29 January 2026
EMA/39428/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kayshild

International non-proprietary name: Semaglutide

Procedure No. EMEA/H/C/006426/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

µL	Microliter
µM	Micromolar
ADA	American Diabetes Association
ADO	8-amino-3,6-dioxaoctanoic acid
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ANCOVA	Analysis Of Covariance
ASMF	Active Substance Master File
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Concentration-Time Curve
$AUC_{0-\infty}$	Area Under the Concentration-Time zero to infinity
AUC_{0-t}	Area Under the Concentration-Time zero to given timepoint
BBB	Blood-brain barrier
B/R	Benefit/Risk
BMI	Body Mass Index
BW	Body Weight
CAT	Committee for Advanced Therapies
CCI	Commercially Confidential Information
CDAA-HFD	Choline Deficient Amino Acid defined High Fat Diet
cDNA	Complementary DNA
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
CI	Confidence Interval
CKD	chronic kidney disease
CKD	Chronic Kidney Disease
CL	Clearance
CL/F	Apparent clearance
CL/F	Apparent Clearance Following Extravascular Administration
CMA	Conditional Marketing Approval
Cmax	Maximum Concentration
CMH	Cochran–Mantel–Haenszel
CNS	Central Nervous System
COA	Clinical outcome assessments
COVID-19	CoronaVirus Disease 2019
Cpk	process capability
CQA	Critical Quality Attribute
CRN	Clinical Research Network
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CTD	Common Technical Document
CTR	Clinical Trial Regulation
CV	Coefficient Of Variation
CVOT	Cardiovascular Outcomes Trial
CYP	Cytochrome P450
DBL	Database Lock
DBP	Diastolic Blood Pressure
DDI's	Drug-drug interaction
DIO	Diet-Induced Obese
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DP	Drug Product
DPP-4	Dipeptidyl Peptidase-4
DS	Drug Substance

EAC	Event Adjudication Committee
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram
EFD	Embryo-fetal development
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESLD	End-Stage Liver Disease
ETD	Evidence to Decision
EU	European Union
EURD	European Union Reference Dates
FAS	Full Analysis Set
FAST	FibroScan-AST
FDA	Food And Drug Administration
FGF	Fibroblast Growth Factor
FPen	Penetration factor
FPG	Fasting Plasma Glucose
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
Glu	Glutamic acid
GMP	Good Manufacturing Practice
GOF	Goodness of Fit
h	hour
HbA1c	Hemoglobin A1c
HCC	hepatocellular carcinoma
HCV RNA	hepatitis C virus ribonucleic acid
HDL-c	High-Density Lipoprotein Cholesterol
HEK293	Human embryonic kidney 293 cells
hERG	human ether-a-go-go-related gene
HIV	Human Immunodeficiency Virus
HMWP	High Molecular Weight Protein
HOMA-IR	Homeostasis Model Assessment for Insulin Resistance
HR	Hazard Ratio
hsCRP	High-sensitivity C-reactive protein
HV	Healthy Volunteers
i.v.	Intravenous
ICH	International Council for Harmonisation
ID	Identification
INN	International Nonproprietary Name
ipGTT	intraperitoneal glucose tolerance test
ISO	International Organization for Standardization
ITT	Intent- To-Treat
KA	Absorption rate constant
KD	Dissociation Constant
kDA	Kilo Dalton
KG	Kilogram
L	Liter
LC-MS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDL-c	Low-Density Lipoprotein Cholesterol
LLOQ	Lower Limit of Quantitation
LMW	Low Molecular Weight
LOCI	Luminescent Oxygen Channeling Immunoassay
LPLV	Last patient, Last visit
MAA	Marketing Authorisation Application
MACE	major adverse cardiovascular events
MASH	non-cirrhotic metabolic dysfunction-associated steatohepatitis

MASLD	Metabolic dysfunction-associated steatotic liver disease
MCB	Master Cell Bank
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for end-stage liver disease
MEN 2	Multiple endocrine neoplasia 2
MG	Milligram
MI	Myocardial infarction
ml	Milliliter
MoA	Mode of action
MRE	Magnetic Resonance Elastography
MRHD	Maximum Recommended Human Dose
MRI	Magnetic Resonance Imaging
MS	Milliseconds
MTC	Medullary Thyroid Cancer
NA	Not applicable
NAb	Neutralizing antibody
NAFLD	non-alcoholic fatty liver diseases
NAION	Non-arteritic anterior ischaemic optic neuropathy
NAS	NAFLD Activity Score
NBO	Notified Body Opinion
NEP	Neutral Endopeptidase
ng	Nanogram
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
OD	Once Daily
OR	Odds Ratio
PACMP	Post-Approval Change Management Protocol
PAES	Post-Authorisation Efficacy Study
PAM-REC	Post Authorisation Measure Recommendation
PASS	Post-Authorisation Safety Study
PD	Pharmacodynamics
PDCO	Paediatric Committee
PDs	Protocol Deviations
Ph. Eur.	European Pharmacopoeia
pI	Charge heterogeneity
PI	Product Information
PIP	paediatric investigation plan
PK	Pharmacokinetics
PK/PD	Pharmacokinetics- Pharmacodynamics
PL	Package Leaflet
PopPK	Population Pharmacokinetics
PPD	Protected Personal Data
PPND	Pre- and postnatal development
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	PRIority MEdicine
PRM	Primary Reference Material
PRO	Patient-reported outcomes
PSUR	Periodic Safety Update Report
PT	Preferred Terms
PV	Process Validation
PYE	Patient years of exposure
PYI	Patient years of risk
PYO	Patient years of observation
QWP	Quality Working Party
RA	receptor agonist
RMP	Risk Management Plan
RP-HPLC	Reversed-Phase High-Performance Liquid Chromatography
RS	Reference Standard
RSE	Relative Standard Error
s.c	Subcutaneous

SAE	Serious Adverse Event
SAG	Scientific Advisory Group
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SEE	substantial evidence of effectiveness
SE-HPLC	Size-Exclusion High-Performance Liquid Chromatography
SmPC	Summary Of Product Characteristics
SoC	Standard of Care
SoE	Strength of Evidence
SRM	Secondary Reference Material
T2DM	Type 2 diabetes Mellitus
TG	Triglycerides
Tmax	Time to Maximum concentration
TSH	thyroid stimulating hormone
ULN	Upper Normal Limits
US	United States
V/F	Apparent volume of distribution
VLDL	Very-Low-Density Lipoprotein
VLDL	Very-low-density lipoprotein
VPC	Visual Predictive Checks
WCB	Working Cell Bank

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Kayshild
Active substance	Semaglutide
INN or common name	Semaglutide
Applicant	Novo Nordisk A/S Novo Alle 1 2880 Bagsvaerd DENMARK
EMA product number	EMEA/H/C/006426
ATC code and pharmacotherapeutic group	A10BJ06 L2: a10drugs used in diabetes, L3: a10bblood glucose lowering drugs, excl. insulins, L4: a10bj glucagon-like peptide-1 (glp-1) analogues
Pharmaceutical form(s) and strength (s)	Solution for injection 0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg
Packaging	cartridge (glass) in pre-filled pen (FlexTouch)
Package size(s)	1 pre-filled pen + 4 needles
Route of administration	Subcutaneous use
Device or diagnostic	The pen-injector for semaglutide is a drug-device combination
Orphan designation	No
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Conditional
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Kayshild is indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).
New active substance status	Not applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality / non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
15 October 2020	Non-clinical and clinical	EMEA/H/SA/1359/7/2020 /III	The Scientific advice pertained to the following non-clinical and clinical aspects: Acceptability of cross-referencing to the non-clinical package for the T2D indication. Potential CMA strategy. Clinical development plans.
9 November 2023	Quality and clinical	EMA/SA/0000138184	The Scientific advice pertained to the following quality, and clinical aspects: Human factors engineering planning Clinical development aspects

The applicant received Scientific Advice on two occasions, as mentioned in the table above for the development of Semaglutide for treatment of NASH/MASH. The Scientific Advice pertained to the following quality, pre-clinical and clinical aspects:

- Human factors engineering planning
- Acceptability of cross-referencing to the non-clinical package for the T2D indication.
- Potential CMA strategy based on results from phase 2; proposal for additional evidence generation to fulfil the condition for the CMA pathway in the non-cirrhotic population considering standard of care treatment, selected events for adjudication and their definitions, process for digitalisation and reading of histopathological slides prepared from biopsied tissue, statistical analyses plan, secondary efficacy endpoints, plan for interim analysis, blinding and communication of the prespecified interim results, target dose selection and dose escalation regimen. Clinical pharmacology plans. Immunogenicity strategy. PROs to evaluate pain, ability to refer to evidence from T2DM and weight management programmes for safety, efficacy and clinical pharmacology, modelling analysis plan.

1.3. Eligibility to the centralised procedure

The applicant Novo Nordisk A/S submitted on 4 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Kayshild (semaglutide), through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 September 2023.

The applicant applied for the following indication: treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) in adults with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

1.4. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and/or blibliographic literature substituting/supporting certain test(s) or study(ies).

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0464/2021 on the agreement of a paediatric investigation plan (PIP) and on the granting of a waiver for a subset of the paediatric population.

At the time of submission of the application, the PIP P/0464/2021 had not yet been completed as some measures had been deferred.

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request(s) for consideration

1.7.1. Conditional marketing authorisation (CMA)

The applicant requested consideration of its application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of Regulation (EC) No 726/2004. See section 9.6.3.3 of this document.

1.7.2. Request for additional marketing protection

The applicant requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004. The applicant has decided to withdraw the application for the additional 1 year of marketing protection during the procedure.

1.8. Patient experience data

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application				***Section where discussed (if applicable)***
☐	Patient experience data submitted by the applicant:			
	☐	Clinical outcome assessments (COAs) such as		
		X	Patient-reported outcomes (PRO)	5.3.2.
		☐	Other	
	☐	Patient preference studies		
	☐	Observational studies/RWD designed to capture patient experience data		
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)		
	☐	Other (please specify)		
☐	Other patient experience data not submitted by the applicant but considered in this evaluation:			
	☐	Input informed from participation in meetings or public hearings with patient stakeholders		
	☐	CHMP early dialogue with patient organisations		
	☐	Third party interventions from patients and patient groups		
	☐	Other (e.g. medical literature, summaries/analysis from patient engagement activities - please specify)		

1.9. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Patrick Vrijlandt
Co-rapporteur:	Robert Porszasz

The application was received by the EMA on	4 March 2025
The procedure started on	27 March 2025
The CHMP rapporteur's first assessment report was received on	16 June 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	18 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	30 June 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	24 July 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 September 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	20 October 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 October 2025
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	13 November 2025
The applicant submitted the responses to the CHMP list of outstanding issues on	10 December 2025
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs´ Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	14 January 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kayshild on	29 January 2026

1.10. Final CHMP outcome

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed paediatric investigation plan (PIP) P/0464/2021 and the results of these studies are reflected in the summary of product characteristics (SmPC) and, as appropriate, the package leaflet. Relevant paediatric statement in Section 5.1 of the SmPC that the EMA has deferred a paediatric development has also been included.

1.10.2. Considerations related to orphan market exclusivity

Not applicable

1.10.3. Final opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kayshild is favourable in the following indication(s):

Kayshild is indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

The CHMP, therefore, recommends the granting of the conditional marketing authorisation subject to the conditions described in the following sections.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder shall submit periodic safety update reports every 6 months.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder has requested to align the DLP of the new EURD list entry with the DLP of the existing entry for semaglutide.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.6.2. Additional risk minimisation measures

No additional risk minimisation measures are proposed in the RMP.

1.10.7. Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Table 3: Specific obligations

Description	*Due date*
Post-authorisation efficacy study (PAES): NN9931-4553 (ESSENCE) In order to confirm the efficacy and safety of semaglutide in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), the MAH shall submit the final results of NN9931-4553 (ESSENCE), a phase III, double-blind, randomized, placebo-controlled study.	31 December 2029

1.10.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. Introduction

2.1. Therapeutic context

Note: The nomenclature for fatty liver disease has undergone revisions and a new nomenclature was announced at EASL Congress 2023. The term Non-alcoholic Fatty Liver Disease (NAFLD) has been updated to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Non-alcoholic Steatohepatitis (NASH) has been updated to Metabolic Dysfunction-Associated Steatohepatitis (MASH). In line with latest consensus, the term MASH has been used throughout the document.

