NASH and Alzheimer's disease

CMD22
CAPITAL MARKETS DAY

3 MARCH

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NADIA SADI
Nadia lives with NASH
Denmark

Forward-looking statements

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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

[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

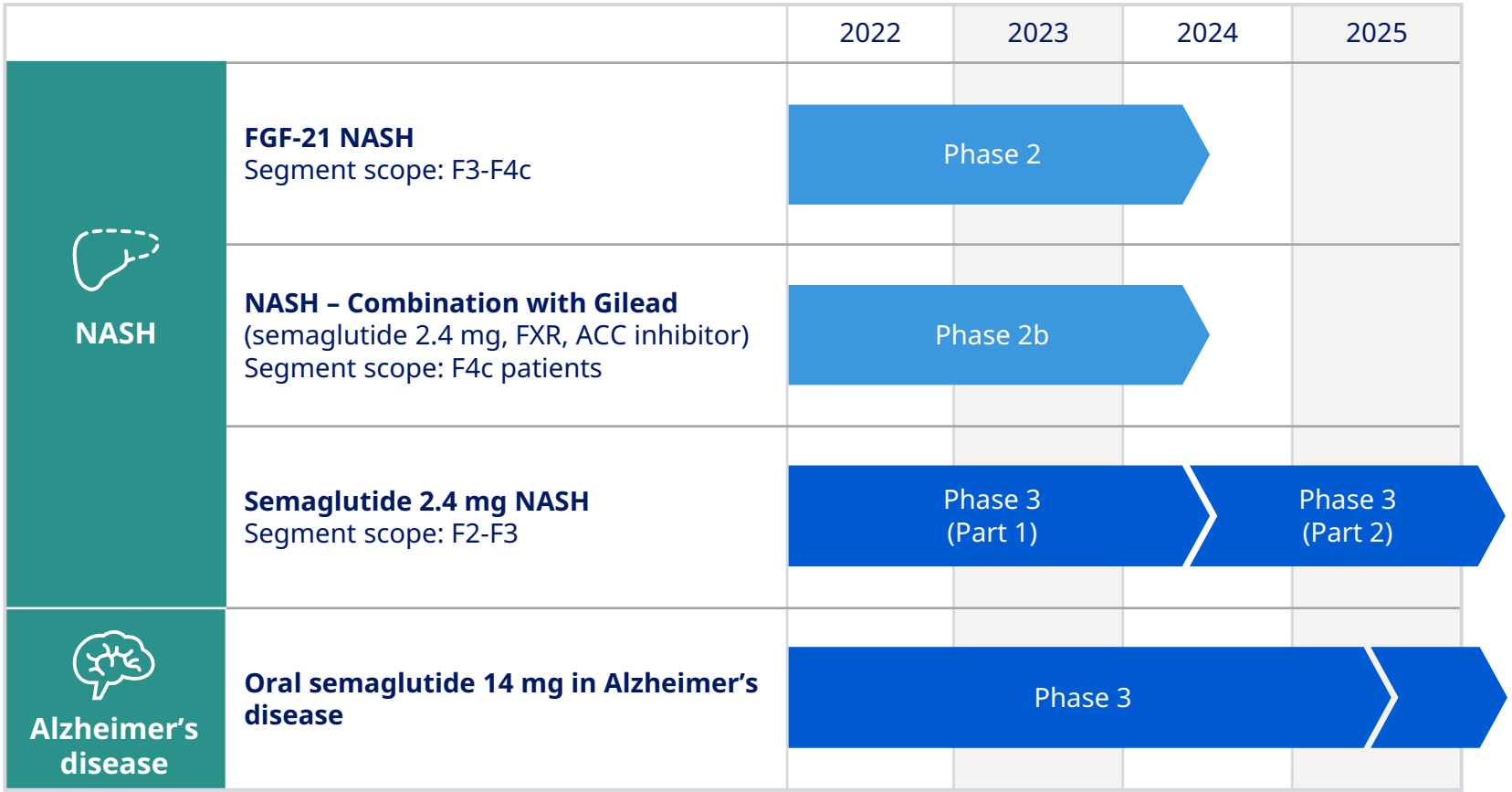
NASH:

- 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

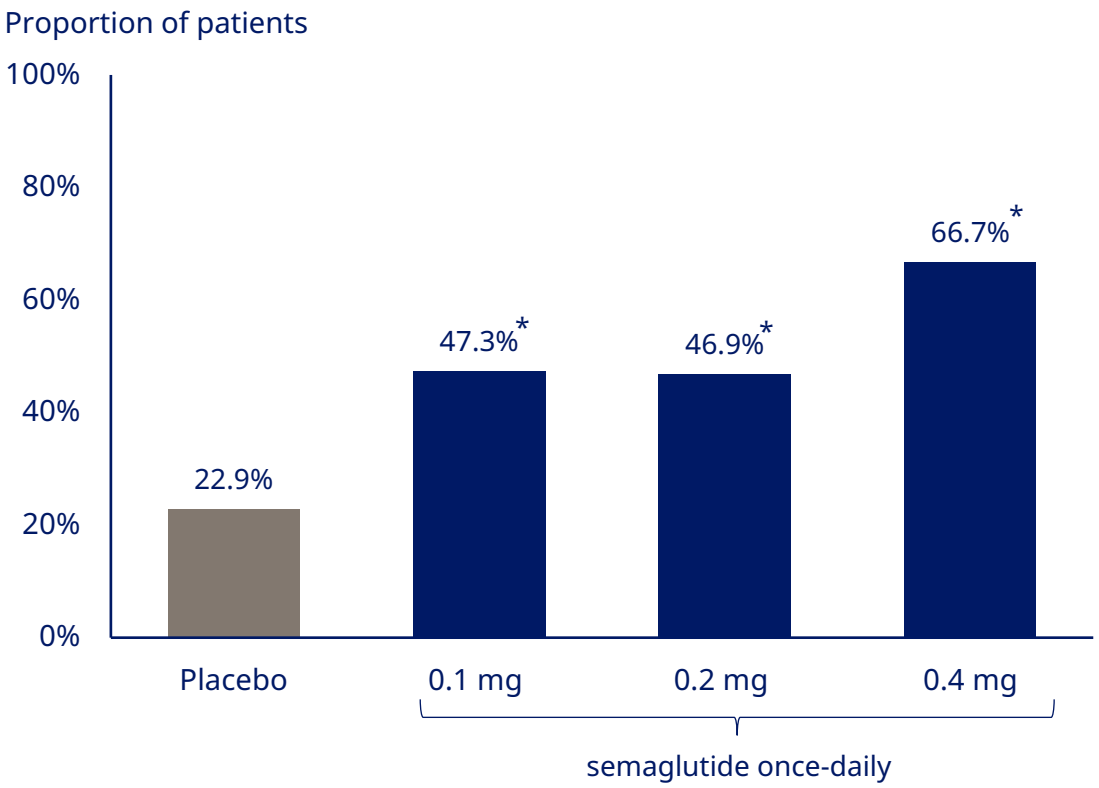
Pipeline overview



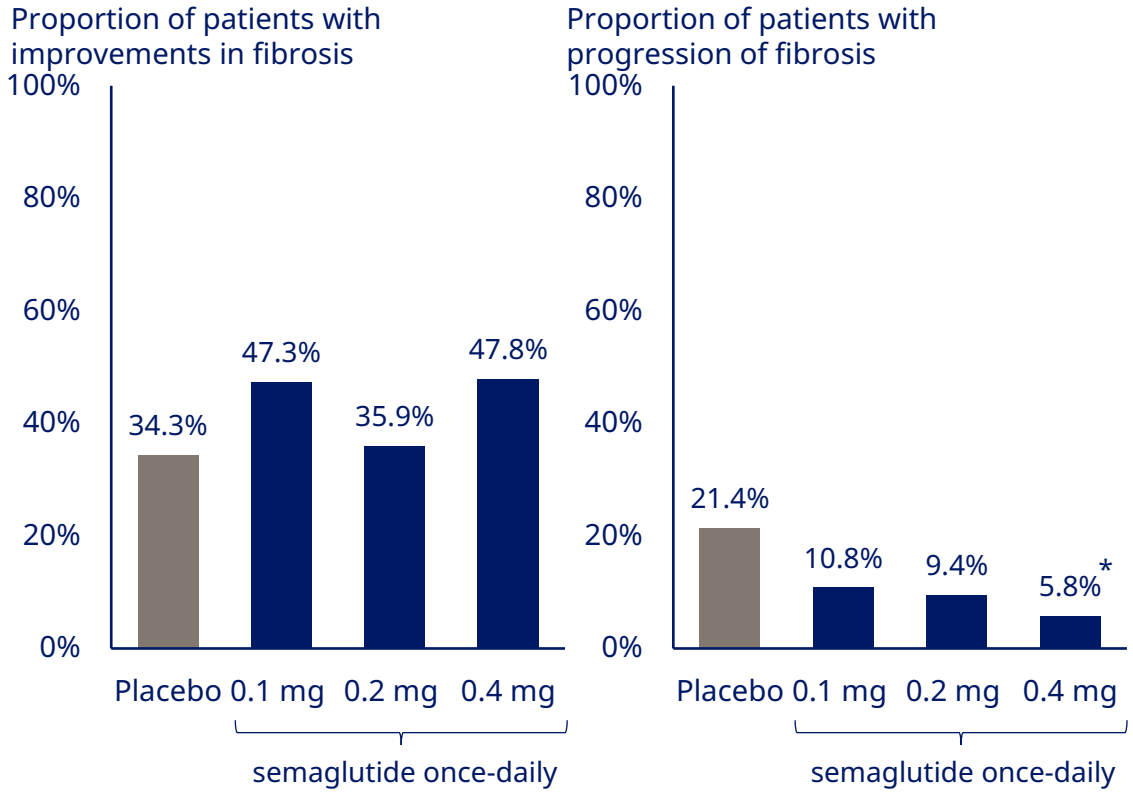
NASH: Non-alcoholic hepatitis; AD: Alzheimer's Disease; F: Fibrosis stage; F4c: compensated cirrhosis; ACC: firsocostat; FXR: Cilofexor Farnesoid X inhibtor

In phase 2, semaglutide showed significant improvements in NASH resolution

Semaglutide showed resolution of NASH with no worsening of fibrosis versus placebo in the phase 2 trial[1]



Semaglutide showed numerical improvements in fibrosis and fewer patients had progression of fibrosis vs placebo in phase 2 trial[1]



