretation of histological results.

[1]Radcliffe Department of Medicine, University of Oxford, Oxford, UK; [2]Antwerp University Hospital, Antwerp, Belgium; [3]Novo Nordisk A/S, Søborg, Denmark; [4]Clínica Universitária de Gastrenterologia, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; [5]PathAI Inc., Boston, MA, USA; [6]Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France.

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