

GLP-1 RA BACKGROUNDER AND INVESTIGATIONAL DATA FOR NASH/MASH



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RATIONALE FOR GLP-1 RAs FOR NASH/MASH

Rationale for GLP-1 RAs for NASH/MASH

Learning Objectives

Upon completion of this chapter, you should be able to:

- Understand the rationale for studying glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for nonalcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (NASH/MASH)
- Understand the mechanism of action of the GLP-1 RA class
- Recall the Food and Drug Administration (FDA)-approved indications for semaglutide
- Understand the current guidelines on the use of GLP-1 RAs for NASH/MASH.



QUICK FACT: Nomenclature Update

Note there has been a recent nomenclature shift initiative in this field, resulting in nonalcoholic steatohepatitis (NASH) now being referred to as metabolic dysfunction-associated steatohepatitis (or MASH), nonalcoholic fatty liver (NAFL) as metabolic dysfunction-associated steatotic liver (or MASL), and nonalcoholic fatty liver disease (NAFLD) as metabolic dysfunction-associated steatotic liver disease (or MASLD). The terms were changed in large part to emphasize the causative factors for the disease.

Rationale for GLP-1 RAs in NASH/MASH

Nonalcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease (NAFLD/MASLD) and its most aggressive form, nonalcoholic **steatohepatitis**/metabolic dysfunction-associated steatohepatitis (NASH/MASH), are highly prevalent in patients with obesity and type 2 diabetes. The **glucagon**-like peptide-1 receptor **agonists** (GLP-1 RAs), which are approved by the Food and Drug Administration (FDA) to treat obesity and diabetes, have shown beneficial metabolic effects including weight loss, improved glycemic control, and reduced risk of cardiorenal complications, as well as improvements in liver enzymes and inflammatory markers. The finding that obesity and diabetes are prominent drivers of NAFLD/MASLD development and progression suggests that GLP-1 RAs may have a role in NASH/MASH treatment. As a result, GLP-1 RAs are now under investigation for the treatment of NASH/MASH.

steatohepatitis

deposition of fat in the liver

glucagon

hormone secreted by the pancreas that increases blood glucose by stimulating the liver to convert stored glycogen into glucose; it opposes the action of insulin

agonist

drug that binds to the receptor and stimulates its function

incretin

one of several peptide hormones produced in the small intestine or colon in response to glucose; it stimulates secretion of insulin and inhibits secretion of glucagon

Rationale for GLP-1 RAs for NASH/MASH

Mechanism of Action of GLP-1 RAs

Glucagon-like peptide-1 (GLP-1) is an intestinal **incretin** hormone that stimulates insulin release in response to an oral glucose load; this process is attenuated or absent in patients with type 2 diabetes. GLP-1 RAs have several effects on the body (**Figure 1-1**):

- Increase the release of insulin
- Decrease glucagon secretion
- Decrease gastric emptying
- Reduce appetite, which helps patients lose weight
- Have favorable effects on lipid and cardiac parameters