Non-alcoholic steatohepatitis (MASH) is a progressive liver disease, part of the spectrum of non-alcoholic fatty liver diseases (NAFLD). It is estimated that the global prevalence of NAFLD is approximately 30% and increasing, with the highest prevalence seen in South America and the Middle East. The global prevalence of MASH in the general population is estimated to be between 4% and 7%, based on data from 2019. More recent data suggest a prevalence of asymptomatic MASH of 14% in a study of middle-aged people from the US.

In approximately 20% of people with NAFLD, fatty liver disease progresses to MASH, which is characterised by the presence of hepatic steatosis in at least 5% of hepatic cells with inflammation and hepatocyte injury (also known as hepatocyte ballooning), with or without evidence of liver fibrosis. As NASH progresses, fibrosis can lead to cirrhosis, which is associated with further complications such as hepatic decompensation events, liver failure and hepatocellular carcinoma (HCC). Consequently, NASH is one of the main indications for liver transplantation in many countries. The risk of mortality in NAFLD/MASH increases with disease severity, with cardiovascular disease being the most common cause of death in people with NAFLD. MASH progression is associated with increased risk of complications, and late diagnosis of MASH is associated with higher risk of complications. In people with MASH and advanced fibrosis, liver-related events are the most frequent complication. A strong association between NAFLD/MASH and increased cardiovascular risk is recognised with cardiovascular disease being the overall most frequent complication. NAFLD/MASH and cardiovascular disease share several cardiometabolic risk factors, including obesity, T2D, metabolic syndrome, hypertension, dyslipidaemia, and chronic kidney disease (CKD).

NAFLD and MASH are closely associated with metabolic abnormalities, such as visceral obesity, dyslipidaemia and insulin resistance, and may precede the development of obesity and T2D. Further, the presence of obesity and T2D increases the risk of fibrosis progression in MASH. Liver disease and mortality related to NAFLD are predicted to continue to rise with the increase in the prevalence of obesity and diabetes, and an ageing population.

The prevalence of NAFLD is higher amongst people with obesity than in the general population and is especially high amongst those with severe obesity (up to 90% according to some estimates).

Around 34% of people with obesity are believed to have MASH. NAFLD and MASH therefore occur in individuals without obesity, and global estimates indicate that 19% of people with NAFLD are lean (BMI<25 kg/m^2 for non-Asians and <23 kg/m^2 for Asians).

Amongst people with T2D, global data indicate that around 66% have MASH, with 41% having significant liver fibrosis.

NAFLD and MASH are multifactorial diseases. Contributing factors include dysregulation of the lipogenic pathway, oxidative stress, genetic predisposition, altered immune responses, and gut microbiome dysbiosis. There is a growing body of evidence linking NAFLD and MASH pathogenesis with

mechanisms of metabolic dysfunction, through liver lipid accumulation, insulin resistance, inflammation, apoptosis, and liver fibrosis.

The pathological features of MASH include steatosis, hepatocyte injury, inflammation, and varying degrees of fibrosis. Hepatocyte lipotoxicity and immune-mediated inflammation both play key roles in the pathogenesis of MASH. Hepatic steatosis is associated with lipotoxicity and cellular stresses such as oxidative stress and endoplasmic reticulum stress, which result in hepatocyte injury and apoptosis. Injured hepatocytes and activated Kupffer cells are thought to release proinflammatory cytokines and chemokines that trigger inflammation and fibrosis.

Clinical symptoms of MASH can be absent, and some such as abdominal pain or fatigue are not entirely specific to MASH and can also be difficult to quantify outside of validated questionnaires. Thus, MASH remains underdiagnosed, and people with MASH often present with advanced fibrosis or cirrhosis late in their disease course. Accordingly, there is a marked need for early diagnosis of MASH to manage the disease and the associated complications and avoid the diagnostic inertia that contributes to the substantial clinical and economic burdens of MASH.

Liver biopsies are sufficiently validated to assess the presence of MASH; however, the procedure is invasive and burdensome, contributing to diagnostic inertia. In alignment with current regulatory guidance, liver biopsies are, however, applied in clinical trials, including in the assessment of the degree of liver fibrosis and MASH disease activity. Histological evidence of fibrosis is classified from F0 (no fibrosis) to F4 (cirrhosis) on the MASH CRN fibrosis scale based on pathologist evaluation of a liver biopsy. The fibrosis progression rate in MASH is estimated at 7 years per stage of fibrosis.

MASH is a serious progressive disease with substantial clinical, humanistic, and economic burdens. Still, with liver fibrosis being reversible, the evolution of MASH can be bidirectional, and the progression of MASH could potentially be stabilised or even reversed. However, pharmacotherapeutic options for MASH are sparse and an urgent unmet need for development of novel therapies remains.

Excess body weight is an important risk factor for the development of MASH and progression of liver fibrosis. Although patients may achieve weight loss through lifestyle intervention, many are unable to maintain their weight loss. Global clinical practise guidelines recommend that clinicians consider pharmacotherapy for weight management (with a preference for GLP-1 RAs such as semaglutide 2.4 mg) as adjunctive therapy to lifestyle modification for individuals with obesity and NAFLD or MASH to promote cardiometabolic health and treat or prevent T2D, cardiovascular disease, and other end-stage manifestations of obesity.

2.2. Aspects of development

The application for semaglutide s.c. 2.4 mg (hereafter 'semaglutide 2.4 mg') once-weekly for MASH includes data from four clinical studies in the MASH development programme. Table 4 provides an overview. The present application is based on an interim evaluation of the pivotal trial 4553 at week 72, i.e., on data from part 1 of trial 4553. Data from a pivotal dose-finding phase 2 trial (trial 4296) and two supportive trials (trials 4381 and 4492) also contribute to the application.

Non-clinical and clinical information from previous clinical development programmes for semaglutide for the treatment of T2D (project ID NN9535; Ozempic®) and for weight management (project ID NN9536; Wegovy®) also support the present application.

Data from the cardiovascular outcomes trial (CVOT) SELECT (trial ID EX9536-4388) conducted by the applicant are included to confirm a beneficial effect of semaglutide 2.4 mg on cardiovascular risk in people at risk of MASH. Study EX9536-4388 demonstrated that Wegovy® reduces the risk of major adverse cardiovascular events (MACE; a composite outcome comprising cardiovascular death, non-fatal

myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight[46].

Population pharmacokinetic (PK) analysis was made based on phase 2 and phase 3 data in patients with MASH and F1 to F4 with regards to age, gender, race, and ethnicity.

There are limited data from the use of semaglutide for MASH in pregnant women.

Table 4: Clinical trials in the NN9931 programme supporting the present application

Study and MASH population	**Number of subjects** [a]	**Description**
Clinical pharmacology		
Study 4381 NAFLD (supportive)	67 subjects	72-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial investigating the effect of semaglutide s.c. 0.4 mg once daily versus placebo on liver fibrosis assessed by magnetic resonance elastography in subjects with NAFLD and increased liver stiffness.
Phase 2		
Study 4296 MASH F1-F3 (pivotal)	320 subjects, including 230 subjects with MASH F2/F3	72-week randomised, double-blind, placebo-controlled, six-arm, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. once-daily at three different doses (0.1, 0.2 or 0.4 mg) versus placebo in subjects with MASH F1-F3.
Study 4492 MASH F4c (supportive)	71 subjects	48-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial comparing the effect and safety of once-weekly semaglutide s.c. 2.4 mg with placebo in participants with MASH F4c.
Phase 3a		
Study 4553 MASH F2-F3 (pivotal)	800 subjects [b] / 1197 subjects [b]	240-week randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once-weekly versus placebo in participants with MASH F2-F3. Study 4553 has two parts with distinctive objectives: Part 1: To demonstrate that treatment with semaglutide improves liver histology compared to placebo after 72 weeks of treatment. Part 2: To demonstrate that treatment with semaglutide lowers the risk of liver-related clinical events compared to placebo after 240 weeks of treatment. The present application is based on data and results from an interim evaluation of trial 4553, i.e., on part 1.

F: fibrosis stage; F4c: compensated cirrhotic MASH (fibrosis stage F4c); SEE: substantial evidence of effectiveness.
a. number of randomised subjects.

b. According to the trial protocol, trial 4553 is planned to include a total of 1200 randomised subjects. By the data

cut-off date (05 September 2024), 1197 subjects had been randomised. The present application is based on an evaluation of data from the first 800 randomised subjects with respect to efficacy-related analyses and on data from all exposed subjects (1195 subjects) by the data cut-off date with respect to safety-related evaluations.

2.3. Description of the product

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue with 94% homology to human GLP-1. It is classified as a GLP-1 receptor agonist (RA). To prolong its half-life to approximately 1 week by slowing the degradation of semaglutide in circulation and decrease its renal clearance, a fatty acid moiety is attached to the peptide backbone of semaglutide. In addition, structural modifications to the backbone have been introduced to increase stability against the DPP-4-mediated degradation and to increase binding of semaglutide to albumin.

Substantial clinical experience with semaglutide for weight management and for the treatment of type 2 diabetes (T2D) are available. Semaglutide s.c. 2.4 mg once weekly (Wegovy®) is approved for weight management in several countries and regions. In the US, Canada and other places, Wegovy® is also approved for cardiovascular risk reduction. Once-weekly semaglutide s.c. (at dose levels 0.5, 1.0 and 2.0 mg) is approved for the treatment of T2D (Ozempic®) and, in the US, also for cardiovascular risk reduction in people with T2D and established cardiovascular disease. Oral semaglutide once daily is approved for the treatment of T2D (Rybelsus®).

The effects of semaglutide in the body are mediated via specific activation of the GLP-1 receptor and are generally well characterised. Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness and lowering feelings of hunger. Trials with semaglutide have shown reduced energy intake during an *ad libitum* meal, improved control of eating, less food cravings (for dairy and savoury foods), less desire for sweet food and less preference for high fat food compared to placebo. The mechanism of decreased energy intake is well-studied and involves GLP-1 receptors expressed in the pancreas and the brain in regions that regulates satiety and appetite. Semaglutide lowers blood glucose by a mechanism that increases insulin secretion and reduces glucagon secretion, both depending on the level of glucose in blood.

GLP-1 receptors are also expressed in the heart, blood vessels, as well as on kidney cells and cells of the immune system. However, the GLP-1 receptor has not been detected on liver cells.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

No inspection required.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection required.

3. Quality aspects

3.1. Introduction

The finished product (FP) is presented as Kayshild, solution for injection in pre-filled pen (0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg) containing 0.68 mg/mL, 1.34 mg/mL, 2.27 mg/mL and 3.2 mg/mL of Semaglutide as active substance (AS). Other ingredients are: Disodium phosphate dihydrate, Propylene glycerol, Phenol, Hydrochloric acid (for pH adjustment), Sodium hydroxide (for pH adjustment) and water for injections.

The product is available in 1.5 mL or 3 mL glass cartridge (type I glass) closed at the one end with a rubber plunger (chlorobutyl) and at the other end with an aluminium cap with a laminated rubber sheet (bromobutyl/polyisoprene) inserted. The cartridge is assembled into a disposable pre-filled multidose PDS290 pen made of polypropylene, polyoxymethylene, polycarbonate and acrylonitrile butadiene styrene. For the pre-filled pen, FlexTouch (0.25, 0.5, 1, 1.7 and 2.4 mg), a pack size of 1 pre-filled pen and 4 disposable NovoFine Plus needles is available.

Semaglutide, the active substance contained in Kayshild, is a glucagon-like peptide-1 (GLP-1) analogue substituted with a linker and a fatty acid side chain. It is produced using recombinant DNA technology in *Saccharomyces cerevisiae* followed by chemical modifications. Semaglutide is the same active substance contained in the currently authorised products Ozempic and Wegovy.

The Kayshild dossier includes a full Module 3 quality documentation. As this is a new application, all the data has been assessed accordingly.

3.2. Active substance

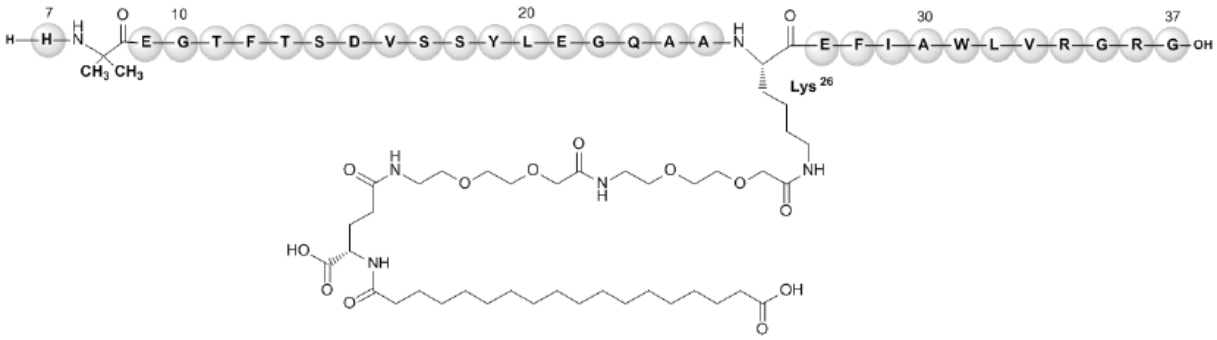
The information on semaglutide as described in Module 3.2.S. of this marketing authorisation application (MAA) is identical to Module 3.2.S of the Ozempic and Wegovy dossiers.

