Paris NASH Meeting

International Think Tank

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Institut Pasteur
9th edition

Future MASH Therapies

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Novo Nordisk, DK

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Conflict of interest disclosure

- Novo Nordisk (employment and shareholder)

Broad engagement within MASH

Clinical trials, research and external activities

Drug development

- Semaglutide monotherapy
- Combination therapies
- New mechanisms of action

Real World Evidence

- Linking biomarkers and liver histology to outcomes
- Disease understanding & evidence on clinical care pathways

External collaborations

- Consortia: LITMUS, NIMBLE, Liver Forum, IHI projects
- Translational collaborations: Academia, other pharmaceutical companies, and diagnostic companies

Biomarker research

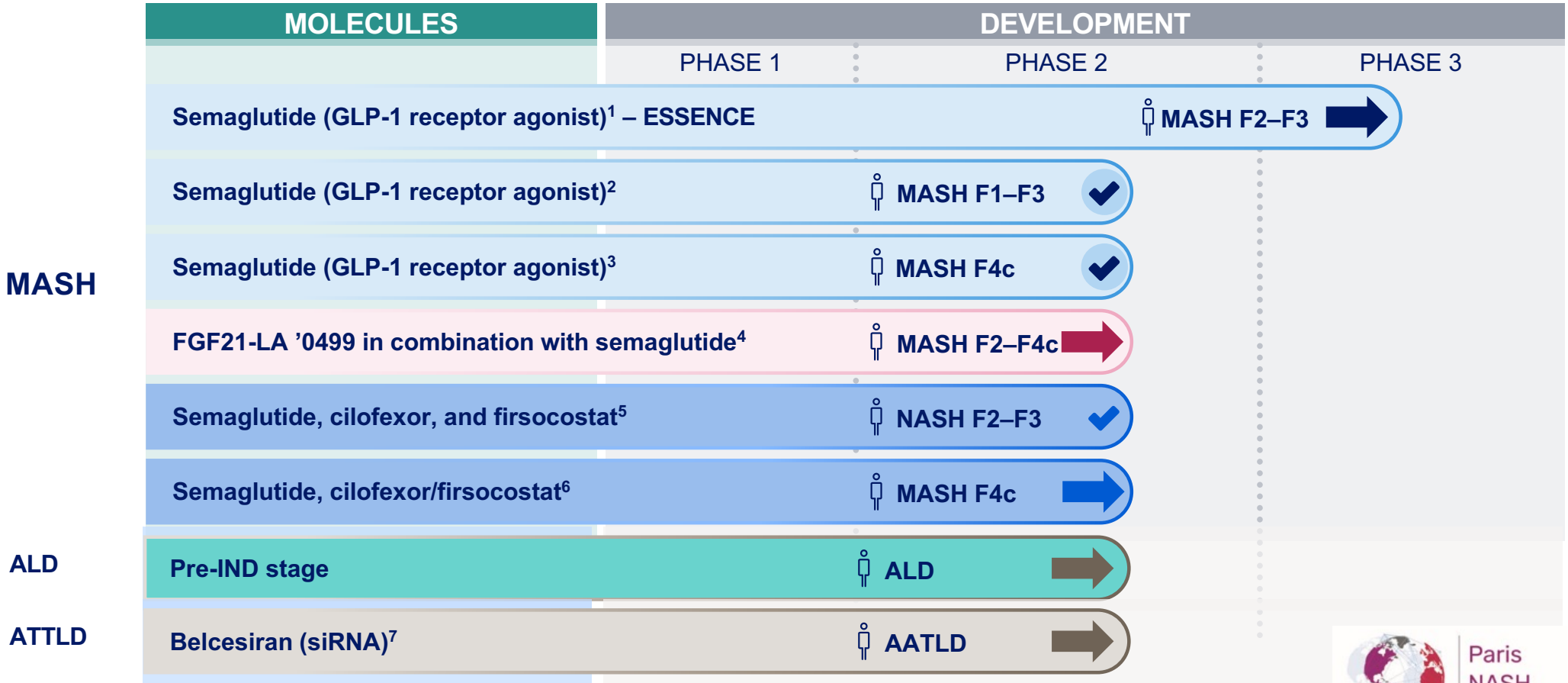
- Strategy to identify diagnostic, prognostic, and/or monitoring biomarkers in clinical trials
- Partnerships with diagnostic companies

NASH, non-alcoholic steatohepatitis.