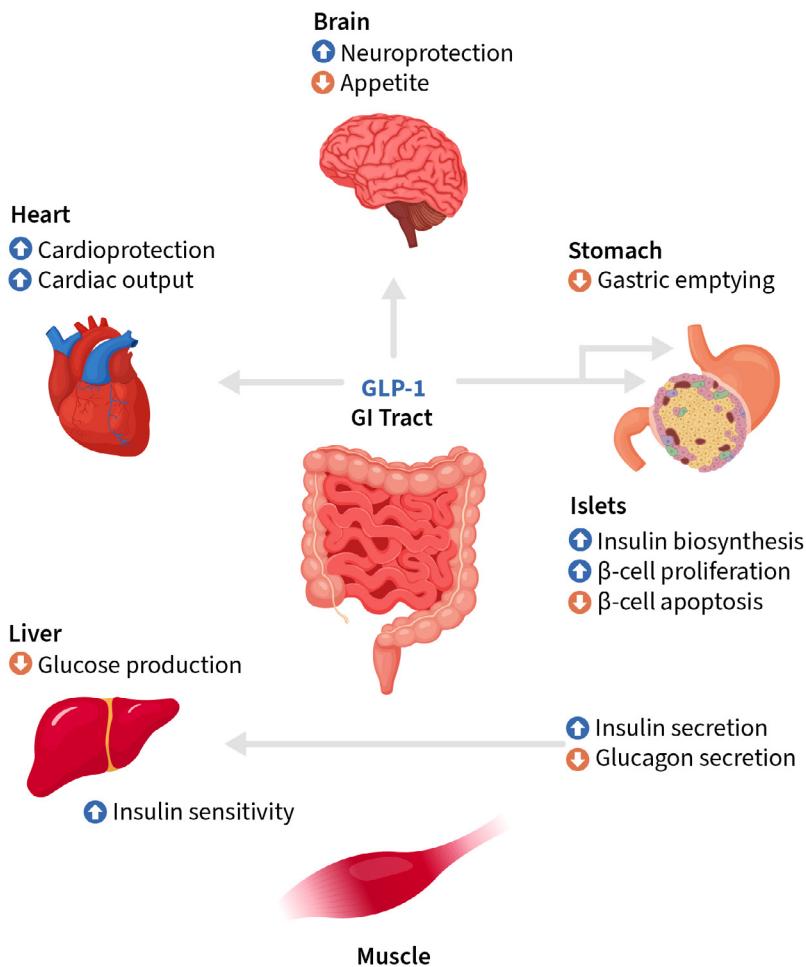


Figure 1-1: Mechanism of Action of GLP-1 RA

Rationale for GLP-1 RAs for NASH/MASH

FDA-Approved GLP-1 RA Drugs

As a class, GLP-1 RAs (eg, semaglutide, liraglutide, exenatide, dulaglutide) are generally used to treat type 2 diabetes; some are also approved for obesity and for decreasing cardiovascular risk in specific patient populations. For example, semaglutide is available in 3 formulations (Ozempic® and Rybelsus® for type 2 diabetes and Wegovy® for weight loss) and liraglutide is marketed in 2 formulations (Victoza® for type 2 diabetes and Saxenda® for weight loss). The GLP-1 RAs are typically injectable medications that exert their effects via the glucose-insulin interaction; all drugs in this class are administered by subcutaneous injection except for Rybelsus®, which is taken in an oral tablet.

Semaglutide from Novo Nordisk is a GLP-1 RA that improves glycemic control and induces weight loss; it is FDA-approved for the treatment of type 2 diabetes in both an injectable formulation (Ozempic®) and an oral tablet (Rybelsus®). Semaglutide is the only GLP-1 RA drug currently in a phase 3 trial for treatment of NASH/MASH. The following chapter will outline the phase 3 trial data on semaglutide.

Table 1-1 lists the commonly available semaglutide GLP-1 RAs and their indications.

Rationale for GLP-1 RAs for NASH/MASH

Table 1-1. Commercially Available Semaglutide GLP-1 RAs FDA-Approved for Type 2 Diabetes, Obesity, and Cardiovascular Disease

Generic name	Semaglutide		
Proprietary name	Ozempic®	Wegovy®	Rybelsus®
Company	Novo Nordisk	Novo Nordisk	Novo Nordisk
Dose route	Subcutaneous (injection); titrated upward	Subcutaneous (injection); titrated upward	Oral tablet
Dosage	<p>Initial dose: 0.25 mg SC once weekly for 4 weeks</p> <p>Escalation: after 4 weeks, increase to 0.5 mg once weekly, after another 4 weeks if additional glycemic control is needed, increase to 1 mg once weekly, then 2 mg once weekly</p> <p>Maximum dose: 2 mg once weekly</p>	<p>Initial dose: 0.25 mg SC once weekly for 4 weeks</p> <p>Escalation: gradually increase to minimize gastrointestinal adverse reactions: weeks 5–8, 0.5 mg; weeks 9–12, 1 mg; weeks 13–16, 1.7 mg</p> <p>Maintenance dose: 2.4 mg (recommended) or 1.7 mg once weekly</p>	<p>Initial dose: 3 mg once daily for 30 days</p> <p>Escalation: after 30 days, increase the dosage to 7 mg once daily; if additional glycemic control is needed after at least 30 days on 7 mg, dosage may be increased to 14 mg once daily</p>
Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; also to reduce risk of MACE	Adjunct to diet and exercise to reduce risk of MACE; also to reduce excess body weight in adults and pediatric patients (age \geq 12 years) with obesity	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

BMI, body mass index; CVD, cardiovascular disease; FDA, Food and Drug Administration; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events (defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)

Rationale for GLP-1 RAs for NASH/MASH

Investigational Use of GLP-1 RAs in NASH/MASH

Clinical guidelines including those from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver, European Association for the Study of Diabetes, and European Association for the Study of Obesity (EASL-EASD-EASO) support the use of GLP-1 RAs as **concomitant** therapy for individuals with diabetes or obesity who also have NASH/MASH. This recommendation reflects the ability of GLP-1-RAs to achieve glycemic control and weight loss and reduce the risk of cardiorenal complications; data also suggest reductions in steatohepatitis without worsening of **fibrosis**. It is important to note that GLP-1 RAs are not liver-directed therapies and are currently not FDA-approved for the treatment of NAFLD/MASLD or NASH/MASH.

concomitant

taking place at the same time as something else

fibrosis

repair and replacement of inflamed cells by connective tissue cells (fibroblasts), eventually resulting in replacement of normal organ tissue by scar tissue