3.2.1. General information

The active substance of Kayshild is semaglutide. Semaglutide (INN) is a long-acting analogue of human glucagon like-1 peptide i.e. an Aib^{8}, Arg^{34}-GLP-1(7-37) analogue substituted on the ε-amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23- triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae) and chemical modification.

The structural formula of semaglutide is given in Figure 1.

Figure 1: The Chemical structure of semaglutide



Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once-weekly subcutaneous administration. The principal mechanism of protraction is albumin binding, which results in decreased renal clearance and protection from metabolic degradation. Furthermore, semaglutide is stabilised against degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme. Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner.

Reference to a current marketing authorisation, already held by Novo Nordisk, with the semaglutide active substance

Kayshild is very similar to multiple other authorised products of the applicant Novo Nordisk, namely Rybelsus (EMEA/H/C/004953) Ozempic (EMEA/H/C/004174) and Wegovy (EMEA/H/C/005422). Full module 3 quality documentation is included in the Kayshild dossier. The Applicant states that the module 3 documentation for semaglutide AS is identical to the already authorised products Ozempic and Wegovy. The manufacturing process of semaglutide AS for Rybelsus is slightly different to accommodate further processing into tablets for oral use. Nevertheless, as this concerns a new application, full information for the AS is provided and assessed accordingly. Satisfactory evidence of GMP compliance has been provided.

Following EMA approval of Ozempic and Wegovy, multiple variations have introduced changes to their dossiers. With respect to the active substance semaglutide, the most notable change to the module 3 documentation is the change from manufacturing process A to manufacturing process B, which resulted in a new yeast strain for production and a modified fermentation and recovery process. This change is approved for Wegovy under EMEA/H/C/005422/X/0016 and Ozempic under EMEA/H/C/004174/X/0043.

3.2.2. Manufacture, characterisation, and process controls

Manufacturing process

Semaglutide bulk active substance manufacturing is done at the Novo Nordisk A/S site in Kalundborg, Hallas Alle 1, DK-4400, Denmark. The sites listed here are already authorised for the manufacture and control of semaglutide bulk AS for Ozempic and Wegovy.

Semaglutide is manufactured in yeast (*Saccharomyces cerevisiae*) by expression of an extended semaglutide precursor polypeptide, which is subsequently cleaved enzymatically by enterokinase into the semaglutide precursor and chemically modified to form the final semaglutide molecule. The active

substance manufacturing process is split into fermentation, recovery, purification, modification and acylating agent synthesis parts, with the distinct steps described in flow diagrams, including the operational parameters and in-process tests. Critical in-process controls are marked. The description of the manufacturing process, process parameters and in-process tests is clear and adequate.

The intermediates and the final active substance are isolated and have defined storage containers, conditions and shelf life (24 months at -20 °C). The final active substance is freeze dried and stored -20 °C for up to 48 months. Overall, the description of the manufacturing process is considered acceptable.

Control of raw materials

Detailed descriptions of the raw materials used during the manufacturing of semaglutide Active substance are provided, with emphasis on the cell substrate, cell bank system, API starting materials (including materials for synthesis of the acylating agent). The construction of the expression plasmid and the source and history of S. cerevisiae strain producing the extended semaglutide precursor is described in detail. The cell banking system of master cell bank (MCB) and working cell bank (WCB) is explained and characterisation of MCB and WCB is reported. Stability results of MCB and WCB are available and raise no concerns.

No animal (or human) derived materials are used in the manufacturing of semaglutide.

The selection of starting materials is identical to that of the already approved product Wegovy.

Controls of Critical Steps and Intermediates

The critical in-process controls (the combination of critical operational parameters and critical in-process test) for the manufacturing process of semaglutide active substance (fermentation, recovery and purification) and the synthesis of the acylating agent are described. Critical in-process controls for fermentation, recovery and purification were selected through process justification studies in laboratory scale. For the acylating agent specification, limits are mainly based on the classification and fate of the impurities in this intermediate. The control strategy for the acylating agent is considered appropriate to ensure the quality of the material. Overall, the proposed critical in-process controls and their limits are described in sufficient details, are well justified and considered acceptable.

Process validation

The evaluation and validation of the semaglutide active substance manufacturing process (process B) is described. The fermentation and recovery processes were previously adopted from the approved Rybelsus product, which was validated in 2017, and validation of this part of the process was not repeated for Kayshild. Process validation for the purification part of the process was based on three consecutive batches for each step.

Laboratory scale process justification studies were used to establish and confirm the ranges for the (critical) in-process controls (parameters and testing) for the semaglutide process B and subsequently design the setup and acceptance criteria for process validation studies. The process validation acceptance criteria were based on a combination of the critical and non-critical operational parameters, critical in-process tests, additional testing (selected non-critical in-process tests to show consistent product quality) and specification tests on semaglutide active substance.

All the results of the fermentation, recovery, purification and final active substance batches met the set acceptance criteria. The removal of product and process related impurities was investigated during the validation of the purification part of the process. The levels of a large number of impurities were monitored over the course of the purification steps and the process was consistently capable of clearing those impurities to acceptable levels.

Additional process validation studies were performed to support changes introduced to the initial manufacturing process, appropriately validating the impacted parts of the process. The collection of reported process validation studies indicate that semaglutide can be consistently manufactured with acceptable quality and purity according to the established process B. The proposed commercial manufacturing process for active substance for Kayshild is considered validated.

Manufacturing process development

Semaglutide active substance was originally developed as the product of a synthetic manufacturing process. and semaglutide from this synthetic process was used for early phase 1 and phase 2 clinical trials. For clinical phase 3, the manufacturing process was transformed into a recombinant version of the process (process A), which was approved and initially commercialised for Ozempic and later for Wegovy. Recently, Process A was replaced with Process. This change involved the introduction of a different yeast strain which expresses an extended semaglutide precursor polypeptide, requiring the addition of the enterokinase cleavage step and an updated downstream purification process in the manufacture of subcutaneous semaglutide. Comparability between the pre- and post-change products has been demonstrated at the time. The AS manufacturing process now intended for the commercialisation of Kayshild is in accordance with the AS manufacturing process approved for Ozempic and Wegovy.

A clear overview of the differences of each of the iterations of the synthetic and recombinant versions of the semaglutide manufacturing process are provided including which version of the manufacturing process is used for which clinical trial, and which studies showed comparability of this version of the process and the process intended for market. Identical process development steps have been made for the authorised products Ozempic and Wegovy and the comparability assessments of the MAH have been approved for these products

Multiple comparability studies were performed to support the changes to the manufacturing process during development. Most notably, the comparability study between active substance batches manufactured with process A (used for clinical phase 3 trials) and the current manufacturing process B (intended for commercialisation) assessed aspects such as release specifications (and their historical ranges), stability trends, impurity and degradation profiles and verification and characterisation of structural and physico-chemical properties.

Overall, the changes made to the active substance manufacturing process during development have not negatively impacted the quality, safety, or efficacy of the product.

Characterisation

Data is presented from studies that characterised the structural and physico-chemical properties of semaglutide and the product related impurities that arise during the manufacturing process of the molecule and acylating agent.

The characterisation of the molecule was sufficiently thorough, confirming the semaglutide (primary) structure and determining the physico-chemical characteristics (appearance, solubility, pH in water, charge heterogeneity (pI), UV absorbance and water absorption) and properties (hydrophobicity, hydrodynamic radius).

Extra emphasis was put on the characterisation of the biological activity in relation to the content of semaglutide in active substance and finished product, as determined by RP-HPLC. In general, the specific bioactivity of semaglutide in active substance and finished product was shown to be very stable. A strong correlation was visible between the main peak content and the specific bioactivity of semaglutide, regardless of the purity of the sample. The main peak content determination with the RP-HPLC method offers a reliable measure of the bioactivity of semaglutide in both AS and FP.

Thorough investigations were performed into the fate of potential product related impurities in semaglutide active substance, evaluating their clearance during the different steps in the manufacturing process. This allowed the development of control strategies to ensure the quality of the manufactured active substance. Overall, the identification and characterisation of impurities presented is considered adequate.

The results from forced degradation studies show that semaglutide active substance and finished product are susceptible to degradation under most stress conditions (acidic and basic pH, heat, light, reduction and oxidation) but is resistant to mechanical stress.

The suitability of the RP-HPLC method to determine the levels of degradation products of semaglutide subjected to stress conditions was investigated. The specificity of the method was shown by confirming that placebo samples that were exposed to stress conditions did not generate peaks that interfered with semaglutide or semaglutide degradation product peaks. Additionally, evaluation of the mass balance of degraded samples showed that the RP-HPLC method is capable of detecting the majority of the degradation products of semaglutide subjected to extreme conditions. In summary, the RP-HPLC method is suitable for its intended purpose.

Similarly, the SE-HPLC method was shown to be suitable for the determination of the HMWP degradation products, which were found to be a major degradation product of light exposure/stress.

Taken together, the applicant has performed sufficiently thorough characterisation studies into the structure, physical/chemical properties and bioactivity of semaglutide, as well as the formation of degradation products when the molecule is exposed to stress conditions. The information gathered in these studies was used for the design of control strategies for semaglutide quality.

3.2.3. Specification

Specifications

The active substance specification is presented and includes tests for appearance, identity, content, hydrophilic impurities, hydrophobic impurities, sum of impurities, high molecular weight proteins, specific bioactivity, bacterial endotoxins, Total Aerobic Microbial Count, loss of drying and host cell proteins.

The control strategy for semaglutide active substance was developed, largely based on the identified critical quality attributes. For those attributes where a need was identified to control them at active substance release, specifications were set based on an approach focused on process capability (Cpk) calculations. Over 300 batches were used for setting specifications, including batches used for clinical phase 3 trials, commercial production for Process A and Process B and including PV batches. The presented specifications are identical to those of the already approved product Wegovy and are considered justified and acceptable.

A number of items are not controlled by the active substance specification, mostly process related impurities. This is justified by their highly effective removal during the manufacturing process of semaglutide. Residual DNA levels for process B batches were consistently below the WHO guideline limits. Similarly, the residual enterokinase levels were consistently below the limit of quantification of the analytical method. Therefore, the exclusion of these process related impurities from the specification is considered acceptable.

Analytical procedures and reference standards

The non-pharmacopeial analytical procedures from the active substance specification are provided. The controls to assess method performance are generally acceptable. For the Host Cell Protein determination, additional information is provided regarding the coverage of the antibody reagents used in this method, which is considered acceptable.

Compendial methods have been verified to be suitable for semaglutide active substance, and non-compendial methods have been validated according to ICH guidelines. Dilutional linearity was included as a validation parameter of the Host Cell Proteins method. Clear validation summaries of the non-compendial methods are provided. Taken together, the validation data presented for the analytical procedures of semaglutide active substance show that they are suitable for their intended purpose.

A two-tiered reference standard system is in place for Kayshild, consisting of a semaglutide primary reference material (PRM) and a semaglutide secondary reference material (SRM). The same reference materials are used for the approved semaglutide products Ozempic and Wegovy.

Extensive characterisation testing results are shown for the PRM. Because there is a well-defined correlation between content and bioactivity, the semaglutide unit for bioactivity is defined as one unit (U) is equal to one milligram of semaglutide. The content of semaglutide in the PRM batch is assigned by determining the nitrogen content (total protein content) and correcting this with the sum of impurities determined with RP-HPLC. This approach was used to calibrate and assign the content (with RP-HPLC) and specific bioactivity of the semaglutide SRM batches which are in turn used for the determination of the content and specific bioactivity of semaglutide active substance. Additionally, the semaglutide PRMs and SRMs serve as reference materials for identity determination.

Protocols for new reference standard lots are included in the dossier. Overall, the information provided regarding reference standards of semaglutide is considered adequate.