Semaglutide, FGF21-LA '0499, cilofexor, firsocostat, and belcesiran are either investigational or being investigated for (a) new use(s). Safety and efficacy have not been established. There is no guarantee that any of these compounds will become commercially available for the use(s) under investigation.

RATIONALE FOR MASH TREATMENT PATHWAYS

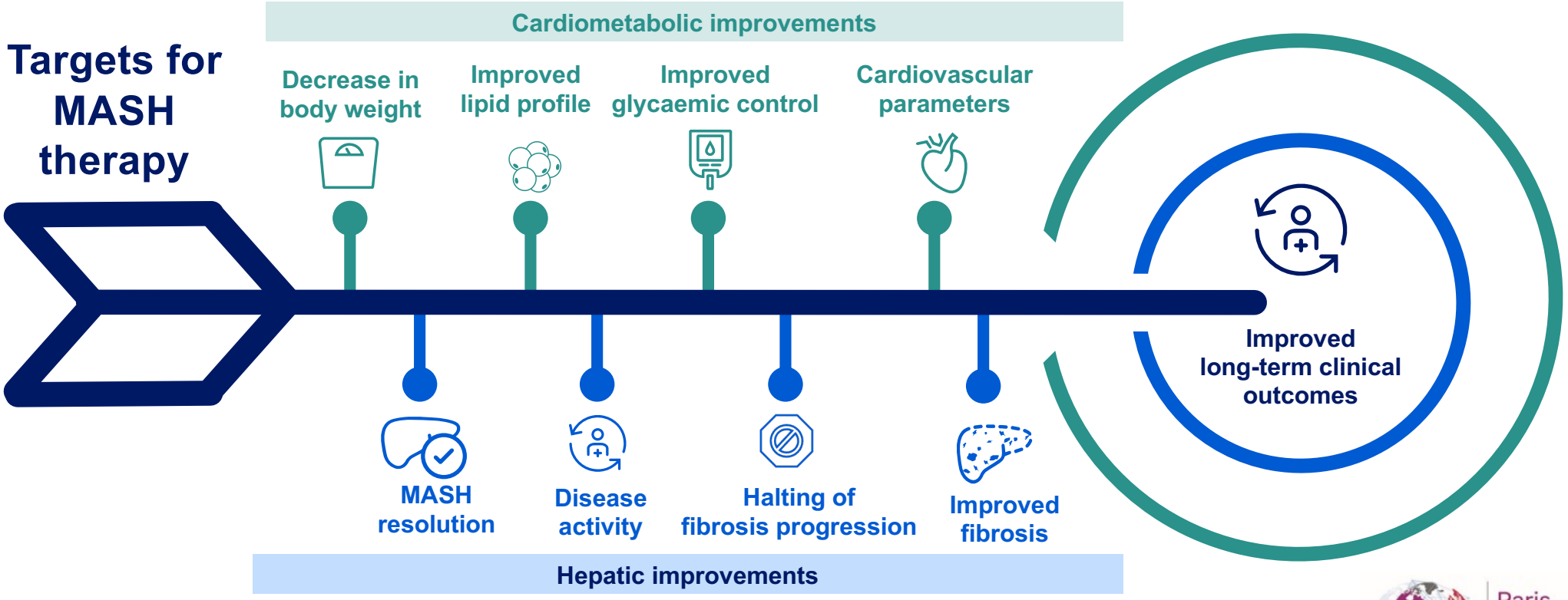
Novo Nordisk liver disease pipeline



AATLD, alpha-1 antitrypsin deficiency-associated liver disease; C, cirrhosis; F, fibrosis stage; FGF21-LA '0499, fibroblast growth factor 21 long-acting analog NNC0194-0499; GLP-1, glucagon-like peptide-1; NASH, nonalcoholic steatohepatitis; siRNA, small interfering ribonucleic acid.
1. NCT04822181. Available at: https://clinicaltrials.gov/ct2/show/NCT04822181/. Accessed October 2022; 2. NCT02970942. Available at: https://clinicaltrials.gov/ct2/show/NCT02970942. Accessed October 2022; 3. NCT03987451. Available at: https://clinicaltrials.gov/ct2/show/NCT03987451. Accessed October 2022; 4. NCT05016882. Available at: https://clinicaltrials.gov/ct2/show/NCT05016882. Accessed October 2022; 5. NCT03987074. Available at: https://clinicaltrials.gov/ct2/show/NCT03987074. Accessed February 2022; 6. NCT04971785. Available at: https://clinicaltrials.gov/ct2/show/NCT04971785. Accessed October 2022; 7. NCT04764448. Available at: https://clinicaltrials.gov/ct2/show/NCT04764448. Accessed October 2022.

MASH INVESTIGATIONAL PHARMACOTHERAPY TARGETS

Pharmacological management of MASH should aim to stabilise liver disease activity and address cardiometabolic comorbidities



NASH, non-alcoholic steatohepatitis.