Rationale for GLP-1 RAs for NASH/MASH

Key Concepts

- NAFLD/MASLD and its most aggressive form, NASH/MASH, are highly prevalent in patients with obesity and type 2 diabetes.
- Medications that are FDA-approved to treat obesity and diabetes, including GLP-1 RAs, are under investigation for the treatment of NASH/MASH.
- GLP-1 is an intestinal incretin hormone that stimulates insulin release in response to an oral glucose load; this process is attenuated or absent in patients with type 2 diabetes.
- GLP-1 RAs increase insulin release, decrease glucagon secretion, decrease gastric emptying, and reduce appetite, which helps patients lose weight; they have also shown favorable effects on lipid and cardiac parameters.
- The GLP-1 RA class (eg, semaglutide, liraglutide, exenatide, dulaglutide) is generally used to treat type 2 diabetes; some are also FDA-approved for obesity and for decreasing cardiovascular risk in appropriate patients.
- Most commercially available GLP-1 RAs are administered by subcutaneous injection and are titrated upward from the initial dose.
- GLP-1 RAs are recommended as concomitant therapy for individuals with diabetes or obesity who also have NASH/MASH.
- GLP-1 RAs are not liver-directed therapies and are not FDA-approved for the treatment of NAFLD/MASLD or NASH/MASH.
- Semaglutide from Novo Nordisk is FDA-approved for the treatment of type 2 diabetes in both an injectable formulation (Ozempic®) and an oral tablet (Rybelsus®).
- Semaglutide is the only drug candidate of the GLP-1 RA class currently in a phase 3 trial for treatment of NASH/MASH.

Rationale for GLP-1 RAs for NASH/MASH

Check Your Progress

- 1. What is the rationale for studying GLP-1 RAs for NASH/MASH?**
 - A. GLP-1 RAs are already used to treat several other kinds of liver diseases
 - B. Obesity and diabetes are prominent drivers of NAFLD/MASLD development and progression
 - C. The drug class is already recommended for NASH/MASH in clinical guidelines
 - D. There are no other FDA-approved therapies for NASH/MASH

- 2. Which semaglutide drugs are FDA-approved for type 2 diabetes?**
 - A. Saxenda® and Ozempic®
 - B. Ozempic® and Rybelsus®
 - C. Rybelsus® and Saxenda®
 - D. Wegovy® and Victoza®

- 3. Which of the following explains the mechanism of action of the GLP-1 RAs?**
 - A. Decrease insulin release and glucagon secretion
 - B. Decrease insulin release, increase glucagon secretion
 - C. Increase insulin release and glucagon secretion
 - D. Increase insulin release, decrease glucagon secretion

- 4. What are the current guidelines for the use of GLP-1 RAs for NASH/MASH?**
 - A. Recommended as FDA-approved liver-directed therapy for all patients with NASH/MASH
 - B. Recommended for patients with diabetes or obesity plus cirrhosis of the liver
 - C. Recommended as concomitant therapy for patients with diabetes or obesity who also have NASH/MASH
 - D. Recommended as second-line therapy after a trial of other medications for NASH/MASH

VIEW CORRECT ANSWERS

Rationale for GLP-1 RAs for NASH/MASH

Answers

- 1. What is the rationale for studying GLP-1 RAs for NASH/MASH?**
 - A. GLP-1 RAs are already used to treat several other kinds of liver diseases
 - B. Obesity and diabetes are prominent drivers of NAFLD/MASLD development and progression**
 - C. The drug class is already recommended for NASH/MASH in clinical guidelines
 - D. There are no other FDA-approved therapies for NASH/MASH
- 2. Which semaglutide drugs are FDA-approved for type 2 diabetes?**
 - A. Saxenda® and Ozempic®
 - B. Ozempic® and Rybelsus®**
 - C. Rybelsus® and Saxenda®
 - D. Wegovy® and Victoza®
- 3. Which of the following explains the mechanism of action of the GLP-1 RAs?**
 - A. Decrease insulin release and glucagon secretion
 - B. Decrease insulin release, increase glucagon secretion
 - C. Increase insulin release and glucagon secretion
 - D. Increase insulin release, decrease glucagon secretion**
- 4. What are the current guidelines for the use of GLP-1 RAs for NASH/MASH?**
 - A. Recommended as FDA-approved liver-directed therapy for all patients with NASH/MASH
 - B. Recommended for patients with diabetes or obesity plus cirrhosis of the liver
 - C. Recommended as concomitant therapy for patients with diabetes or obesity who also have NASH/MASH**
 - D. Recommended as second-line therapy after a trial of other medications for NASH/MASH

STUDY DATA ON SEMAGLUTIDE FOR NASH/MASH: ESSENCE TRIAL

Learning Objectives

Upon completion of this chapter, you should be able to:

- Understand the study design of the phase 3 ESSENCE Trial for the use of semaglutide in the treatment of NASH/MASH
- Recall the interim study results of the ESSENCE Trial

Study Methods

ESSENCE is a 5-year, phase 3 trial of semaglutide injection in patients with NASH/MASH designed to evaluate resolution of steatohepatitis, improvement of liver fibrosis, and cirrhosis-free survival (NCT04822181). Sponsored by Novo Nordisk A/S, this study is titled “Research Study on Whether Semaglutide Works in People With Nonalcoholic Steatohepatitis (NASH) (ESSENCE).”