Batch analysis

Results from batch analyses of batches of semaglutide active substance manufactured according to process B are presented. Additionally, results from batches used during development (manufactured according to process A) are presented. The batches presented have been used in early phase 1 trials, phase 2 trials, clinical pharmacology studies and phase 3 trials and in some cases for clinical trials for other development products. All results complied with the proposed specification limits at the time of release.

Some of the batches have been used to support claims of comparability between batches manufactured for clinical studies and batches manufactured with the proposed commercial process. Results for batches which were manufactured to support the last manufacturing process change for semaglutide and therefore represent the intended commercial process, indicate consistent manufacturing of semaglutide active substance.

Container closure

Semaglutide active substance is a solid (freeze-dried) substance and stored in containers with screw caps below or at -20 °C. Stability samples are stored in equivalent containers of reduced size. The same storage container was used for storage of semaglutide active substance intended for use in clinical trials. The selection of the container closure system for semaglutide active substance is considered justified.

3.2.4. Stability

A shelf life of 48 months is claimed for semaglutide active substance when stored at −20 °C ± 5 °C. This claim is based on stability studies at the long-term storage condition and at the accelerated condition (+5 °C ± 3 °C). Active substance batches (three) manufactured with the manufacturing process B are considered the primary stability batches, and three process B PV batches and four process A batches are also included in the stability study. Currently, the stability studies at accelerated conditions are all finalised just like the studies for batches manufactured with process A. Studies at the long-term storage condition for batches manufactured with process B have 36 and 18 months of data reported. The applicant has committed to finalize these ongoing studies.

Stability testing items are acceptable, with a focus on impurities from the RP-HPLC and SE-HPLC methods. For both the long-term storage condition and the accelerated condition, the presented stability study data are within the acceptance criteria and show no changes over time. As process A and process B have been shown to be comparable and have the same storage container and conditions, and 60 months of stability data at the long-term storage condition has been reported for process A, the proposed shelf-life of 48 months at −20 °C ± 5 °C for semaglutide active substance is endorsed.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

Semaglutide finished products (0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg) are solutions for injection and are presented in four different concentrations containing 0.68 mg/ml, 1.34 mg/ml, 2.27 mg/ml and 3.2 mg/ml. The finished product is a colourless or almost colourless liquid free from turbidity and essentially free from particulate matter.

- Semaglutide 0.68 mg/mL is filled in a 1.5 ml cartridge and in a 3 ml cartridge (Semaglutide doses 0.25 and 0.5 mg both contain 0.68 mg in one mL but have different injectable volumes).
- Semaglutide 1.34 mg/mL, semaglutide 2.27 mg/ml and semaglutide 3.2 mg/ml are filled in a 3 ml cartridge

All finished products are assembled in a PDS290 pen-injector for semaglutide.

The composition of semaglutide 0.68 mg/ml, semaglutide 1.34 mg/ml, semaglutide 2.27 mg/ml and semaglutide 3.2 mg/ml is identical except for the content of the active pharmaceutical ingredient.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The primary container closure system of Kayshild Finished Product is a cartridge of either 1.5 mL or 3 mL. The cartridges are made of glass and are closed at one end with a cap with a (non-natural) rubber disc and at the other end with a rubber plunger. The cartridges are assembled in a PDS290 Pen-injector.

Reference to a current marketing authorisation, already hold by Novo Nordisk, with the semaglutide active substance

Kayshild is very similar to multiple other authorised products of the applicant Novo Nordisk, namely Ozempic (EMEA/H/C/004174) and Wegovy (EMEA/H/C/005422). Full module 3 quality documentation

for Semaglutide (the active substance of Kayshild), is included in the Kayshild dossier.

Kayshild is presented as a finished product in five distinct strengths filled in a multi-dose (PDS290) pen-injector. This is highly comparable with the approved product Wegovy, which offers the same strengths and an identical multi-dose PDS290 pen-injector. It should be noted that Wegovy offers two presentations for the delivery of 0.5 mg doses, i.e. 1.34 mg/mL, 1.5 mL cartridge and 0.68 mg/mL, 3 mL cartridge, whereas Kayshild 0.5 mg will only be available in the 0.68 mg/mL, 3 mL cartridge presentation. The main differences between the Kayshild and Wegovy submissions are related to streamlining of the documents that were submitted for Wegovy through variations and the exclusion of the 1.34 mg/mL, 1.5 mL cartridge multi-dose and the single dose pre-filled pen presentations of Wegovy.

Pharmaceutical development

The Kayshild finished products in a PDS290 pen-injector are developed based on the Quality Target Product Profile (QTPP) adopted from Wegovy. The semaglutide finished products intended for market are identical to the products approved as Wegovy and there are no differences in the physical, chemical and overall quality attributes compared to Wegovy.

The compositions of the finished products used during clinical trials and intended for market are described. All the multidose formulations intended for market were tested in the phase 3 clinical trial and these formulations are identical to those approved for Wegovy.

Single use prefilled syringes were also used for Phase 3 clinical trials (but are not intended for market). The used device is identical to the Wegovy single dose pen-injector system, and bio-equivalence with the multidose pen-injector has been appropriately demonstrated.

The development of the manufacturing process of Kayshild Finished Product for manufacturing of batches for Phase 1 and 2, Phase 3 and intended for market is described. The manufacturing process is identical to the process of Wegovy and has remained essentially the same from the manufacture of finished products for the clinical trials to the manufacturing process intended for the market. Comparability of the finished product used in clinical development and intended for market is demonstrated through the primary stability data and the process validation data of processes intended for market.

Extractable and leachable studies have been performed with the cartridge components and raised no concerns. The primary container closure system and PDS-290 pen injector were shown to be fully compatible with the Kayshild Finished Product.

Manufacture

The applicant provides an overview of all the sites involved in the manufacturing of Kayshild finished product. Formulation, filling and quality control of finished product cartridges is performed at the Novo Nordisk sites in Denmark (Bagsvaerd and Hilleroed) and at the Novo Nordisk site in Clayton, United States. Assembly, packaging and quality control of finished product is performed at the Novo Nordisk Site in Chartres, France and at Novo Nordisk Bgsvaerd, Denmark. The manufacturing responsibilities of sites for Kayshild are identical to those sites involved in Wegovy finished product manufacturing and control. Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The manufacturing process for Kayshild finished product is described through flow diagrams which include the process controls. The manufacturing process is identical to the process of Wegovy.

Following sterilizing filtration the product is filled aseptically into depyrogenated and sterilised cartridges. Closed cartridges are inserted into assembled pen-injectors forming the final finished

product. Non-critical process parameters for each manufacturing site and batch size as well as the manufacturing steps and process controls for the Pen-Injector are clearly presented in a separate document. The process time from the end of formulation to the end of filling of the sterile filtered final solution is described and is limited by the media fill validation for the specific site and batch size. Overall, the description of the manufacturing process and parameters is adequate.

The manufacturing process for the PDS290 Pen-injector for Kayshild is described clearly with a flow diagram showing the pre-assembly and final assembly steps. Additionally, exploded views of the parts of the spring and motor modules (that are pre-assembled) and their final assembly are shown.

Process controls

The controls of critical steps and intermediates of the finished product manufacturing process for Kayshild are described, including the actions when the limits are exceeded. Critical steps were identified through risk assessments (see also 3.2.P.3.5) and limits were set during process justification studies. The pH of the formulated solution and the temperature of the final solution were identified as critical and in-process controls and accompanying limits were set as described in this section. More general critical in-process controls include the bioburden before sterile filtration, the container closure integrity and extractable volume of the cartridges and the inspection for visible foreign particles. Sterilizing filtration is performed after formulation and at filling point and filter integrity testing is performed according to described instructions and limits.

Overall, the proposed critical in-process controls and their limits are described in sufficient detail, are well justified and considered acceptable.

Process validation / verification

The process validation and verification activities performed by the applicant to support Kayshild finished product manufacturing are a combination of process design, process validation and continued process verification. Kayshild finished product and the corresponding manufacturing process and manufacturing sites are the same as for the approved product Wegovy. The initial process development is based on experience from laboratory scale experiments, pilot/manufacturing scale batches for clinical trials, manufacturing scale batches for process design, process validation studies and continued process verification. Findings from the process design activities are described in process justification reports which also include the risk assessments that are the basis of the design of the critical process controls. The information provided by the applicant related to process design for Kayshild finished product is acceptable.

Initially the finished product (formulation and filling) manufacturing process was validated at the Bagsvaerd site and subsequently the Hilleroed and Clayton sites were added. The validation design and acceptance criteria are generally aligned between those sites, and a bracket design was applied including the lowest and highest semaglutide concentrations. The acceptance criteria for each site include the In-process controls, extensive sampling and non-critical process parameters. The process time from end of formulation sterile filtration to end of filling was included in the validation and at any time limited by the performed media fill validation for the specific process and the specific site. Sterile filter validation is described and the operational parameters for sterile filtration and filter integrity testing are supported. Validation of the assembly process of the PDS290 pen-injector included the appearance, injection time and activation force parameters that are in place as critical in-process controls. The process validation summary reports and the results contained in them raise no concerns and the established manufacturing process is capable of consistently and reproducibly producing Kayshild finished product.

3.3.2. Product specification

Specifications

A finished product specification is presented for each of the different concentrations and cartridge volumes of the finished product of Kayshild (0.68 mg/mL – 3.2 mg/mL, 1.5 mL and 3 mL cartridge). The specifications include appearance, identity, content, pH, high molecular weight proteins, impurities, bacterial endotoxins, sterility, identity and content of preservative, particulate matter, dose accuracy, and extractable volume.

The Kayshild finished products intended for market are identical to the products approved as Wegovy and there are no differences in the physical, chemical and overall quality attributes compared to Wegovy. Therefore, the control strategy and specification limits for Kayshild finished product are identical to those for Wegovy. A risk-based approach was used to establish the control strategy and to identify manufacturing process parameters that have an impact on the CQAs. The specifications and in-process controls for critical steps were based on this.

Specification limits are justified from a safety perspective. The levels of impurities in finished Product (HWMP, Hydrophilic and Hydrophobic impurities) used in non-clinical studies were always higher than the acceptance criteria during the entire finished product shelf-life. As the acceptance criteria for Kayshild finished Product are identical to the acceptance criteria of the approved product Wegovy, they are also considered clinically justified.

The proposed specifications are considered justified and the design of the finished product control strategy for Kayshild is considered acceptable.

Analytical procedures and reference standards

The non-pharmacopeial analytical procedures from the finished product specification are provided. For other methods, compliance to Ph. Eur. is claimed or ISO guidelines (Dose Accuracy) are referenced. The controls to assess method performance are generally acceptable. Only minimal changes were introduced going from procedures used during clinical trials and procedures to be used for Kayshild intended for the market.

Compendial methods have been verified to be suitable for Kayshild finished product and non-compendial methods have been validated according to ICH Q2 (R1) guideline. Clear validation summaries of the non-compendial methods are provided. The dose accuracy method (which is based on ISO-11608) was verified for suitability of testing the PDS290 Pen-injector for semaglutide finished products. Taken together, the validation data presented for the analytical procedures of Kayshild finished product show they are suitable for their intended purpose.

Reference Standards are described in the Active Substance Section.

Batch analysis

Batch release data for Kayshild finished product are provided supporting process validation, clinical trials and comparability. An overview of batch analysis results comparing multiple batches from the different commercial manufacturing sites shows that Kayshild finished product can be consistently manufactured with comparable quality.

Characterisation of impurities

For Kayshild finished product, risk assessments for elemental impurities and nitrosamine impurities were performed according to the appropriate guidance. Based on worst case calculations, none of the elemental impurities exceeded the 30% control threshold of ICH Q3D. The nitrosamine risk assessment (which takes into consideration semaglutide active substance, excipients, primary packaging materials and the finished product) concluded a negligible risk. The conclusions from the risk assessments for

elemental impurities and nitrosamine impurities are endorsed.

The characterisation of impurities in Kayshild finished product is described. The manufacturing of finished product introduces no impurities that were not present in the semaglutide active substance. During storage of the finished product, the formation of degradation products is visible. The impurities formed after storage at accelerated conditions were characterised to confirm their identity. No new impurities were found in degraded finished product batches, and the batches representative of the clinical trials had the same degradation products as the batches representative of the commercial process. The characterisation of Kayshild finished product impurities was sufficiently thorough and raises no concerns.

