NASH and Alzheimer’s disease

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CAPITAL MARKETS DAY
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NADIA SADI
Nadia lives with NASH
Denmark
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Important drug information

Victoza® and Ozempic® are approved for the management of type 2 diabetes only
Saxenda® and Wegovy® are approved in the USA and the EU for the treatment of obesity only
Strategic aspirations 2025

Purpose and sustainability (ESG)
- Progress towards zero environmental impact
- Being respected for adding value to society
- Being recognised as a sustainable employer

Innovation and therapeutic focus
- Further raise the innovation-bar for diabetes treatment
- Develop a leading portfolio of superior treatment solutions for obesity
- Strengthen and progress the Rare disease pipeline
- Establish presence in Other serious chronic diseases focusing on CVD, NASH and CKD

Commercial execution
- Strengthen Diabetes leadership - aim at global value market share of more than 1/3
- More than 25 billion DKK in Obesity sales by 2025
- Secure a sustained growth outlook for Rare disease

Financials
- Deliver solid sales and operating profit growth
  - Deliver 6-10% sales growth in IO
  - Transform 70% of sales in the US\(^1\)
- Drive operational efficiencies across the value chain to enable investments in future growth assets
- Deliver free cash flow to enable attractive capital allocation to shareholders

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1 From 2015 to 2022, 70% of sales to come from products launched from 2015. IO: International Operations; CVD: Cardiovascular disease; NASH: Non-alcoholic steatohepatitis; CKD: Chronic kidney disease.

Note: The strategic aspirations are not a projection of Novo Nordisk’s financial outlook or expected growth.
# NASH and Alzheimer’s disease pipeline overview

## Establishing a presence in NASH and AD

### NASH:
- Address an unmet need with no currently available treatment options
- Aim for effect on resolution of NASH and no worsening of fibrosis, improvement in fibrosis and no worsening in steatohepatitis

### Alzheimer’s disease:
- Opportunistic opportunity to slow clinical progression in people with early Alzheimer’s disease

### Pipeline overview

<table>
<thead>
<tr>
<th>NASH – Combination with Gilead: (semaglutide 2.4 mg, FXR, ACC inhibitor) Segment scope: F4c patients</th>
<th>2022</th>
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<td>NASH - FGF-21 NASH Segment scope: F3-F4c</td>
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NASH: Non-alcoholic hepatitis; AD: Alzheimer’s Disease; F: Fibrosis stage; F4c: compensated cirrhosis; ACC: firsocostat; FXR: Farnesoid X inhibitor
Novo Nordisk®

Semaglutide showed resolution of NASH with no worsening of fibrosis versus placebo in the phase 2 trial.\(^1\)

*Statistically significant at 72 weeks (p<0.05 vs placebo). Based on a complete case analysis, using people with an evaluable biopsy at end of trial. Analysis included patients with fibrosis stage 1, 2, or 3 at baseline. Data is from the semaglutide in NASH phase 2 trial. NASH: non-alcoholic steatohepatitis.

In phase 2, semaglutide showed significant improvements in NASH resolution

Semaglutide showed numerical improvements in fibrosis and fewer patients had progression of fibrosis vs placebo in phase 2 trial.\(^1\)

Note: *statistically significant at 72 weeks (p<0.05 vs placebo).
Following phase 2 data and breakthrough therapy designation, one phase 3 trial is expectedly needed for regulatory submission.

**Phase 3a ESSENCE trial in NASH**

**ESSENCE trial** | NASH F2–F3 patients

- **N = 1,200**
- **Semaglutide 2.4 mg sc. OW + SoC**
- **Placebo + SoC**

**Structure**

- **Part 1**
  - 72 weeks
  - Biopsy

- **Part 2**
  - 240 weeks
  - Biopsy

**Primary objectives and endpoints for Part 1 and 2**

**Part 1** | Improves liver histology vs placebo

Two binary histology endpoints at week 72:
- Resolution of NASH and no worsening of liver fibrosis
- Improvement in liver fibrosis and no worsening of NASH

**Part 2** | Lowers the risk of liver-related clinical events vs placebo

Time to first outcome (composite endpoints) at week 240:
- Histological progression to cirrhosis
- Death (all cause)
- Liver-induced MELD score ≥ 15
- Liver transplant
- Hepatic decompensation events

Regulatory submission expected to be based on part 1 of the trial combined with the results of the already completed phase 2 trial.

F: Fibrosis stage; NASH: non-alcoholic steatohepatitis; OW: once weekly; R: randomisation; SoC: standard of care (GLP-1s disallowed); MELD: Model for End-stage Liver Disease; BTD: Break-through Designation
Novo Nordisk is supporting use of non-invasive tests for diagnosis

Development and adoption of non-invasive tests (NITs)

Liver biopsy → NITs

Guidelines: NITs represented in guidelines

Practitioners: ~80% of HCPs perform NASH diagnostics with use of various NITs, while biopsies are seldomly used

NIT development: Several available NITs in clinical practice. ELF test is first prognostic tool to be granted FDA De Novo marketing authorisation

Pharma companies: Embedding validation of NITs in clinical trials

Novo Nordisk activities supporting non-invasive tests in NASH diagnosis

Real world
- Linking biomarkers and liver histology to outcomes
- Disease understanding

External
- Consortia
- Collaborations with academia and other healthcare companies

Phase 2 trial with FGF21
Phase 3 ESSENCE trial (part 1 and 2), incl. screening data

Validate diagnostic tests
Validate tests for monitoring
Validate tests for prognosis

Note: FDA De Novo provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.