Inclusion/Exclusion Criteria

Inclusion Criteria

- Age ≥18 years
- Histologic evidence of NASH/MASH based on a central pathologist evaluation of the baseline liver biopsy; the baseline biopsy can be obtained within 180 days before the screening visit
- Histologic evidence of fibrosis stage 2 or 3 based on a central pathologist evaluation of the baseline liver biopsy
- Histologic Nonalcoholic Fatty Liver Disease Activity Score (NAS) ≥4 with a score of ≥1 in **steatosis**, lobular inflammation, and hepatocyte **ballooning** based on a central pathologist evaluation of the baseline liver biopsy



QUICK FACT: NAS

The Nonalcoholic Fatty Liver Disease Activity Score (NAS) is a measure of disease activity including steatosis (score 0–3), lobular inflammation (score 0–3), and hepatocellular ballooning (score 0–2). The scores are added and higher scores indicate greater disease severity, with a score of >5 indicating NASH/MASH.

steatosis

abnormal accumulation of fat inside cells or organs, common in obesity and type 2 diabetes

ballooning

swelling of cells typically seen in microscopic examination; ballooning of hepatocytes (liver cells) denotes cell degeneration characterized by swelling and enlargement as found in steatohepatitis due to NASH/MASH

ascites

accumulation of fluid in the peritoneal cavity (abdomen), can be due to several causes including obstructed blood flow to the liver and cirrhosis

variceal

pertaining to a varix, a twisting dilatation of a blood vessel (vein)

hepatic encephalopathy

brain dysfunction in patients with chronic liver disease and portal hypertension due to failure of the liver to detoxify the blood; may result in cognitive impairment and coma

pioglitazone

oral drug in the thiazolidinedione class used as an adjunct to diet and exercise for management of type 2 diabetes

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Exclusion Criteria

- Documented causes of chronic liver disease other than NAFLD/MASLD
- Positive hepatitis B surface antigen (HBsAg), positive anti-HIV, positive hepatitis C virus (HCV) RNA at screening, or any known HBsAg or HCV RNA within 2 years of screening
- Presence or history of **ascites**, **variceal** bleeding, **hepatic encephalopathy**, spontaneous bacterial peritonitis, or liver transplantation at randomization
- Excessive consumption of alcohol (>20 g/day for women or ≥30 g/day for men) or alcohol dependence
- Treatment with vitamin E (at doses ≥800 IU/day) or **pioglitazone** or medications approved for treatment of NASH/MASH not at a stable dose in the period from 90 days before the screening visit
- Treatment with GLP-1 RAs within 90 days before the screening visit
- Treatment with glucose-lowering agent(s) (other than GLP-1 RAs), lipid-lowering medication, or weight loss medication not stable from 90 days before the screening visit

Study Design

ESSENCE is a randomized, double-blind, parallel-group trial in 2 parts; Part 1 is double-masked while in Part 2, the sponsor will be unblinded. Patients are randomized 2:1 to receive semaglutide 2.4 mg or placebo added to standard care for 240 weeks.

Study Dosing

- Treatment group: semaglutide once weekly by subcutaneous injection, with dose escalation every 4 weeks (to 0.25 mg, 0.5 mg, and 1.0 mg, at Weeks 4, 8, and 12, respectively, and to 1.7 mg at Week 16) until reaching the target dose of 2.4 mg semaglutide* + standard of care
- Placebo group: placebo + standard of care administered once weekly by subcutaneous injection

*One or more dose steps can be prolonged, or the dose can be lowered if the actual dose is not tolerated

Study Endpoints

Primary Outcome Measures

- Resolution of steatohepatitis with no worsening of liver fibrosis (Yes/No) from randomization (week 0) to week 72 (in study Part 1)
- Improvement in liver fibrosis with no worsening of steatohepatitis (Yes/No) from randomization to week 72 (in study Part 1)
- Cirrhosis-free survival from randomization to week 240 (in study Part 2)

Secondary Outcome Measures

A wide variety of secondary endpoints are planned for the ESSENCE Trial. **Table 1-2** presents the secondary outcome measures.

**GLP-1 RA
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SF-36

Medical Outcomes Study 36-Item Short-Form Health Survey; tool that measures perceived health status in 8 domains that include responses on physical, social, pain, mental health, emotional, vitality, and general health

transient elastography

noninvasive measure of liver stiffness, measured by a device marketed as FibroScan®; elasticity of the liver is closely associated with the degree of fibrosis

controlled attenuation parameter (CAP)

ultrasound-based noninvasive tool used to assess liver fat

C-reactive protein (CRP)

protein that binds with phospholipids on foreign substances and activates the immune system; stimulates the production of inflammatory molecules such as cytokines; elevated blood levels of CRP are found in many infectious and inflammatory diseases

glycated hemoglobin (HbA1c)

long-term measure of blood glucose control

lipoprotein

any of the conjugated chemicals in the bloodstream consisting of simple proteins bound to fat; cholesterol, phospholipids, and triglycerides are all fatty components of lipoproteins; lipoproteins are classified by their degree of density

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Table 1-2. Secondary Endpoints in the ESSENCE Trial