Container closure

The primary container closure system of Kayshild finished product is a cartridge of either 1.5 mL or 3 mL. The cartridges are identical to those used for Wegovy presentations of the PDS290 pen-injector and are made of chemically inert colourless glass as defined as Type I in Ph. Eur. 3.2.1. The cartridges are siliconized prior to depyrogenation and the silicon used for this was assessed in extractable studies. The cartridges are closed at the one end with a cap with a double layered laminated (non-natural) rubber disc. The layer that is in contact with the finished product is made of bromobutyl rubber. At the other end, a chlorobutyl rubber plunger closes the cartridge. The plunger is siliconized prior to sterilisation. Both the cap and the plunger meet the Ph. Eur. requirements for type I rubber. The description of the materials primary container closure system components is adequate.

The PDS290 multi-dose pen injector for Kayshild is already approved for use and commercialised by the applicant for other products, such as Wegovy. The PDS290 pen-injector for semaglutide variants can deliver 4 doses of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg or 2.4 mg of semaglutide per cartridge, in a volume of 370 µL or 750 µL. Compliance of the pen injector with ISO 13485 and ISO 11608-1:2014 is stated.

A detailed summary of the features of the different PDS290 pen-injectors indicate that the design, user interface, intended use and use environments of the Kayshild pen-injector overlap within the PDS290 family. This is leveraged to justify the bridging of studies on biological evaluation, human factors engineering and design verification. Technical information is provided detailing the operation principles of the PDS290 Pen injector and its key functional and additional features. The information provided is sufficient and raises no concerns.

The verification of the functional performance of the design of the PDS290 pen-injector for semaglutide is described. Testing of deliverable volume, dose accuracy, activation force, injection time and visual inspection were included. Based on the results reported it can be concluded that under a range of expected and extreme conditions, the PDS290 pen-injector for Kayshild functions adequately. The dose accuracy, injection time and activation force have been implemented in the control strategy for Kayshild finished product as specifications and in-process control testing providing an extra level of control of the quality of the PDS290 pen-injector.

The compatibility between the NovoFine plus needles (which are co-packaged with the PDS290 pen injector for Kayshild) and the PDS290 pen-injector was shown.

The applicant has performed various risk assessments according to ISO standards to identify and evaluate hazards and hazardous situations of the use of the PDS290 pen-injector. All identified risks have been reduced as far as reasonably possible. Reference is made to a human factors engineering and usability study report included in the submission. From the risk assessments and usability studies it can be concluded that the PDS290 finished products are safe and effective for the intended use.

A Declaration of Conformity (TÜV SÜD) is provided in the dossier. A notified body opinion confirming

compliance of the PDS290 pen-injector with the relevant safety and performance requirements according to Article 117, Regulation (EU) 2017/745 on Medical Devices is provided in the dossier.

3.3.3. Stability of the product

A description of the stability programme for Kayshild finished product is presented along with a summary of the purpose of each study, the batches included and their batch volume, storage conditions and the status at the time of the submission. The following studies are included:

- Primary stability studies
- Stability studies on PV batches from site Bagsvaerd, Hilleroe and Clayton
- Stability in device
- Stability testing of device functional parameters
- Stability studies on semaglutide manufactured using active substance process B
- In-use stability
- Photo stability

Studies were performed according to applicable ICH guidelines where relevant. For Kayshild finished product, the applicant proposes a 36 months shelf life at 5 °C ± 3 °C for finished product assembled in the PDS290 pen-injector, with an in-use period of 42 days (6 weeks) below 30 °C. The applicant indicates that no changes in formulation or in the materials that are in contact with the finished product were introduced between the primary stability batches and the batches of finished product manufactured with active substance from process B (intended for market). The stability studies were either performed in the primary containers (1.5 mL or 3 mL cartridge) or primary containers assembled into the PDS290 pen-injectors. The design of the described stability studies for Kayshild finished product is acceptable.

At the long-term storage condition (5 °C ± 3 °C), primary stability batches show some upward trends in the impurity levels over the course of 36 months, while content of semaglutide remains stable. However, all results remain within the shelf-life acceptance criteria for long term-storage, over all the 16 primary stability batches. No changes are observed for attributes. Stability studies at the long term-storage condition for batches from Process Validation, batches assembled in the PDS-290 pen injector and batches manufactured with active substance material from Process B are not all finalised yet but follow the same trends.

When the primary stability batches are stored at accelerated stability conditions (25 °C ± 2 °C), similar trends are visible compared to the long-term storage condition. Trends in impurities are more pronounced, as expected. A slight decrease in semaglutide content is visible. Batches from Process Validation, batches assembled in the PDS-290 pen injector and batches manufactured with active substance material from Process B follow the same trends.

A Stability study of the PDS290 pen-injector functional parameters (Dose Accuracy, Injection time, Activation force) support the proposed shelf life of 36 months at 5 °C ± 3 °C.

The proposed in-use period for Kayshild is 42 days below 30 °C and the in-use stability studies on primary batches support this. This includes in-use simulation close to manufacturing date, mid-shelf life and near the end of shelf life. The efficacy of the preservative phenol is maintained during the in-use period, in line with the requirements in Ph. Eur. Dose accuracy of the pen-injector was confirmed at the end of the in-use period.

Photostability studies in line with ICH guidelines showed that finished product in PDS290 Pen-injector with the cap on is stable when exposed to light, indicating that the device provides adequate protection from product degradation. Without the cap, the finished product shows increased degradation. In line with the findings in the photostability studies, instructions regarding the pen cap are found in the SmPC: "Keep the pen cap on when the pen is not in use in order to protect it from light".

Finally, the applicant reports that freezing of Kayshild finished products poses a risk for the sterility of the product and should therefore be avoided. Appropriate instructions are included in the SmPC: "Store in a refrigerator (2 °C-8 °C). Keep away from the cooling element. Do not freeze".

Based on the data presented in the Kayshild finished product stability studies, the applicant proposes a 36 months (3 years) shelf-life for finished product assembled in the PDS290 pen-injector at 5 °C ± 3 °C. This is endorsed. The proposed shelf life and in-use period are correctly reflected by the SmPC.

3.3.4. Post approval change management protocols

A set of Post-Approval Change Management Protocols is included in this submission. All of the PACMPs presented for semaglutide active substance for Kayshild or for Kayshild finished product have been previously approved for Wegovy and in some cases the Type IB variation for the specific change detailed in the protocols has also been approved.

PACMP for equipment at the site Kalundborg

A protocol for the introduction of an additional equipment at the Kalundborg site of Novo Nordisk is described. This protocol is a generic protocol which can be used for the introduction of equipment at this specific site and has been already executed for the introduction of an additional equipment for the manufacturing of semaglutide active substance for Wegovy and is included in the current dossier for Kayshild.

The protocol is written in line with EMA/CHMP/CVMP/QWP/586330/2010, Questions and answers on post approval change management protocol, with clearly described changes, a risk assessment of the proposed change, the design of a comparability study and the reporting category and documents to be submitted. The comparability study proposed contains an assessment of active substance release specification data, comparative characterisation of impurity profiles by HPLC and stability trends at accelerated conditions. The PACMP for an additional equipment at site Kalundborg is acceptable.

PACMP for Additional Purification Facility - Building KA, Kalundborg, Denmark

A protocol for the introduction of an additional purification facility for semaglutide in Kalundborg is presented. This protocol was approved for Wegovy and no reporting variation has been submitted for Wegovy or for Kayshild.

In the protocol, it is proposed to introduce an additional purification facility for semaglutide active substance at the Kalundborg site. A site-specific technical adaptation will be introduced.

The change is described clearly and is accompanied with a risk assessment of the impact of the described changes. The process validation and comparability studies proposed to support this change are designed based on this risk assessment. The comparability study assesses data from Critical in-process tests, active substance release tests, HPLC impurity profiles, stability studies at accelerated conditions and additional tests for process related impurities, and the design is endorsed.

The protocol is written in line with EMA/CHMP/CVMP/QWP/586330/2010, Questions and answers on post approval change management protocol and raises no concerns.

PACMP for Additional Finished Product Manufacturing Sites

A general protocol for the introduction of an additional manufacturing site for the formulation, filling and inspection of bulk semaglutide finished products is presented. The formulation, method of manufacture, filling, container closure system, testing, and specifications at the proposed facility will be the same as that of the currently approved manufacturing site(s). This protocol is highly similar to a protocol approved for Wegovy.

The protocol contains a risk evaluation of adding the additional manufacturing site and a testing plan to demonstrate comparability. Process validation will be performed according to a scenario that depends on which finished product concentrations and/or cartridge volumes will be manufactured at the new site.

Testing to support the change includes validation testing (including extensive sampling to evaluate homogeneity, in-process control testing, release testing (against specifications and for comparability) and stability testing. The validation strategy is in-line with the validation strategy described for Kayshild finished products. This is endorsed. When applicable, analytical test methods for Kayshild finished product quality control will be transferred to the new site without introducing any changes. The protocol is written in line with EMA/CHMP/CVMP/QWP/586330/2010, Questions and answers on post approval change management protocol and raises no concerns.

3.3.5. Adventitious agents

The Semaglutide that is used as an active substance in Kayshild is manufactured recombinantly in yeast. *Saccharomyces cerevisiae* does not support the propagation of mammalian viruses. No raw materials or excipients of human or animal origin are used for the manufacture of semaglutide AS or Kayshild FP. Testing for bacteria, fungi and mycoplasma is performed adequately. The conclusion of the applicant that the finished product is safe with regards to virus, transmissible spongiform encephalopathy agents, bacteria, mycoplasma, and fungi is endorsed.

3.3.6. Genetically modified organisms (GMO)

Not applicable.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Kayshild is a preparation of the GLP-1 agonist semaglutide, suitable for once-weekly subcutaneous injection. Kayshild is very similar to multiple other authorised products of the applicant Novo Nordisk, namely Ozempic (EMEA/H/C/004174) and Wegovy (EMEA/H/C/005422).

The presented information on development, manufacture and control of the semaglutide active substance is satisfactory.

Kayshild is presented as a finished product in five distinct strengths filled in a multi-dose (PDS290) pen-injector. This is highly comparable with the approved product Wegovy, which offers the same strengths and an identical multi-dose PDS290 pen-injector. The presented information on development, manufacture and control of the finished product is satisfactory.

3.5. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

Semaglutide has a 94% structural homology to native GLP-1, a molecular weight of 4113,58 g/mol and is good soluble in an aqueous solution. Semaglutide is suitable for once-weekly administration in humans.

The pharmacological mechanism of GLP-1R agonists is well described in the literature, with blood glucose lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1R agonists are the pancreas (beta-cells), the gastrointestinal system and the brain. The amino acid sequence of GLP-1 is preserved in mammals and only one receptor, the GLP-1R, has been identified. Rat and human GLP-1R have 90% homology and monkey and human 99%. The GLP-1R is a G-protein coupled receptor and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase leading to increased cAMP accumulation.

Semaglutide is approved in the EU for treatment of type 2 diabetes mellitus and for weight management. Two new non-clinical studies dosing semaglutide 2.4 mg are presented to support the proposed indication:

- DIO-NASH mouse (Diet-Induced Obese Non-Alcoholic SteatoHepatitis, study 321911), Semaglutide efficacy on NASH-relevant parameters in male C57Bl/6 mice fed a DIO-NASH (high fat, -fructose, -cholesterol) diet

- CDAA-HFD-NASH mouse (Choline Deficient Amino Acid defined High Fat Diet Non-Alcoholic SteatoHepatitis, study 321945), Effect of semaglutide on NASH-relevant parameters in male C57Bl/6 mice fed a CDAA HFD (choline-deficient, amino acid-defined) diet.

4.2. Analytical methods

The methods developed for analysis of semaglutide in plasma with LC-MS/MS (mouse, rat, monkey) and ELISA (mouse, rabbit, monkey) were sufficiently validated with satisfactory assay performance.

The LOCI assay was affected by interference from the plasma matrix and dilution linearity issues with a larger impact on low concentrations leading to underestimation of semaglutide exposures (rat, rabbit, monkey). For this reason, the plasma assay in rat and monkey was replaced by LC-MS/MS and ELISA. In the rabbit embryo-foetal development study (207360), measured concentration were below 200 nM, where Hook effect occurred and the values for dose-normalised average concentrations (Cavg) did not deviate from the other tests.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

In support of the present indication for MASH, two non-clinical studies were conducted to evaluate the biological activity and mechanism of action of semaglutide in the liver: DIO-NASH mouse model (Diet-Induced Obese Non-Alcoholic SteatoHepatitis) and CDAA-HFD-NASH mouse model (Choline Deficient Amino Acid defined High Fat Diet Non-Alcoholic SteatoHepatitis).