Figure adapted from Francque S and Vonghia L. *Adv Ther.* 2019;36:1052–74.

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Semaglutide is not approved for treatment of NASH or MASH

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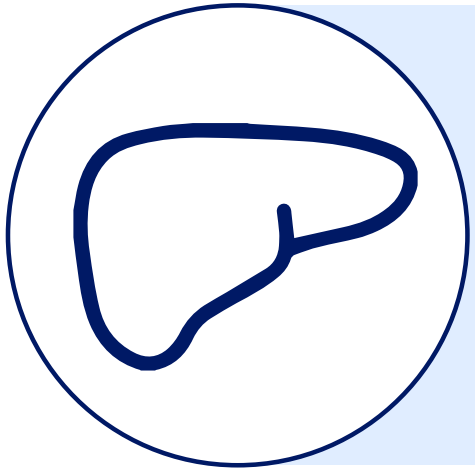
The MoA of semaglutide in MASH

Integrating clinical with animal model data for a better understanding of clinical outcomes



- **Weight loss**
  - **Reduced steatosis**
- Metabolic effects
  - Reduced insulin, glucagon
  - Reduced postprandial TG, ApoB48

- **Reduced inflammation**
- Smaller, secondary effects reducing and/or preventing further fibrosis

GLP-1 receptors are not expressed in hepatocytes, or in other liver cell types. GLP-1R expression is mostly found in **the pancreas, brain and intestine**

GLP-1 **may reduce inflammation** via receptors in intestine, brain, peripheral nervous system, bone marrow, some T-cells

ApoB, apolipoprotein B; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; MoA, mechanism of action; TG, triglycerides.
Knudsen LB and Lau J. Front Endocrinol 2019;10:155.

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SemaMASH is an investigational medicinal product. Semaglutide is not approved for treatment of NASH or MASH

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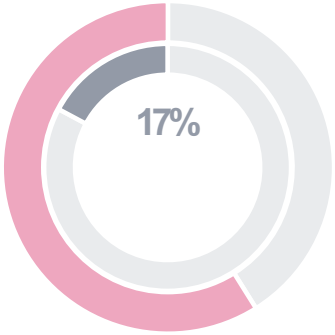
OVERVIEW OF TREATMENT EFFICACY IN THE SEMAMASH CLINICAL DEVELOPMENT PROGRAMME

In clinical trials, semaglutide treatment was shown to improve MASH resolution but not liver fibrosis when assessed by histology in patients with MASH

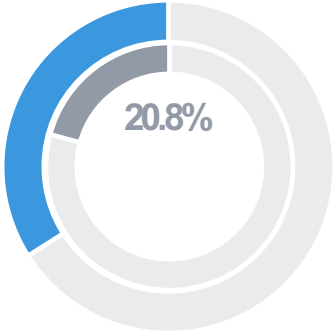
MASH resolution

59%



patients with
F2–F3 (trial 4296)*[1]