Measure	Endpoint*
Prespecified secondary endpoints	
Change in body weight	Week 72 and 240
Resolution of steatohepatitis and improvement in liver fibrosis	Week 72
Changes in SF-36 Physical Component Summary, Mental Component Summary, and Bodily Pain	Week 72 and 240
Other secondary endpoints	
Improvement in steatohepatitis with ≥2-point reduction in NAS and no worsening of fibrosis	Week 72
Change in histology-assessed liver collagen proportionate area	Week 72
Worsening in steatohepatitis	Week 72
Improvements in histology-assessed ballooning, inflammation, and steatosis	Week 72
NASH/MASH resolution (ballooning of 0, inflammation of 0–1) and ≥2-point NAS reduction with no worsening of fibrosis	Week 72
Progression of liver fibrosis in patients with or without F2 at baseline	Week 72
Resolution of steatohepatitis and no worsening of liver fibrosis	Week 240
Improvement in liver fibrosis and no worsening of steatohepatitis	Week 240
Changes in liver stiffness by transient elastography (FibroScan®)	Week 72 and 240
Change in CAP values by transient elastography (FibroScan®)	Week 72 and 240
Changes in liver enzymes (ALT and AST)	Week 72 and 240
Change in inflammation assessed by high-sensitivity CRP	Week 72 and 240
Changes in HbA1c , triglycerides, and free fatty acids	Week 72 and 240
Changes in lipoproteins (LDL and HDL)	Week 72 and 240
Time to first MACE (composite endpoint)	Week 240
Major cardio-hepatic event-free survival	Week 240

*All measures are compared to week 0 (randomization).

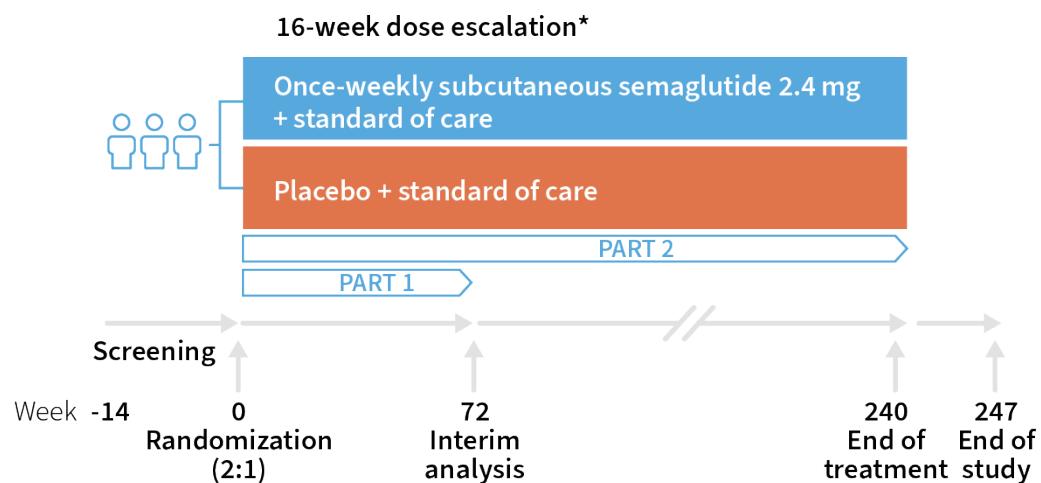
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, Controlled Attenuation Parameter; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; NAS, Nonalcoholic Fatty Liver Disease Activity Score; NASH, nonalcoholic steatohepatitis; MASH, metabolic syndrome-associated steatohepatitis; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey.

Interim Study Results

Preliminary reports on ESSENCE were presented at the 2024 AASLD meeting.

Study Design and Patient Characteristics

A total of 800 participants (out of a planned sample of 1200) were randomized 2:1 to receive semaglutide 2.4 mg or placebo once weekly, added to standard care, for 240 weeks. The study design is presented in **Figure 1-2**.



*Uptitration every 4 weeks for a total of 16 weeks. Initial dose is 0.25 mg SC once weekly for weeks 1-4. Dosage is gradually increased at weeks 5-8 to 0.5 mg; weeks 9-12, 1.0 mg; and weeks 13-16, 1.7 mg. One or more dose steps can be prolonged, or the dose can be lowered if the actual dose is not tolerated. Maintenance dose is 2.4 mg (recommended) or 1.7 mg once weekly. If the target dose of once-weekly SC semaglutide 2.4 mg is not tolerated, patients may stay at a lower dose level.

Figure 1-2: ESSENCE Study Design

Among the 800 participants, mean age was 56 years, 57% were female, mean BMI was 34.6 kg/m², and 56% had type 2 diabetes; 250 patients had F2 fibrosis and 550 had F3 fibrosis. **Table 1-3** presents the patient characteristics.