In the DIO-NASH model, NASH-progression is driven by metabolic dysfunction and mice display significantly elevated quantitative markers of liver lipid accumulation, inflammation and liver fibrosis. Semaglutide reduced body weight and liver weight compared to vehicle, and reduced circulating markers of liver injury, reduced inflammation and disease activity as measured by the NAS score. Maximum effects were reached by dosing 123 µg/kg subcutaneously daily for 16-24 weeks. In the liver, semaglutide decreased lipid accumulation. Non-fasted plasma insulin was elevated in the DIO NASH model compared to chow vehicle and semaglutide significantly reduced the glucose excursion in an intraperitoneal glucose tolerance test (ipGTT).

In the CDAA-HFD model, NASH progression is driven by blocked export of very-low density lipoproteins secondary to choline deficiency and mice are lean and show non-metabolic driven increases in hepatomegaly, plasma liver enzymes, steatosis, inflammation and progressive fibrotic development. Semaglutide reduced body weight and liver weight compared to vehicle and reduced circulating markers of liver injury and inflammation. Maximum effects were reached by dosing 20 µg/kg subcutaneously daily for 6-12 weeks. However, semaglutide did not reduce lipid accumulation in the liver, nor did it decrease disease activity. When challenged in an ipGTT, semaglutide treatment did not further affect glucose excursions. Fasting insulin was reduced in animals on CDAA HFD diet compared to chow fed animals. On request it was clarified that it was expected that semaglutide would not reduce hepatic triglyceride levels in the CDAA-HFD mouse model, therefore translatability to humans is not limited. In the CDAA-HFD model, the choline deficiency coupled with lower levels of dietary methionine blocks the export of triglycerides in VLDL particles and severely limits fat oxidation. Consequently, it becomes nearly impossible to dispose of the fat trapped within the liver in this pre-clinical model. This does however still allow for supporting the MoA understanding: the beneficial effects observed following treatment with semaglutide despite persistent hepatic steatosis suggest that semaglutide does not decrease MASH and hepatic fibrosis solely through reduction of hepatic lipids. To study the effect of semaglutide on hepatic steatosis, the GAN DIO NASH model is a better translational choice of model and, indeed, hepatic lipids are reduced following treatment with semaglutide similar to what is observed in patients.
In the CDAA-HFD model, only terminal blood samples were included. Accordingly, study specific ALT/AST measurement at pre-dose i.e., baseline for the semaglutide and chow reversal group are not available. However, there is no reason to believe that the semaglutide and chow reversal groups should be different at week 6 compared to the baseline group as all groups had been on the same diet and none of the groups had been dosed at this point in the study. Accordingly, it can be assumed that the starting levels of ALT/AST were identical across groups. With that in mind, a reduction in ALT/AST was observed between week 6 and week 12 (the two last timepoints for which ALT/AST data are available) in the vehicle group. If semaglutide had no effect on liver enzymes, the decrease in ALT/AST should follow the same pattern. However, this is not the case: ALT/AST was decreased already after 6 weeks with semaglutide, showing the effect on liver enzymes with treatment. Hereafter, the effect

"plateaus out" allowing the vehicle group to 'catch up' and eliminating the possibility to detect an effect of semaglutide at this later timepoint. In support of this interpretation, longitudinal data on ALT and AST have been reported by *Matsumoto et al (2013)* in the CDAA-HFD model showing that liver enzyme levels peak around six weeks after initiating the CDAA-HFD and then continuously decline during the subsequent 12 weeks.

A scientific discussion about how semaglutide directly and indirectly modulates MASH was provided on request. In MASH, insulin resistance in hepatic and adipose tissues alongside enhances hepatic *de novo* lipogenesis increases lipolysis in the adipose tissue. The increased lipolysis promotes the accumulation of lipids in the liver and delivers an excessive amount of toxic lipid species which may cause cellular stress and inflammation. Semaglutide treatment improves insulin resistance thereby restoring the metabolic balance in the liver and adipose tissue. Furthermore, though the GLP1 receptor is not expressed in liver, central GLP1R activation by semaglutide decreases circulating levels of TNFα via adrenergic and opioid receptor signalling and attenuates systemic inflammation and contributes to the beneficial effects of semaglutide on liver fibrosis. Given the lack of GLP1 receptor expression in the liver of both humans and mice, the effects on MASH are considered indirect, likely mediated both by the weight-loss *per se* and by weight-loss-independent mechanisms. The current non-clinical data does not discern weight-loss-dependent from weight-loss-independent effects as weight-matched control groups, i.e. a group in which food intake was reduced to induce a weight loss identical to semaglutide, were not included.

On request it was clarified why no non-rodent species or independent fibrotic model (e.g., carbon tetrachloride, bile duct ligation) was included to confirm reproducibility of antifibrotic activity and to ensure translational validity. The applicant has conducted pharmacology studies in the non-clinical NASH models considered to offer the highest degree of translation to humans. The model selection is supported by the international LITMUS consortium which ranked the GAN DIO-NASH Mouse model among the highest, most translational murine models of NASH. At the time of study conceptualisation, rodent models were more thoroughly characterised in terms of disease progression and, especially, response to pharmacotherapy compared to non-rodent models. Consequently, it was decided not to use non-rodent models. Presently, human data is available to support the effect of semaglutide in patients with MASH and show translation between the applied mouse models and humans. Bridging studies in non-rodent species are not planned to be performed, in accordance with the 3Rs, as they are considered to provide minimal additional value.

Toxin-induced models do not recapitulate the lipo-toxicity which is central to the pathogenesis of NASH. As the GLP-1 receptor is not expressed by the liver and the beneficial effects of semaglutide in MASH are indirect, the applicant considered that the toxin-induced models are of less translational relevance also with regards to fibrosis. In contrast, the lipo-toxicity is reflected in both the GAN DIO NASH model and in the CDAA-HFD model and these, therefore, offer more relevant and translational alternatives to study the effect of semaglutide in MASH. There is no rat model equivalent to the GAN DIO NASH mouse model and the mouse CDAA-HFD model was selected instead of a rat CDAA-HFD model because the mouse model had been much better characterised. This was accepted by the CHMP.

In support of semaglutide for type 2 diabetes mellitus and for weight management data was assessed at the time of marketing authorisation application. The efficacy pharmacodynamic studies using semaglutide have been conducted *in vitro*, *ex vivo* as well as in vivo in normal, diabetic and obese rodent models and normal pigs and minipigs. The studies have shown that semaglutide has pharmacological properties consistent with a GLP-1R agonist showing increases of insulin secretion, plasma glucose lowering and weight lowering due to a reduction of food intake. Furthermore, it was confirmed that semaglutide crosses the BBB, and that its effects include central homeostatic mechanisms involving the hypothalamus and brain stem.

4.3.1.2. Secondary pharmacodynamics

A broad profiling screening panel using 68 biochemical receptors, ion-channels and neurotransmitter transporters did not show a competitive interaction with semaglutide. Also, semaglutide, up to 10 µM, did not activate the glucagon receptor. No secondary pharmacology effects are expected from semaglutide.

4.3.1.3. Safety pharmacology

The safety pharmacology studies were designed to investigate the effect of semaglutide on major organ function (central nervous system, respiratory system and cardiovascular system). Exposure measurements in both the rat CNS study and in the cynomolgus monkey cardiovascular study exposure of treated animals confirmed exposure of treated animals could correlate effects to the exposure. Due to differences in dosing frequency between humans (once weekly) and animals (daily/biweekly), the mean maximal plasma concentration (Cmax) at the maximum recommended human dose (MRHD) of 2.4 mg/week has been used for exposure comparison in the safety pharmacology section. A value of ~75 nM has been taken as the mean Cmax in humans at MRHD.

The effect of semaglutide on the central nervous system was studied in the rat CNS (Irwin) study. In this study no significant gross behavioural or physiological changes were observed, during the 24 h post-dose period in rats receiving subcutaneous treatment with semaglutide. Abnormal gait (walking on toes), passivity, decreased touch response, increased urination, lethargy and piloerection were observed in animals administered 95 µg/kg semaglutide, which corresponds to ~0.6 fold the maximal plasma (Cmax) exposure at the maximum recommended human dose (MRHD). The observed effects are considered to be pharmacology related and likely due to the activity at GLP-1 receptors in the CNS. The No Observed Adverse Effect Level (NOAEL) was determined to be 22 µg/kg.

Semaglutide, given subcutaneously at doses up to 84 µg/kg, had no statistically significant effects on respiratory rate, tidal volume or minute volume up to 24 hours after dosing in male SD rats.

Treatment with semaglutide (>100-fold higher concentration than the mean maximal plasma concentration at the MRHD) produced no inhibition of hERG channel tail current recorded in HEK293 cells stably transfected with hERG cDNA, nor an effect on action potential parameters in isolated female rabbit Purkinje fibres. This indicates that semaglutide has a low potential for QT prolongation.

The acute effect of semaglutide on cardiovascular function was studied in male conscious unrestrained cynomolgus monkeys equipped with telemetry transmitters and dosed subcutaneously with ascending doses of semaglutide. No effects related to semaglutide were observed on arterial blood pressure (systolic, diastolic and mean) or the lead II ECG variables examined (RR, PR, QR, QTcF and QTcQ intervals or QRS duration). In conclusion, it was found that there were no clinically relevant findings in cynomolgus monkeys in single doses up to 470 µg/kg (about 6-fold above MRHD based on Cmax).

In addition, in the repeat dose toxicology study at week 13, 26 and 52, the cardiac electrophysiology was monitored by ECG in male and female telemetered cynomolgus monkeys (10, 60 and 360 µg/kg twice-weekly sc). In this 52-week toxicity monkey study, a left-bundle-branch-block was observed in one female animal at high dose of 360 µg/kg (~10-fold above MRHD). The animal exhibited no clinical signs attributable to the ECG finding and histopathology revealed no correlating changes. Cardiac bundle-branch blocks are an occasional finding in monkeys and humans and are in most cases a consequence of other underlying cardiac diseases. Although histopathology revealed no changes in the heart, the ECG finding was considered adverse. When heart rate was analysed as change from baseline, it was shown that there seems to be a transient increase in heart rate at week 26 which

returns to baseline values at week 52 in males but remains elevated at week 52 in high dose females. This finding supports the increase in heart rate seen in patients in the clinical trials.

A renal function study was performed to evaluate the acute effects of semaglutide on the renal system in the rat. Semaglutide caused an acute transient increase in diuresis during the first 8 hours after dosing at the highest doses (23 and 89 µg/kg) and a decrease in the diuresis parameters thereafter. These observations are well known effects of GLP-1R agonists in the rat. Acute effects on diuresis have also been shown in humans with native GLP-1 but not following chronic administration of GLP-1R agonists. The NOAEL was determined to be 5 µg/kg.

4.3.1.4. Pharmacodynamic drug interactions

Non-clinical pharmacodynamic drug interaction studies have not been conducted with semaglutide, which is agreed upon. GLP-1R agonists have been reported to delay gastric emptying but this was evaluated in clinical trials.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

The pharmacokinetics were dose-proportional and there was no gender dependency. The absorption of semaglutide from the subcutaneous injection site was rapid in mouse and rat, but slower in rabbit, monkey and minipig. The time to maximum concentration (Tmax) was 2 to 3 hours in mouse and rat, and about 24 hours in rabbit, monkey and minipig. The bioavailability ranged from 86% (monkey) to 94% (minipig). In human, the bioavailability was equally high (89%), but the absorption was slower (Tmax 60 h).

The mean dose-normalised concentration was similar in monkey and human, while it was lower in mouse, rabbit and rat due to faster clearance. The terminal half-life was estimated to be 8 h in the mouse, 11 h in the rat, 28 h in the rabbit, 51 h in the monkey and 148 h in human.

The distribution volume was low (0.2 L/kg) following i.v. administration in the monkey, which corresponds approximately to the volume of extracellular water and indicates that a high fraction of semaglutide is circulating in plasma and extracellular fluid.

Comparison of single dose pharmacokinetics in monkey after subcutaneous and intravenous dosing indicated that elimination is not limited by the absorption rate from subcutis.

4.3.2.2. Distribution

The pharmacokinetics following repeated dosing of subcutaneous semaglutide showed a linear relationship between doses and exposures. No gender differences were noted. The dose normalised exposure was generally lower for mice, rats, rabbits and minipigs compared to monkeys and humans due to faster clearance. To ensure continued exposure, and to mimic the once-weekly exposure profile in humans, once-daily dosing was used in mice and rats, and twice-weekly dosing was used in monkeys. At these dose intervals, there was no apparent (i.e. < 2-fold) systemic accumulation.

No difference in exposure was observed between pregnant and non-pregnant animals following repeated administration of semaglutide to rats, rabbits and monkeys. However, rabbits showed some accumulation in the embryofoetal development study, but the wide range (1.3 up to 13-fold) and the few data do not permit a clear conclusion.