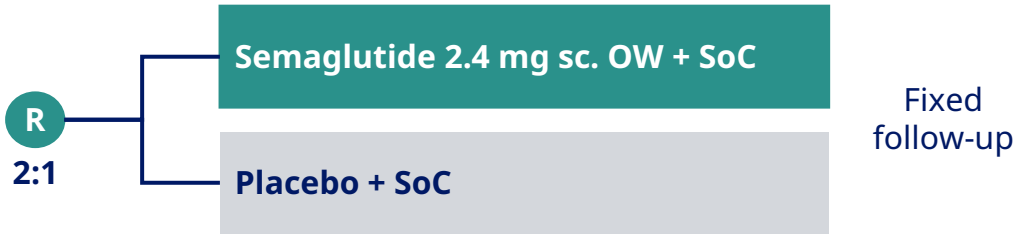
Note: *statistically significant at 72 weeks ($p<0.05$ vs placebo).[1]Based on a complete case analysis, using people with an evaluable biopsy at end of trial. Analysis included patients with fibrosis stage 1, 2, or 3 at baseline. Data is from the semaglutide in NASH phase 2 trial.
NASH: non-alcoholic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

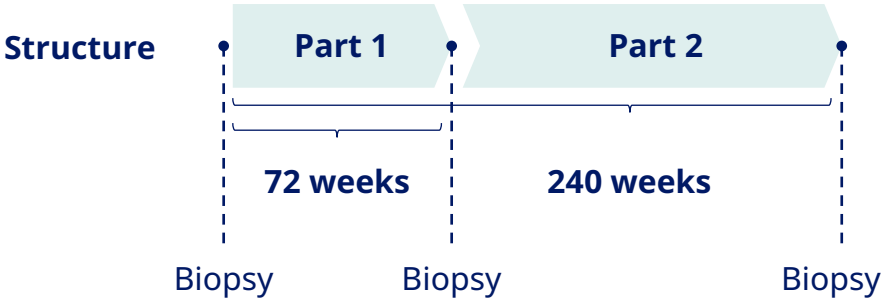
Following phase 2 data and breakthrough therapy designation, one phase 3 trial is expectedly needed for regulatory submission