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Table 1-3. Preliminary Patient Characteristics

Characteristic	Semaglutide 2.4 mg (n=534)	Placebo (n=266)
Age, years, mean (SD)	56.3 (11.4)	55.4 (12.0)
Sex, female, n (%)	313 (58.6)	144 (54.1)
T2D, n (%)	296 (55.4)	151 (56.8)
HbA1c, %, mean (SD)	6.6 (1.1)	6.4 (1.0)
HbA1c, %, mean (SD), with T2D	7.2 (1.1)	6.9 (1.0)
BMI, kg/m ² , mean (SD)	34.3 (7.2)	35.0 (7.1)
ALT, U/L, mean (SD)	67.8 (42.3)	67.9 (44.7)
Fibrosis stage 3, n (%)	365 (68.4)	185 (69.5)
Liver stiffness by VCTE, kPa, mean (SD)	12.8 (6.6)	12.9 (7.6)
ELF™ score, mean (SD)	10.0 (0.9)	10.0 (1.0)
PRO-C3, ng/mL, mean (SD)	52.9 (24.9)	52.9 (28.1)

ALT, alanine aminotransferase; BMI, body mass index; ELF™, Enhanced Liver Fibrosis; HbA1c, glycated hemoglobin; PRO-C3, N-terminal type III collagen; SD, standard deviation; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography

More than 99% of patients had ≥1 of the NAFLD/MASLD cardiometabolic criteria and 43% had 5 NAFLD/MASLD cardiometabolic criteria (defined as elevated BMI or waist circumference, elevated serum glucose or HbA1c, type 2 diabetes, high blood pressure, elevated triglycerides, or hyperlipidemia) (**Figure 1-3**). More than 91% of patients had ≥1 positive noninvasive test (NIT), while more than half of patients had clinically significant fibrosis (F2–F3) and liver stiffness. These clinical findings indicate a high burden of NAFLD/MASLD.

Clinical characteristics

>99%

of participants
met ≥1 MASLD
cardiometabolic criteria

43.3%

of participants
met 5 MASLD
cardiometabolic criteria

NITs

>91%

of participants had
≥1 positive NIT

35.4%

of participants were
identified by 2 NITs

63.3%

of participants had
 $\text{FIB-4} \geq 1.3$

55.5%

of participants had
 $\text{ELF} \geq 9.8$

64.0%

of participants had liver
stiffness $\text{VCTE} > 8 \text{ kPa}$

ELF™, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4 index; MASLD, metabolic dysfunction-associated steatotic liver disease;
NIT, noninvasive test; VCTE, vibration-controlled transient elastography

Figure 1-3: Characteristics of the ESSENCE Patients

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Efficacy and Safety

Primary Endpoints

An interim analysis was conducted at week 72 to evaluate the co-primary endpoints of resolution of steatohepatitis with no worsening of liver fibrosis and improvement in liver fibrosis with no worsening of steatohepatitis. At the interim analysis, 534 patients were taking semaglutide and 266 were taking placebo.

A significantly greater percentage of patients receiving semaglutide versus placebo had resolution of steatohepatitis with no worsening of liver fibrosis (62.9% versus 34.1%), as well as improvement in liver fibrosis with no worsening of steatohepatitis (37.0% versus 22.5%) (**Table 1-4**).

Table 1-4. Preliminary Results of ESSENCE

Outcome	Semaglutide	Placebo	EDP (95% CI)
Resolution of steatohepatitis with no worsening of liver fibrosis	62.9%	34.1%	28.9% (21.3–36.5) <i>P</i> <0.0001
Improvement in liver fibrosis with no worsening of steatohepatitis	37.0%	22.5%	14.4% (7.5–21.4) <i>P</i> <0.0001

CI, confidence interval; EDP, estimated difference in responder proportions.

Secondary Endpoints

Significantly more semaglutide patients achieved the confirmatory secondary endpoint of resolution of steatohepatitis and improvement in liver fibrosis (32.8% versus 16.2%; **Table 1-5**). Improvements were also observed in body weight, liver enzymes, noninvasive markers of liver fibrosis, and cardiometabolic parameters after treatment with semaglutide (**Table 1-5**).

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Table 1-5. Confirmatory Secondary Endpoints in ESSENCE*

Measure	Estimated difference, semaglutide vs placebo, % (95% CI)	P value
Confirmatory secondary endpoints		
Resolution of steatohepatitis and improvement in liver fibrosis	32.8%	16.2%
Body weight, %	-8.5% (-9.6 to -7.4)	P<0.0001
SF-36, units	1.3 (0.0 to 2.7)	P=0.0488
Other secondary endpoints		
Liver enzymes		
ALT, U/L	0.6 (0.6 to 0.7)	P<0.0001
AST, U/L	0.7 (0.6 to 0.7)	P<0.0001
GGT, U/L	0.6 (0.6 to 0.7)	P<0.0001
Noninvasive fibrosis tests		
VCTE, KPa	0.8 (0.7 to 0.9)	P<0.0001
ELF™ score	-0.6 (-0.7 to -0.5)	P<0.0001
Pro-C3, ng/mL	0.8 (0.8 to 0.9)	P<0.0001
Cardiometabolic risk parameters		
SBP, mmHg	-4.0 (-5.9 to -2.1)	P<0.001
DBP, mmHg	-2.1 (-3.4 to -0.9)	P=0.001
HbA1c (without T2D), %	-0.5 (-0.6 to -0.4)	P<0.001
HbA1c (with T2D), %	-1.1 (-1.3 to -0.9)	P<0.001
hsCRP, mg/L	0.6 (0.5 to 0.7)	P<0.001
Total cholesterol, mg/dL	1.0 (0.9 to 1.0)	P=0.04
Triglycerides, mg/dL	0.8 (0.8 to 0.9)	P<0.001
LDL-C, mg/dL	1.0 (0.9 to 1.0)	P=0.37
HDL-C, mg/dL	1.1 (1.0 to 1.1)	P<0.001

