Medical Information Response

Investigational Development of Semaglutide for Non-Alcoholic Steatohepatitis (NASH)

Semaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist that is currently being investigated in a clinical development program for its effect in NASH. It is important to note that semaglutide has not been approved for the treatment of NASH in the United States. Ozempic® (semaglutide) injection, Rybelsus® (semaglutide) tablets, and Wegovy™ (semaglutide) injection, are **not** indicated for the treatment of NASH.[1-3]

Semaglutide NASH Clinical Development Program

Semaglutide is a long-acting GLP-1 receptor agonist that is currently being investigated in a clinical development program for its effect in NASH. A description of the semaglutide NASH clinical development program can be found in **Table 1**.

To date, Novo Nordisk has completed the Phase 1 non-alcoholic fatty liver disease (NAFLD) magnetic resonance (MR) study and a Phase 2 dose finding study.[4,5] The Phase 2 fibrosis stage 4 with compensated cirrhosis (F4c) study and Phase 3 ESSENCE studies are ongoing, and results are not yet available. For more information, please visit www.clinicaltrials.gov.

Table 1. Semaglutide NASH Clinical Development Plan

Phase	NCT Identifier	Brief Description
Phase 1	NCT03357380	**NAFLD MR Study[a]:** Clinical pharmacology study investigating the effect of once-daily subcutaneous semaglutide on liver fibrosis in patients with NAFLD.[4]
Phase 2	NCT02970942	**Dose Finding Study[a]**: Investigating the safety and efficacy of three doses of once-daily subcutaneous semaglutide in patients with NASH.[5]
	NCT03987451	**F4 Compensated Cirrhosis Study[b]**: Investigating the safety and efficacy of subcutaneous semaglutide once-weekly in patients with NASH and F4c.
Phase 3	NCT04822181	**ESSENCE[c]:** Investigating the safety and efficacy of subcutaneous semaglutide once-weekly in patients with non-cirrhotic NASH.

a. Study duration of 72 weeks
b. Study duration of 48 weeks
c. Study is expected to last approximately 5 years
Abbreviations: NAFLD: non-alcoholic fatty liver disease; MR: magnetic resonance; NASH: non-alcoholic steatohepatitis; F: fibrosis stage; F4c: fibrosis stage 4 with compensated cirrhosis

Clinical Collaboration with Gilead Sciences, Inc.

Novo Nordisk and Gilead Sciences, Inc. have jointly completed a 24-week Phase 2a proof-of-concept trial, evaluating subcutaneous semaglutide 2.4 mg once-weekly as a monotherapy or in combination with Gilead's investigational acetyl-CoA carboxylase (ACC) inhibitor oral firsocostat once-daily and/or investigational farnesoid X receptor (FXR) agonist oral cilofexor once-daily in patients with NASH.[6] A Phase 2b trial further investigating the safety and efficacy of this combination is planned.[7]

Prescribing Information for Ozempic®, Rybelsus®, and Wegovy™[1-3]

- Ozempic® is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes and to reduce the risk of major adverse cardiovascular (CV) events (MACE) in adults with type 2 diabetes and established CV disease.[1]
- Rybelsus® is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[2]
- Wegovy™ is a GLP-1 receptor agonist indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:
    - 30 kg/m^2 or greater (obesity) or
    - 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, T2D, or dyslipidemia)[3]
- Ozempic®, Rybelsus®, and Wegovy™ are **not** indicated for the treatment of NASH.[1-3]

If you would like to receive a copy of any of the published references cited in the response, please contact Novo Nordisk Medical Information at (800) 727-6500 or NNMedicalInformation@novonordisk.com.

References

1. Ozempic® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Rybelsus® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
3. Wegovy™ Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
4. Flint A, Andersen G, Hockings P, et al. Semaglutide treatment in subjects with NAFLD: effects assessed by magnetic resonance elastography and magnetic resonance imaging proton density fat fraction. in Oral Presentation 1698 presented at: The Liver Meeting Digital Experience 2020; Nov 13-16, 2020. 2020.
5. Newsome PN, Buchholtz K, Cusi K, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med.* 2020 Link to Access the Full Text
6. Alkhouri N, Herring R, Kabler H, et al. Safety and Efficacy of Combination Therapies Including Semaglutide, Cilofexor, and Firsocostat in Patients with NASH. Oral Presentation LO2 presented at: The Liver Meeting Digital Experience 2020; Nov 13-16, 2020. . 2020.
7. Press Release: Gilead Sciences and Novo Nordisk expand NASH clinical collaboration. 2021. https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=51246