Phase 3a ESSENCE trial in NASH

ESSENCE trial | NASH F2–F3 patients

N = 1,200





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)

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

NN Development

Phase 2 trial with FGF21

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

Validate **diagnostic** tests

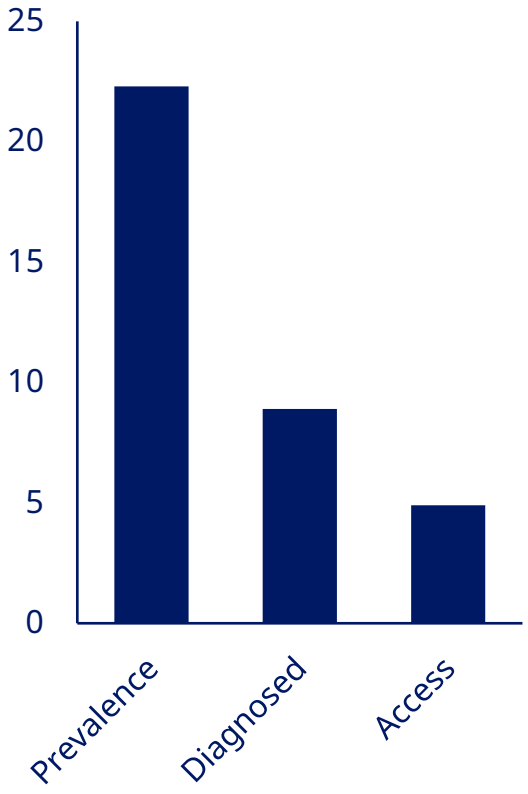
Validate tests for **monitoring**

Validate tests for **prognosis**

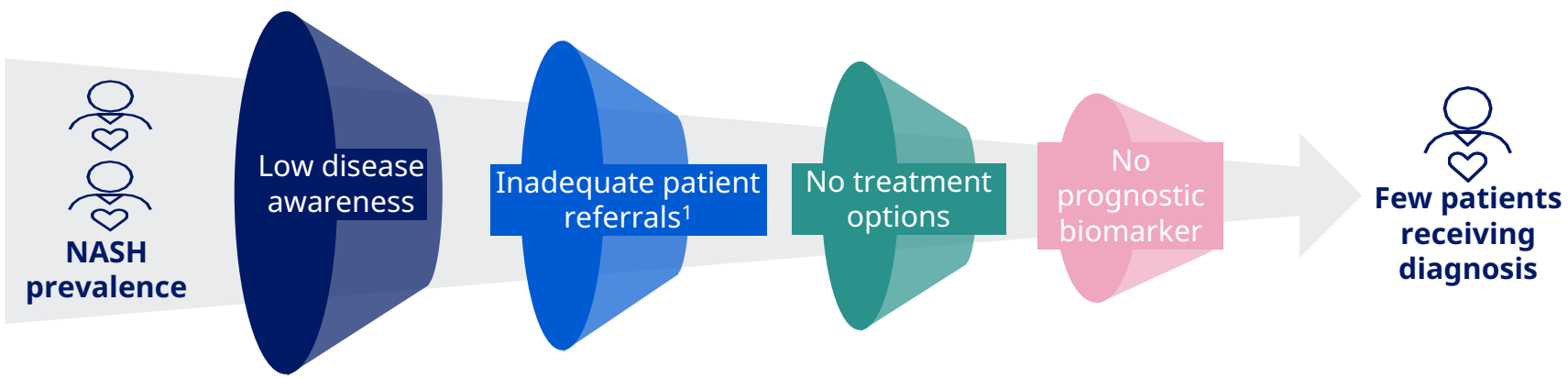
Note: FDA De Novo provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.
NITs: Non-invasive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



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 invesment level

NASH: Non-alcoholic steatohepatitis; Endos: endocrinologist; PCP: primary care physician; NIT: Non-invasive tests; [1]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

Real world evidence trials

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

Danish registry[1]
- **11%** lower risk of dementia per year of GLP-1 exposure

TRUVEN claims database[1]
- **31%** lower risk of dementia after >2 years of GLP-1 exposure