*These results were presented at AASLD, November 2024.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DBP, diastolic blood pressure; ELF™, Enhanced Liver Fibrosis; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MOS, Medical Outcomes Study 36-Item Short Form Survey; Pro-C3, N-terminal type III collagen; SBP, systolic blood pressure; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

Safety

Adverse events (AEs) occurred in 86% of patients with semaglutide and 80% with placebo. Serious AEs (13.4% for both arms), fatal AEs (0.4% vs 1.5%), and AEs leading to trial discontinuation (2.6% vs 3.3%) occurred with similar frequency with semaglutide versus placebo, respectively. The most common AEs with semaglutide were nausea (36%), diarrhea (27%), and constipation (22%).

Preliminary Conclusions

The interim results of study Part 1 indicate that semaglutide 2.4 mg added to standard care in patients with NASH/MASH and moderate to advanced liver fibrosis achieved both of the primary study endpoints in a statistically significant and superior manner compared to placebo at 72 weeks.

Semaglutide is the first GLP-1 RA to demonstrate efficacy in a phase 3 trial of patients with NASH/MASH, with superiority confirmed for semaglutide versus placebo with respect to:

- NASH/MASH resolution with no worsening of fibrosis
- Improvement in liver fibrosis with no worsening of steatohepatitis
- Resolution of steatohepatitis with improvement in liver fibrosis

The benefit of semaglutide versus placebo was additionally supported by statistically significant improvements in all prespecified fibrosis NITs. The ESSENCE Trial confirms the benefits of semaglutide by improving multiple cardiometabolic characteristics, including weight management, HbA1c, hsCRP, and lipid profile versus placebo. Semaglutide demonstrated a safety profile consistent with previous phase 2 NASH/MASH trials and the large body of evidence for semaglutide in other indications.

Future Actions

Novo Nordisk expects to file for regulatory approvals in the United States and Europe during the first half of 2025. Full results from the ESSENCE Trial will be reported at a scientific conference in 2024, and Part 2 trial results (liver-related clinical events at week 240) are expected in 2029. Regulatory authorities still need to fully assess the risk/benefit profile of semaglutide for the treatment of patients with NASH/MASH with F2/F3 fibrosis. As well, patient compliance with treatment is important for an urgent condition like NASH/MASH with F2/F3 fibrosis, and compliance can be difficult with long-term injectable medications such as GLP-1 RAs. Regulatory authorities still need to fully assess the persistency of semaglutide 2.4 mg in this patient population.

Key Concepts

- ESSENCE is a randomized phase 3 trial of semaglutide in patients with NASH/MASH designed to evaluate resolution of steatohepatitis, improvement of liver fibrosis, and cirrhosis-free survival.
- Inclusion criteria are adults with histologic evidence of NASH/MASH and F2–F3 fibrosis in liver biopsy, plus NAS ≥4 with evidence of steatosis, lobular inflammation, and hepatocyte ballooning.
- Patients are randomized 2:1 to receive semaglutide 2.4 mg or placebo once weekly by subcutaneous injection, added to standard care for 240 weeks.
- Primary outcome measures of ESSENCE are:
 - Resolution of steatohepatitis with no worsening of liver fibrosis at week 72
 - Improvement in liver fibrosis with no worsening of steatohepatitis at week 72
 - Cirrhosis-free survival at week 240
- Interim reports of the ESSENCE Trial showed that >99% of patients had ≥1 NAFLD/ MASLD cardiometabolic criteria and 91% had ≥1 positive NIT, as well as other clinical findings indicating a high burden of NAFLD/MASLD.
- Interim results of the ESSENCE Trial at week 72 showed a significantly greater percentage of patients receiving semaglutide achieved resolution of steatohepatitis with no worsening of liver fibrosis and improvement in liver fibrosis with no worsening of steatohepatitis (co-primary endpoints), as well as the combination of both endpoints compared to patients taking placebo.
 - Improvement in liver fibrosis with no worsening of steatohepatitis: 37.0% versus 22.5% for semaglutide versus placebo
 - Resolution of steatohepatitis with no worsening of liver fibrosis: 62.9% versus 34.1% for semaglutide versus placebo
- Secondary endpoints also showed significant improvement:
 - Both primary endpoints combined: 32.8% versus 16.2% for semaglutide versus placebo
 - Statistically significant improvements in body weight, liver enzymes, noninvasive markers of liver fibrosis, and cardiometabolic parameters