NITs: Non-invasive tests; NASH: Non-alcoholic hepatitis; HCPs: Healthcare professionals; FDA: the US Food and Drug Agency; NN: Novo Nordisk; ELF: Enhanced liver fibrosis
NASH patient journey underscores key barriers to overcome for Novo Nordisk to be successful

~22 million people are expected to live with NASH F2-F4c by 2030

Hurdles

NASH prevalence

Low disease awareness

Inadequate patient referrals

No treatment options

No prognostic biomarker

Few patients receiving diagnosis

Market preparation priorities

Build strong presence

- Create urgency to treat in NASH
- Build strong speciality-referral process
- Engage Endos, Hepas and PCPs

Increase diagnosis rate

- Momentum towards NITs in clinical practice and guidelines
- NITs for diagnosis, screening and monitoring

Evidence generation

- Build understanding of importance of addressing underlying cause of disease
- Stop clinical progression amongst physicians and payers

Indicates expected investment level

NASH: Non-alcoholic steatohepatitis; Endos: endocrinologist; PCP: primary care physician; NIT: Non-invasive tests; Referrals and identification; Hepas: hepatologists; F: Fibrosis stage

Source: Estes C, Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease, Hepatology, 2018
Entering phase 3 development of semaglutide in Alzheimer’s disease was based on a number of data points

Randomised controlled trials

53% lower risk of dementia diagnosis with liraglutide/semaglutide in NN’s CVOTs in T2D

Less decline in cerebral glucose metabolism (FDG-PET) with liraglutide in AD

Reduced incidence of major adverse CV events in T2D with semaglutide incl. stroke

Systemic anti-inflammatory effects with semaglutide

Short-term memory improvement with liraglutide in people with obesity

Reduced cognitive decline with dulaglutide in patients with T2D

Real world evidence trials

Four RWE studies show reduced risk of dementia or AD with GLP-1

Danish registry

• 11% lower risk of dementia per year of GLP-1 exposure

TRUVEN claims database

• 31% lower risk of dementia after >2 years of GLP-1 exposure

Danish registry

• 42% lower odds of dementia after GLP-1 exposure

FAERS (FDA database)

• 64% lower odds of AD after liraglutide exposure

Pre-clinical studies

Improved memory function with GLP-1 incl. semaglutide

Reduced phospho-tau accumulation

Reduced neuroinflammation with GLP-1 incl. semaglutide

Reduced atherosclerosis with liraglutide and semaglutide

Systemic anti-inflammatory effects with semaglutide

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AD: Alzheimer’s disease; CI: confidence interval; RWE: Real world evidence

Evoke and evoke+ trials are ongoing with expected completion in 2025

evoke and evoke+ trials have been initiated with 1,840 patients in each trial with a total of 3,680 patients

**Objective**
To confirm superiority of oral semaglutide vs placebo on the change in cognition and function in people with early Alzheimer's disease

**Primary endpoint**
Change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) score from baseline to end of 104 weeks of treatment

**Inclusion criteria**
- Early Alzheimer's disease (mild cognitive impairment or mild dementia)
- Mini-Mental State Examination (MMSE) ≥ 22/30
- Age between 55-85 years
- evoke+ has at least 20% with small vessel pathology

AD: Alzheimer's disease; QD: Once-daily; MCI: mild cognitive impairment; QD: once-daily.
Note: CDR-SB ratings are utilising in six domains are summed to provide a clinical measure = Sum of Boxes. These are: memory, orientation, judgment and problem solving, community affairs, home and hobbies, personal care.
CDR-SB Scores range from 0 to 18 with higher scores representing greater impairment

2025
AD patient journey is complex and underscores key barriers to overcome for Novo Nordisk to be successful

Significant and growing unmet need

Hurdles
- Early symptoms dismissed as normal ageing
- Complex tests and limited screening/diagnosing skills
- Lack of prognostic markers and simple tests
- No DMT options

Few patients receiving diagnosis

Market preparation priorities
- Evidence to better understand the impact of delaying disease progression
- Role of neuroinflammation in disease progression

Support healthcare system preparedness
- Larger number of AD patients expected to enter the system
- May lead to significant bottlenecks and delay to patient care

Increase diagnosis rate
- Support NITs development, e.g. blood-based/digital biomarkers
- Increase AD education and access to screening tools for PCPs and HCP insight

Note: MCI and Mild dementia in the graph are both due to AD.
AD: Alzheimer’s disease; QD: Once-daily; MCI: mild cognitive impairment; DMT: Disease-modifying treatment; PCP: primary care physicians; NITs: Non-invasive diagnostics; HCP: Healthcare professional
Closing remarks

NASH and Alzheimer’s disease impact millions of people globally

Too often the diseases go undiagnosed and have no or limited treatment options

Semaglutide is investigated in specific patient populations for treatment of NASH F2-F3 and MCI and mild dementia due to Alzheimer’s disease