Plasma protein binding

In vitro binding studies showed that the plasma protein binding was high, >99%, and that albumin was the primary protein responsible for binding of semaglutide in plasma. The potential binding to other plasma proteins has not been studied. The fraction unbound was somewhat lower in plasma from mouse, rat and rabbit (0.07-0.28%) as compared to plasma from monkey (0.46%) and human (0.36%).

Distribution to red blood cells

As determined in rats, whole blood concentrations of semaglutide-related material were approximately half of the values in plasma, suggesting no preferential uptake into red cells.

Tissue distribution

Distribution studies in rats showed the highest presence of semaglutide-related material in blood and in highly perfused tissues.

After subcutaneous administration of [3H]-Oct- or [3H]-Tyr-labelled semaglutide, the tissue-to-blood ratios of semaglutide related material were generally below 1. The highest levels were associated with lung, tooth pulp, kidney (cortex and medulla), bladder, adrenal medulla and uterus. The high levels in the bile ducts, up to and including 3 days after dosing, suggests that biliary secretion may have played an important role in elimination by contributing to faecal excretion. In addition, the moderate levels of radioactivity present in the kidneys and bladder also suggest that urinary elimination occurred. The lowest concentrations were present in the central nervous system (brain and spinal cord) and white fat.

The distribution and concentrations of [3H]-Oct-semaglutide related material in male pigmented rats were similar to that in male albino rats, suggesting that semaglutide related material does not bind to melanin or accumulate in pigmented tissues.

Placenta transfer

Semaglutide related material passed the placental barrier in rats and rabbits but distributed to foetal tissue at levels lower than in dam plasma (<4%). This suggests limited distribution across placenta. Nevertheless, a single dose of semaglutide to pregnant rats at GD18, led to low, but measurable levels in foetuses at 24h post dose and effects on the foetus were observed.

Excretion into milk

Semaglutide and metabolites are excreted into rat milk. Mean concentrations were 3-12 times lower than in plasma up to 24 hours after a subcutaneous dose 0.3 mg/kg/day semaglutide. There are no data on the excretion of semaglutide in human milk. A risk to the newborns/infants cannot be excluded. Semaglutide should not be used during breastfeeding.

4.3.2.3. Metabolism

The *in vitro* metabolism of radiolabelled semaglutide was studied in hepatocytes from rats, monkeys and humans. Limited metabolism was observed in all species, and no unique human metabolites were formed. It was shown that semaglutide is metabolised by proteolytic cleavage of the peptide backbone by neutral endopeptidase (neprilysin) and sequential beta-oxidation of the fatty acid side chain.

The *in vivo* metabolism of semaglutide was investigated by chromatographic metabolite profiling of plasma, urine and faeces from rat, monkey and human following administration of radiolabelled semaglutide. The metabolite profiles from plasma were similar across species. The peptide backbone of

semaglutide was metabolised by proteolytic degradation, and the fatty acid moiety was degraded by sequential beta-oxidation.

Semaglutide was the most abundant component in plasma across animal species, accounting for 69-93% of the total amount of semaglutide related material and 4 to 12 metabolites which constituted in total only a small part in relation to the amount unchanged semaglutide.

In human plasma, there were 6 metabolites, each contributing 0.4-7.7% to the total amount of semaglutide-related material, whereas the contribution of unchanged semaglutide was 83%. The largest metabolite (P3) contained at least three components (P3A, P3B and P3C). P3C was characterised as a semaglutide isomer. P3B was identified as a peptide metabolite from semaglutide, following proteolytic cleavage and the loss of the first 13 amino acids. Neprilysin could form the metabolite P3B *in vitro*. No further structural information could be provided P3A and P3C, due to the limited amounts in plasma. All human metabolites are also present in rats, and P3, P5 and P7 are also present in monkeys.

The two primary metabolites in human (U6 and U7) were identified as the free Lys26 amino acid bound to the ADO-linker with butyric (C4) or hexanoic (C6) di-acid side chains attached. These metabolites are products formed from full proteolytic cleavage of the peptide backbone with sequential removal of C2-units by beta-oxidation of the di-fatty acid side chain. The urine metabolite U22 was identified as semaglutide. Only limited amounts of unchanged semaglutide were observed in urine of animals (1%) and humans (3%).

The pharmacological activity of the metabolites has not been evaluated. These metabolites, such as P3B and P3C, may be pharmacologically active since they have structural similarities with semaglutide. The possible contribution of these metabolites to the pharmacological activity of the final product will be minor, because in plasma they are only a small part in relation to the amount of unchanged semaglutide (< 7.7%).

4.3.2.4. Excretion

Semaglutide was extensively metabolised prior to elimination. In human, unchanged semaglutide were observed in small amounts in human urine (3.1%) but was not detected in faeces. In rat and monkey, both urine and faeces were equally important as excretion routes of semaglutide and related material. The contribution of urinary excretion was 37% in rats and 30% in monkey, whereas the contribution of faecal excretion was 35% and 21% in these species, respectively. In human, the urinary excretion was the predominant route of excretion (53%), followed by faeces (18.6%).

In bile-cannulated rats, bile was primary route for excretion of semaglutide-related material into faeces (48%), of which approximately 14% was unchanged semaglutide. Other components in bile were metabolites, each accounting for less than 5% of the administered dose.

4.3.2.5. Pharmacokinetic drug interactions

The results of the *in vitro* and *in vivo* studies on the drug interaction potential of semaglutide have been evaluated in the clinical assessment report.

4.3.2.6. Other pharmacokinetic studies

No other pharmacokinetic studies were reported.

4.4. Toxicology

4.4.1. Single-dose toxicity

A single dose up to 12mg/kg (mouse) or 7.532 mg/kg (rat) was generally well tolerated. Observed major findings such as reduced body weight and food intake showed quick recovery and can be related to the pharmacological action of semaglutide.

4.4.2. Repeat-dose toxicity

Repeated dose studies in mice, rats and cynomolgus monkeys revealed mainly effects related to the pharmacological action of semaglutide. Reduction in food intake and body weight gain were dose limiting, as exceeding the maximum tolerated dose in monkeys led to dehydration consequently followed by euthanisation. However, dose escalation improves tolerability.

Hypertrophy of Brunner's glands of the duodenum was observed in rats after 26 weeks of treatment. This effect is likely due to the high expression of GLP-1R on Brunner's glands. However, there was no progression to hyper- or neoplasia in the rodent carcinogenicity studies, and no similar observations in cynomolgus monkeys dosed for 52 weeks. Therefore, this observation is not considered a safety concern in humans. Thyroid C-cell hyperplasia was only observed in mice at all dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect.

The 52-week monkey study revealed a chronic left bundle-branch-block in one high dose female. Although the abnormal ECG was confined to a single animal, the observation was considered adverse.

An increase in uterus fluid distension and luminal dilatation is seen in rats after 26 weeks of dosing. These findings are likely due to differences in the stage of the sexual cycle which could be treatment related, and likely secondary to reduction in body weight. Daily subcutaneous administration to Sprague-Dawley rats over a treatment period of 13 weeks with 0.48 mg/kg/day and 0.45 mg/kg/day semaglutide respectively, demonstrated generally similar observations between two formulations based on two different manufacturing processes and although there were a few minor differences, none was considered of any toxicological significance.

4.4.3. Genotoxicity

Semaglutide is not genotoxic *in vitro* or *in vivo*.

4.4.4. Carcinogenicity

In carcinogenicity studies in mice and rats, thyroid C-cell adenomas and carcinomas were observed at all dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect. No other tumours were found. Other non-neoplastic effects were secondary to the decreased body weight gain related to the pharmacological action of semaglutide. To determine whether the thyroid C-cell tumours are indeed caused by the same mechanism as is responsible for C-cell tumours observed after treatment with GLP-1 agonists, the applicant performed some mechanistic studies. The activation of the GLP-1R was tested *in vitro* on a thyroid C-cell tumour cell line and compared to GLP-1, exenatide and liraglutide. It was shown that the potency of semaglutide to activate the receptor was similar to liraglutide, and less potent than GLP-1 and exenatide.

Increased plasma calcitonin concentration is considered a marker for increased activation of GLP-1R on the thyroid C-cells. Upon chronic activation this leads to up-regulation of calcitonin synthesis and further to C-cell proliferation and tumour formation. Therefore, the applicant performed *in vivo* studies in mice and rats, which show that even after a single 1 mg/kg dose of semaglutide in mice, plasma calcitonin levels were increased 12 and 24 hours after injection. In rats however, an increase calcitonin level was not seen in females, and not very convincingly in males after 6 weeks of treatment. This could be due to the very short half-life of calcitonin in rats of 4 minutes, or a delayed effect which is still not apparent after 6 weeks. Further, an inconsistent effect on calcitonin levels in rats was also seen for liraglutide. Overall, the mechanism of formation of rodent thyroid C-cell tumours is well known and discussed in the public literature. There is no reason to suggest a different mechanism might be responsible for the C-cell tumours observed after treatment with semaglutide, and therefore the thyroid C-cell tumours are likely rodent specific. Since relevance for humans cannot be completely ruled out, thyroid C-cell tumours are listed in the RMP as potential risk.

4.4.5. Developmental and reproductive toxicity

Semaglutide caused embryotoxicity in the rat. The observed effects included embryo-foetal mortality, growth retardation, and skeletal and visceral abnormalities. The effects were observed at dose levels of 0.03 mg/kg/day and above, with AUC exposures below the clinical exposure at the MRHD of 2.4 mg/week. The applicant describes a mechanism of action for the embryotoxic effects observed in the rat reproduction study, which involves the presence of GLP-1R on the yolk sac. Semaglutide binds to the receptors on the yolk sac, leading to inhibition of transport of nutrients across the membrane. This mechanism is likely rat specific, since rat embryos are dependent on the yolk sac for their nutrient supply which is e.g. less important in other species including humans and monkeys. Moreover, GLP-1R is not expressed on monkey yolk sacs.

It is agreed that the mechanism demonstrated is specific for rats and could explain the malformations seen in the rat foetuses. Although undoubtedly this mechanism is responsible for most of the malformations observed, it cannot be excluded that other mechanisms that may not be rat specific are also involved. This is because not only more and other malformations are present, but also foetal weight is much further reduced in embryos of dams treated up to GD17 as compared to GD13. This is after the period (GD12) in which embryos are solely dependent on the yolk sac for nutrition but also rely on the developing chorioallantoic placenta. Although the additional skeletal abnormalities that occur between GD13 and GD17 could still be due to the impaired yolk sac, due to presence of the GLP-1R on the rat embryo from GD13.5 and presence of low levels of semaglutide in the foetus as measured on GD20, a direct effect of semaglutide on the foetus, of which the clinical relevance is unknown, cannot be excluded. It appears that a potential direct effect of semaglutide is only relevant in the later stages of pregnancy in rats, since the receptor is not present before GD13.5. Timing of receptor expression, if this is relevant for humans at all, is unknown, but a potential risk for humans is mitigated through the labelling in SmPC section 4.6, where it is stated that semaglutide should not be used during pregnancy and women of childbearing potential should use contraception to avoid unplanned pregnancies. Any further risk mitigation measures are not warranted.

A second embryo-foetal toxicity study was performed in rabbits. Once-daily SC administration of semaglutide to pregnant New Zealand White rabbits markedly reduced maternal body weight and food consumption. This coincided with increased post-implantation losses, incomplete ossification of foetal metacarpals/phalanges, and increased incidences of minor skeletal and visceral foetal abnormalities. The increased post-implantation losses and the foetal pathology findings were possibly secondary to the marked maternal effects, but a direct effect of semaglutide could not be excluded. On the other

hand, marked maternal toxicity could also mask a direct effect on the embryo or foetus. Although exposure in the high dose group at GD19 was above the human exposure, it was below human exposure at GD6. The Applicant attributes the observations in the rabbit as described above, primarily to the maternal effects on body weight and food consumption. Delayed ossification observed without concomitant decreases in foetal body weight may warrant increased attention (Carney and Kimmel 2007). However, as the mid and high-dose dams showed lower body weight gains on GD 6-19, and higher than control body weight gains on GD 20-29, any decreased foetal body weights in the mid and high dose groups may have been recovered at termination of the study when the foetal examinations were performed.