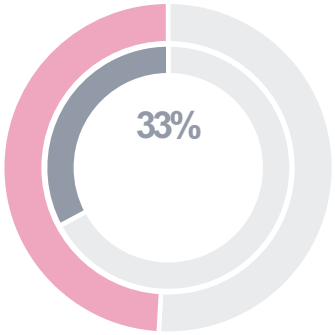
34.0%



patients with
F4c (trial 4492)[2]

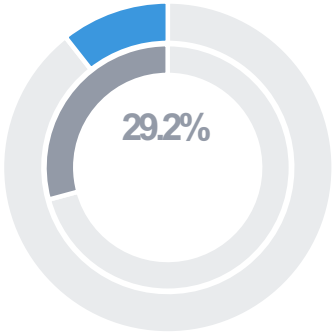
Improvement in fibrosis and no worsening of MASH

43%



patients with
F2–F3 (trial 4296)[1]

10.6%



patients with
F4c (trial 4492)[2]

Sema 0.4 mg OD n=82

72 weeks

Sema 2.4 mg OW n=47

48 weeks

Corresponding placebo
n=80 (4296)
n=24 (4492)

Data based on in-trial period. Two-sided *p*-values from a Cochran-Mantel-Haenszel test. Subjects with missing data handled as non-responders.
*$p \leq 0.0001$.
F, fibrosis stage; NASH, non-alcoholic steatohepatitis; OD, once-daily; OW, once-weekly; sema, semaglutide.
1. Newsome PN et al. *N Engl J Med.* 2021;384:1113–24; 2. Loomba R et al. Presented at the International Liver Congress (European Association for the Study of the Liver), 22–26 June 2022, London, UK.

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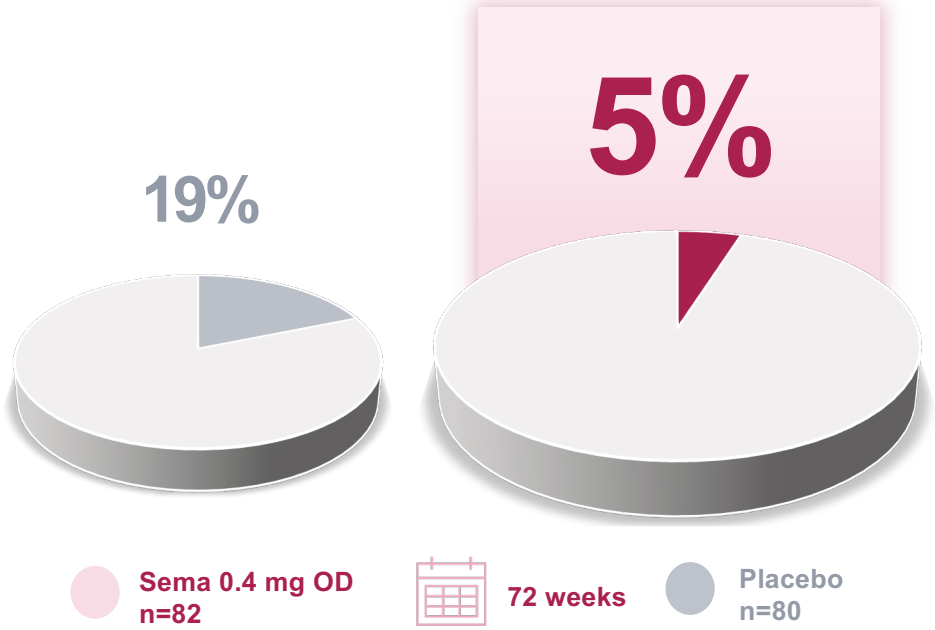
OVERVIEW OF TREATMENT EFFICACY IN THE SEMAMASH CLINICAL DEVELOPMENT PROGRAMME

In clinical trials, semaglutide treatment was shown to halt progression of fibrosis in patients with MASH

Only **5%** of patients with F1–F3 (trial 4296)[1] treated with semaglutide had **worsening of fibrosis stage**



Data based on in-trial period.
C, cirrhosis; F, fibrosis stage; NASH, non-alcoholic steatohepatitis; OD, once-daily; sema, semaglutide.
1. Newsome PN et al. *N Engl J Med.* 2021;384:1113–24.