Danish registry[2]
- **42%** lower odds of dementia after GLP-1 exposure

FAERS (FDA database)[3]
- **64%** lower odds of AD after liraglutide exposure

Randomised controlled trials

53% lower risk of dementia diagnosis with liraglutide/semaglutide in NN's CVOTs in T2D[4]

Less decline in cerebral glucose metabolism (FDG-PET) with liraglutide in AD[5]

Reduced incidence of **major adverse CV events** in T2D with semaglutide incl. stroke[6]

Systemic anti-inflammatory effects with semaglutide[7,8]

Short-term **memory improvement** with liraglutide in people with obesity[9]

Reduced cognitive decline with dulaglutide in patients with T2D[10]

Pre-clinical studies

Improved memory function with GLP-1[11] incl. semaglutide[12]

Reduced phospho-tau accumulation[13]

Reduced neuroinflammation with GLP-1[14,15] incl. semaglutide[16]

Reduced atherosclerosis with liraglutide and semaglutide[17]

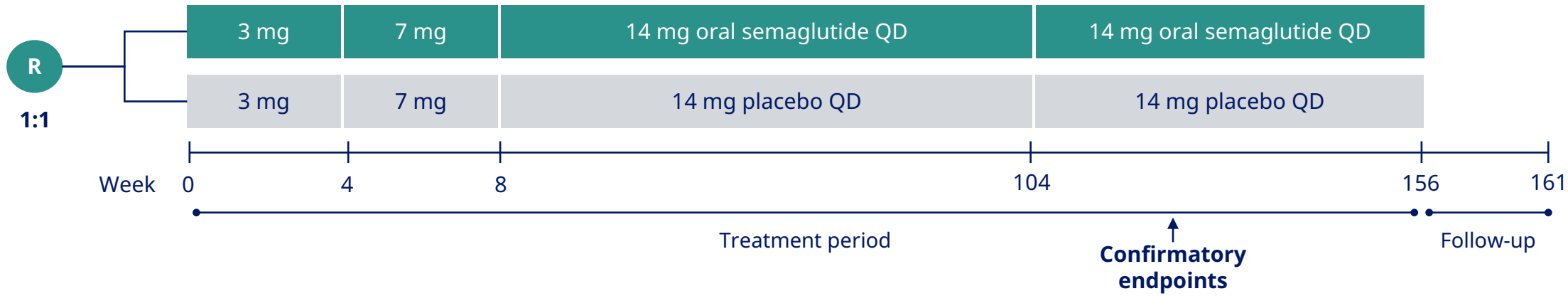
Systemic **anti-inflammatory** effects with semaglutide[17]

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

[1]NN data on file, Danish register: Dementia cases based on diagnosis (ICD10) or treatment (anticholinesterases, memantine) codes; TRUVEN: Dementia cases based on SNOMED ids for all diagnoses (ICD-10) or treatment (anticholinesterases, memantine); [2]Wium-Andersen IK et al. Eur J Endocrinol. 2019;181(5):499-507; [3]Akimoto H et al. Am J Alzheimers Dis Other Demen. 2020;35:1-11; [4]Ballard et al. Presented online at the Alzheimer's Association International Conference (AAIC), 27–31 July 2020; [5]Gejl M et al. Front Aging Neurosci 2016;8:108; [6]Husain M et al. Diabetes Obes Metab 2020;22:442–451; [7]Aroda VR et al. Diabetes Care 2019;42:1724–1732; [8]Rodbard HW et al. Diabetes Care 2019;42:2272–2281; [9]Vadini F et al. Int J Obes (Lond) 2020;44:1254–1263; [10]Cukierman-Yaffe T et al. Lancet Neurol 2020;19:582–590 [11]Hansen HH et al. J Alzheimers Dis 2015;46:877–888; [12]Preliminary data in NN ongoing pre-clinical studies; [13]Hansen HH et al. Brain Res 2016;1634:158–170; [14]Brundin L et al. Nature Med 2018;24:900–902; [15]Yun SP et al. Nature Med 2018;24:931–938; [16]Secher A et al. Oral presentation at Virtual Alzheimer's Disease/Parkinson's Disease International Conference, 9–14 March 2021; [17]Rakipovski G et al. JACC Basic Transl Sci 2018;3:844–857