**Study Data on Semaglutide for NASH/MASH:
ESSENCE Trial**

- AEs occurred in 86% of patients with semaglutide and 80% with placebo.
 - Serious AEs (13.4% for both arms), fatal AEs (0.4% vs 1.5%), and AEs leading to trial discontinuation (2.6% vs 3.3%) occurred with similar frequency with semaglutide vs placebo, respectively.
 - The most common AEs with semaglutide were nausea (36%), diarrhea (27%), and constipation (22%).
- Semaglutide is the first GLP-1 RA to demonstrate efficacy in a phase 3 trial of patients with NASH/MASH, with superiority confirmed versus placebo with respect to:
 - NASH/MASH resolution with no worsening of fibrosis
 - Improvement in liver fibrosis with no worsening of steatohepatitis
 - Resolution of steatohepatitis with improvement in liver fibrosis

Check Your Progress

- 1. Which of the following was an inclusion criterion in the phase 3 ESSENCE Trial?**
 - A. Absence of fibrosis
 - B. Evidence of cirrhosis
 - C. NASH/MASH on liver biopsy
 - D. NAS of <3
- 2. What was the treatment group in the placebo-controlled ESSENCE Trial?**
 - A. Oral semaglutide 2.4 mg, once weekly
 - B. Semaglutide 2.4 mg by subcutaneous injection, once weekly
 - C. Oral semaglutide 4.8 mg, twice weekly
 - D. Semaglutide 2.4 mg by subcutaneous injection, once a month
- 3. Which of the following was a primary endpoint in the ESSENCE Trial?**
 - A. Blood glucose control and weight loss at week 72
 - B. Cirrhosis-free survival at week 72
 - C. Resolution of fibrosis and resolution of steatohepatitis at week 240
 - D. Resolution of steatohepatitis with no worsening of fibrosis at week 72
- 4. True or false? Interim results of the ESSENCE Trial showed that significantly more patients receiving semaglutide achieved both of the primary study endpoints at week 72 compared to those receiving placebo.**
 - A. True
 - B. False
- 5. Which of the following statements is true about the secondary endpoints at week 72?**
 - A. Body weight improved but cardiometabolic parameters did not.
 - B. Invasive tests of fibrosis were improved but liver enzymes were not.
 - C. Cardiometabolic parameters and noninvasive tests of fibrosis were improved.
 - D. There were no changes in cardiometabolic parameters or liver enzymes.
- 6. Which of the following is true about the safety findings?**
 - A. Overall AE rates were identical between groups.
 - B. Serious AEs and AEs leading to discontinuation were similar between groups.
 - C. The most common AEs with semaglutide were headache, vomiting, and COVID-19.
 - D. The semaglutide group had a higher rate of fatal AEs.

VIEW CORRECT ANSWERS

Answers

- 1. Which of the following was an inclusion criterion in the phase 3 ESSENCE Trial?**
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Glossary

agonist	drug that binds to the receptor and stimulates its function
ascites	accumulation of fluid in the peritoneal cavity (abdomen), can be due to several causes including obstructed blood flow to the liver and cirrhosis
ballooning	swelling of cells typically seen in microscopic examination; ballooning of hepatocytes (liver cells) denotes cell degeneration characterized by swelling and enlargement as found in steatohepatitis due to NASH/MASH
concomitant	taking place at the same time as something else
controlled attenuation parameter (CAP)	ultrasound-based noninvasive tool used to assess liver fat
C-reactive protein (CRP)	protein that binds with phospholipids on foreign substances and activates the immune system; stimulates the production of inflammatory molecules such as cytokines; elevated blood levels of CRP are found in many infectious and inflammatory diseases
fibrosis	repair and replacement of inflamed cells by connective tissue cells (fibroblasts), eventually resulting in replacement of normal organ tissue by scar tissue
glucagon	hormone secreted by the pancreas that increases blood glucose by stimulating the liver to convert stored glycogen into glucose; it opposes the action of insulin
glycated hemoglobin (HbA1c)	long-term measure of blood glucose control
hepatic encephalopathy	brain dysfunction in patients with chronic liver disease and portal hypertension due to failure of the liver to detoxify the blood; may result in cognitive impairment and coma
incretin	one of several peptide hormones produced in the small intestine or colon in response to glucose; it stimulates secretion of insulin and inhibits secretion of glucagon
lipoprotein	any of the conjugated chemicals in the bloodstream consisting of simple proteins bound to fat; cholesterol, phospholipids, and triglycerides are all fatty components of lipoproteins; lipoproteins are classified by their degree of density
pioglitazone	oral drug in the thiazolidinedione class used as an adjunct to diet and exercise for management of type 2 diabetes
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey; tool that measures perceived health status in 8 domains that include responses on physical, social, pain, mental health, emotional, vitality, and general health
steatohepatitis	deposition of fat in the liver
steatosis	abnormal accumulation of fat inside cells or organs, common in obesity and type 2 diabetes
transient elastography	noninvasive measure of liver stiffness, measured by a device marketed as FibroScan®; elasticity of the liver is closely associated with the degree of fibrosis
variceal	pertaining to a varix, a twisting dilatation of a blood vessel (vein)

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