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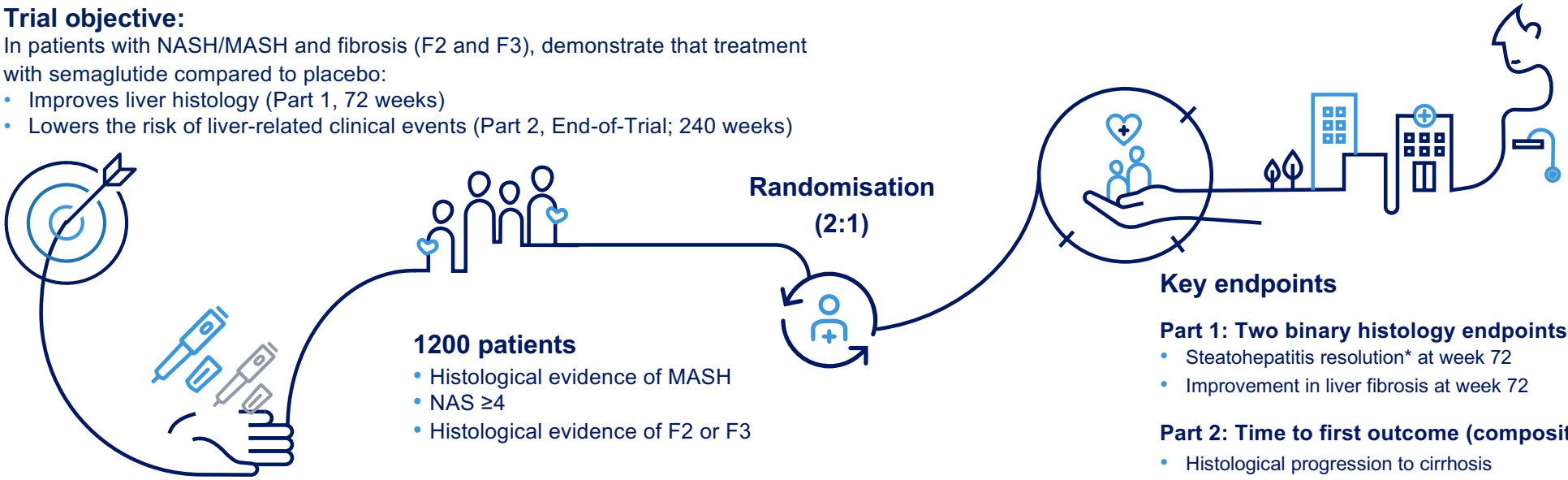
ONGOING CLINICAL TRIAL FOR SEMAGLUTIDE IN MASH

The ESSENCE phase 3 trial is the flagship trial for potential approval of semaglutide monotherapy in MASH

Trial objective:
In patients with NASH/MASH and fibrosis (F2 and F3), demonstrate that treatment with semaglutide compared to placebo:

- Improves liver histology (Part 1, 72 weeks)
- Lowers the risk of liver-related clinical events (Part 2, End-of-Trial; 240 weeks)



Key endpoints

Part 1: Two binary histology endpoints

- Steatohepatitis resolution* at week 72
- Improvement in liver fibrosis at week 72

Part 2: Time to first outcome (composite)

- Histological progression to cirrhosis
- Death (all cause)†
- MELD score ≥15
- Liver transplant
- Hepatic decompensation events†

*Resolution of steatohepatitis is defined as a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. †Adjudicated.
F, fibrosis stage; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; OW, once-weekly; PBO, placebo; sc, subcutaneous; sema, semaglutide.
NCT04822181. Available from https://clinicaltrials.gov/ct2/show/NCT04822181/. Accessed May 2022.