

Hope on the horizon: how pegbelfermin offers a glimmer of hope for NASH sufferers?

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Madam, Non-alcoholic steatohepatitis (NASH), is described as having hepatic steatosis of >5%, inflammation, and hepatocyte damage (such as ballooning), including or excluding fibrosis¹. NASH falls under a group of liver diseases termed Non-alcoholic Fatty Liver Disease (NAFLD) varying from benign steatosis to inflammatory NASH and hepatic fibrosis. It is a prevalent disorder affecting 25% of the world's population, with the Middle East (32%), and South America (31%), having the highest regional incidence. Notably, hepatic fibrosis is the most powerful predictor of both general and disease-specific mortality in NAFLD patients.² NAFLD can lead to severe consequences, such as cirrhosis, liver failure, and hepatocellular carcinoma, making it the primary cause of hepatic failure in Western societies.³ Although there are no FDA-approved medications for NAFLD, lifestyle modifications may help and experimental drugs for NASH are currently being studied, targeting different areas in the pathway of liver fat accumulation, inflammation, and scar tissue formation.⁴ One such experimental drug, Pegbelfermin (PGBF) has recently been studied in a trial called FALCON 1. PGBF (polyethylene glycol-conjugated) is a recombinant homologue of human fibroblast growth factor 21 (FGF21), demonstrating the potential for improving NASH-related outcomes. While its exact mechanism of action is unknown, preclinical studies suggest that it binds to FGFR1/KLB complex in fat tissue, resulting in increased secretion of adiponectin and potentially affecting other metabolic pathways. This results in decreased liver fat content, plasma PRO-C3 (type III collagen propeptide) levels, plasma triglyceride levels, and increased blood HDL-cholesterol levels.⁵

Pegbelfermin was examined as a treatment for patients with NASH and stage 3 fibrosis in the double-blind, randomised, placebo-controlled FALCON 1 trial. This subsequent analysis aims to evaluate the impact of PGBF on NASH biomarkers, assess the correlation between

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invasive and non-invasive tests, and evaluate its response to the main objective at 24 week. The study found that PGBF treatment for 24 weeks in NASH patients with stage 3 fibrosis improved fibrosis without worsening NASH or vice versa (24%-31% across the 10 mg, 20 mg, and 40 mg dosage arms) against placebo (14%), but failed to achieve the main goal due to the absence of dose-dependent response rate difference. The treatment also improved disease-related biomarkers and non-invasive measurements of steatosis, inflammation, and fibrosis. Regardless of this, the investigational post hoc study had limitations, but the most important one mentioned was that the results were applied only to NASH patients and stage 3 fibrosis¹. Thus, we must assess the advantages of using pegbelfermin in every potential stage of fibrosis through further evaluation.

Pegbelfermin is a promising treatment for NASH, demonstrating impressive results in early clinical trials with the potential to improve liver fibrosis and metabolic parameters. However, rigorous clinical trials are necessary and a prompt meta-analysis is needed for more precise conclusions. If successful, Pegbelfermin could be a game-changer, transforming the lives of countless NASH patients, making it a beacon of hope for those suffering from this debilitating condition.

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