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

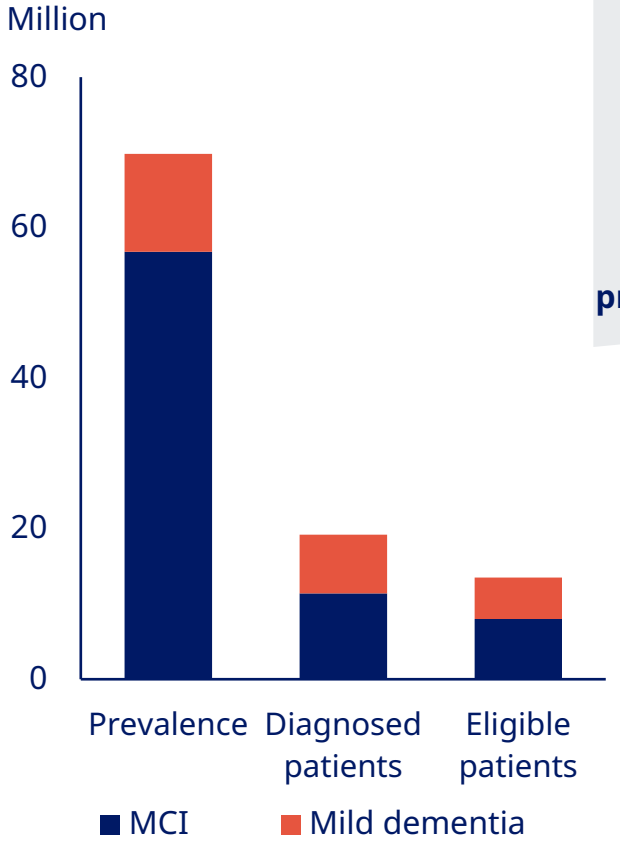
Inclusion criteria

- 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

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

Significant and growing unmet need



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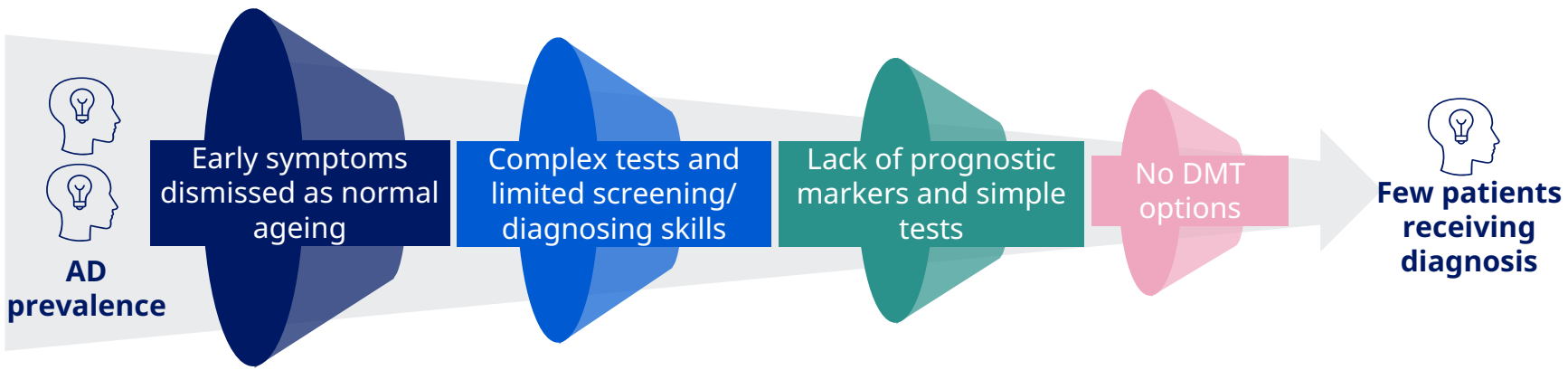

Market preparation priorities

Support healthcare system preparedness

- Larger number of AD patients expected to enter the system
- May lead to significant bottle-necks 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

Evidence generation

- Evidence to better understand the
  - impact of delaying disease progression
  - role of neuroinflammation in disease progression

Indicates expected invesment level

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
Source: Alzheimer's Association report: 2020 Alzheimer's disease facts and figures, 2020 (16:391-460)

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

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