Cynomolgus monkeys were used as a third species for embryo-toxicity testing of semaglutide, since monkeys do not rely on a yolk sac for nutrition. In all dose groups, the pregnant females had an initial loss of body weight, and a lower body weight gain as compared to control animals. There were 2 cases of abortion in all dose groups as compared to 1 in the control group. The incidence of 2 out of 16 (12.5%) is close to the incidence of pregnancy loss in cynomolgus monkey controls reported in literature of 11.5% up to GD75 (*Jarvis et al, Birth Defects Research (Part B) 89:175–187 (2010)*).

Further, two major malformations were reported in the study. In the mid-dose group, a single foetus had a fused kidney, and in the high dose group there was one foetus with a misshapen brain. These effects have not previously been reported in historical controls from the same testing site. However, a relevance for humans is unlikely due to the lack of a mechanistic relation to semaglutide and lack of similar findings in other studies. Moreover, any potential risk is mitigated through the labelling in SmPC section 4.6.

There was no effect on postnatal development in offspring of cynomolgous monkeys treated with semaglutide until GD140. Initial maternal body weight losses likely led to an increased incidence of early pregnancy loss and reduced foetal weight in the mid and high dose. No other effects were observed.

A juvenile study was performed where rats from the age of 21 days were dosed for 11 weeks. Apart from general signs of toxicity, sexual maturation and fertility were investigated. Sexual maturation was delayed for both sexes, but this did not coincide with effects on fertility or mating performance. No histopathological findings were noted, and therefore it is considered likely that the delay is due to the decreased body weight gain of the treated animals. No new findings were seen in these juvenile animals that were not seen in the adult animals. This study is of limited relevance in the current procedure, as the indication applied for is in adults only.

4.4.6. Toxicokinetics and exposure margins

The average plasma exposure for semaglutide at dose of 2.4 mg/week in subjects with non-alcoholic steatohepatitis was of the same magnitude as the exposure in subjects with obesity. Exposure multiples in pivotal toxicity studies were 9 and 10 in repeated dose studies in rat (26 wk) and monkey (52 wk), resp.; 22 in carcinogenicity study in mouse (2 yr) and 2 in rat (2 yr); 0.4, 0.8, 5 in rat, rabbit, monkey EFD studies resp.; 3 in monkey PPND study; and 8 in rat juvenile toxicity study.

4.4.7. Local tolerance

In a local toxicity study in pigs using the subcutaneous route of administration only mild effects related to the vehicle or injection procedure were seen. Further, in all pivotal toxicity studies the subcutaneous route of administration was applied, and therefore local toxicity is considered sufficiently investigated and no concerns for human safety were identified.

In clinical practice it is possible that the product will be administered by intravenous, intra-arterial or intramuscular routes by mistake. Therefore, possible adverse effects were investigated in rabbits using these routes of administration. No adverse effects were seen other than mild effects related to the vehicle or injection procedure.

4.4.8. Other toxicity studies

No dedicated studies were performed. Evaluation of potential antigenicity and immunotoxicity were included in the repeated dose toxicity studies.

4.4.9. Ecotoxicity/environmental risk assessment

This application concerns a proposed new indication: treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) in adults with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), which may have an impact on the market penetration factor (F_{PEN}) used in the risk assessment. However, the conclusions of the ERA which has been previously assessed for Ozempic and Wegovy are still valid. The active substance is a peptide, the use of which will not alter the concentration or distribution of the substance in the environment; therefore, it is not expected to pose a risk to the environment.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacodynamics

The company has not conducted any new non-clinical safety studies to support the MASH indication for semaglutide. Instead, the justification relies on the previously established non-clinical safety package generated in the context of the type 2 diabetes (T2D) indication, which was subsequently also used to support the weight management indication. These studies have already undergone regulatory assessment by health authorities globally. To address the pharmacological aspects of the MASH indication, two additional animal pharmacology studies were conducted in NASH mouse models: the diet-induced obesity (DIO-NASH) model and the choline-deficient, amino acid-defined, high-fat diet (CDAA-HFD-NASH) model. Both are well-established in preclinical research.

The applicant submitted data from rodent models demonstrating improved metabolic parameters (e.g. insulin sensitivity, glucose tolerance, body weight reduction), which are presumed to lead to secondary hepatic benefits such as reduced steatosis and inflammation. However, no direct receptor occupancy studies were conducted in animals or human tissues, and the GLP-1R engagement was inferred based on pharmacological class effect and systemic readouts.

Plasma insulin is increased in non-fasted DIO-NASH mice and was strongly reduced by semaglutide to a similar degree as chow reversal. In animals on CDAA-HFD diet, fasting insulin was reduced compared to chow fed animals. After semaglutide treatment, insulin concentrations in plasma were around LLOQ and no effects from semaglutide administration could be measured. In previously assessed non-clinical pharmacology studies, semaglutide stimulated plasma insulin secretion, whereas in non-fasted DIO-NASH mice plasma insulin was increased and subsequently reduced by semaglutide. No effects on

fasting insulin were seen in the CDAA HFD model. Upon request, the applicant elaborated why semaglutide stimulated insulin secretion in a pancreas model and in a beta-cell-reduced Göttingen minipig model, whereas it reduced insulin secretion in a DIO-NASH model and was not affected in the CDAA HFD model. In DIO NASH mice insulin secretion was not measured, but the insulin levels were collected as terminal samples and lower in semaglutide treated animals. This model is characterised by insulin resistance and the low insulin levels in terminal samples might reflect improved insulin sensitivity upon treatment with semaglutide. The results do not indicate that semaglutide inhibits insulin secretion per se. CDAA-HFD mice have enhanced insulin sensitivity and semaglutide might be able to further enhance insulin sensitivity as observed in the DIO NASH model, however, insulin levels were decreased to, or below, the lower limit of quantification and no further changes could be detected, resulting in unaltered insulin levels in the CDAA-HFD model.

Both models have inherent limitations. The DIO-NASH model typically results in only mild-to-moderate fibrosis and requires long-term dietary intervention to achieve liver injury, whereas the CDAA-HFD model fails to reproduce the metabolic alterations that are central to human MASH. Both studies were conducted exclusively in mice, without confirmatory data from a second species or a more translationally relevant disease model.

Given the above, the inclusion of at least one additional pre-clinical model would have been scientifically warranted. For instance, the STAM model or a Western diet–based DIAMOND model could have provided complementary evidence, particularly with regards to fibrosis progression or long-term hepatic outcomes such as hepatocellular carcinoma. A third model would have reduced the potential for model-specific bias, strengthened the translational validity of the non-clinical pharmacological findings, and increased confidence in the relevance of GLP-1 receptor agonism for the treatment of MASH. In the absence of such data, the pharmacological evidence was interpreted with appropriate caution.

Ex vivo studies with human tissue (e.g. precision-cut liver slices or primary hepatocyte cultures) could have strengthened the translational evidence base.

Furthermore, variability in PD responses related to sex, age, or metabolic phenotype was not explored, and no subpopulation analyses were performed.

However, a scientifically sound rationale was provided during assessment for the model selection strategy applied in the non-clinical pharmacology programme. The use of rodent NASH models (GAN DIO-NASH and CDAA-HFD) was well justified based on their translational relevance and alignment with the pathophysiological mechanisms of metabolic and lipotoxic injury that underline human MASH. The reference to the international LITMUS consortium ranking of the GAN DIO-NASH model among the most translationally valid supports this approach. The decision not to include non-rodent species is acceptable, given the limited characterisation and pharmacological responsiveness of non-rodent NASH models at the time of study conception. Furthermore, the ethical justification under the principles of the 3Rs is acknowledged. The availability of confirmatory human data demonstrating consistency with the preclinical findings further supports the translational validity of the programme. The decision not to employ toxin-induced fibrosis models (e.g., CCl_4, bile-duct ligation) is scientifically reasonable, as these models do not reproduce the lipotoxic and metabolic components that are central to the pathogenesis of MASH. The applicant's explanation that semaglutide's effects are indirect, mediated through metabolic improvement rather than direct hepatic GLP-1 receptor activation, is consistent with the known pharmacodynamic mechanism of GLP-1 receptor agonists.

Semaglutide failed to reduce steatosis despite significant body weight loss and this apparent disconnect could limit translatability to human NAFLD/MASH. Upon request, a scientifically sound explanation was provided that the lack of steatosis reduction in the CDAA-HFD model is model-intrinsic rather than compound-specific. The CDAA-HFD diet's choline deficiency and reduced

methionine content impair VLDL export and fatty-acid oxidation, creating a context in which hepatic triglycerides are effectively "trapped" and resistant to pharmacologically driven lipid mobilisation. Under these conditions, the absence of a steatosis signal is expected and does not contradict pharmacodynamic benefit.

The argument that semaglutide's MASH improvements may arise indirectly (e.g., via weight loss, improved insulin sensitivity and inflammation) rather than through direct hepatocellular GLP-1 receptor activity is consistent with the known mechanism of GLP-1 receptor agonists. Importantly, the applicant indicated that in the GAN DIO-NASH model—considered more permissive for lipid turnover—semaglutide reduces hepatic lipids, aligning with observations in patients. This cross-model pattern adequately reconciles the apparent disconnect and supports translational validity.

In the data on plasma biomarkers of liver injury and inflammation; ALT, AST, TNF alpha, and MCP-1, it is stated that the loss of statistical significance at 12 weeks is attributed to enzyme decline in the vehicle group. Upon request, it was adequately clarified that baseline ALT/AST data were not collected due to the study design, which involved only terminal sampling. While the absence of within-animal longitudinal enzyme data precludes a direct statistical confirmation of the proposed interpretation, the explanation provided is scientifically reasonable and consistent with known temporal enzyme kinetics in the CDAA-HFD model. The assumption that all groups had comparable baseline ALT/AST values prior to dosing is acceptable, given that all animals were on the same diet regimen and randomised before treatment initiation. The reported early decline in ALT/AST after six weeks in semaglutide-treated animals versus the later spontaneous decline in the vehicle group provides a plausible mechanistic explanation for the observed loss of statistical significance at week 12. Furthermore, the reference to external published data (*Matsumoto et al., 2013*) supports the interpretation that liver enzyme levels naturally peak around six weeks and then decrease thereafter in this dietary model, lending credibility to the applicant's rationale. The observed temporal dynamics are thus consistent with expected model behaviour and do not undermine the interpretation of semaglutide's early pharmacodynamic effect.

In reply to a question raised during previous EMA Scientific Advice, the applicant indicates in the non-clinical overview that the mechanism for the beneficial effects in MASH is not only due to removal of hepatic lipids (direct effect), but also involves several distinct mechanisms resulting in reduction of markers of liver injury (indirect effect) and fibrosis markers.as supported by the non-clinical data in two NASH models in mice. In addition, mechanisms underlying the effect of semaglutide on MASH were investigated by analysis of the liver transcriptome, collagen expression and collagen turnover. The Applicant provided a scientific discussion about how semaglutide directly and indirectly modulates MASH. In MASH, insulin resistance in hepatic and adipose tissues alongside enhanced hepatic *de novo* lipogenesis increases lipolysis in the adipose tissue, because the inhibitory effect of insulin on fat cells is reduced. The increased lipolysis promotes the accumulation of lipids in the liver and delivers an excessive amount of toxic lipid species which may cause cellular stress and inflammation. Semaglutide treatment improves insulin resistance thereby restoring the metabolic balance in the liver and adipose tissue. Furthermore, though the GLP1 receptor is not expressed in liver, central GLP1R activation by semaglutide decreases circulating levels of TNFα via adrenergic and opioid receptor signalling and attenuates systemic inflammation and contributing to the beneficial effects of semaglutide on liver fibrosis. Given the lack of GLP1 receptor expression in the liver of both humans and mice, the effects on MASH are considered indirect. These indirect effects are likely mediated both by the weight-loss *per se* and by weight-loss-independent mechanisms.

The current non-clinical data does not discern weight-loss-dependent from weight-loss-independent effects as weight-matched control groups, i.e. a group in which food intake was reduced to induce a weight loss identical to semaglutide, were not included. Thus, a direct effect of semaglutide has not been demonstrated in NASH/MASH models.

4.5.2. Conclusions

In conclusion, the non-clinical pharmacodynamic tests support for the MASH indication of semaglutide is primarily based on legacy T2D and obesity data. Two murine models (GAN DIO-NASH and CDAA-HFD) were used to explore semaglutide's activity in MASH. The model selection and supporting justification substantiate the metabolic and antifibrotic findings within the intended translational context. Other models including non-rodent species do not reproduce the lipotoxic and metabolic components that are central to the pathogenesis of MASH. Additional receptor occupancy studies would have strengthened confidence in GLP-1 receptor agonism as a treatment strategy for MASH.

Semaglutide treatment improved insulin resistance thereby restoring the metabolic balance in the liver and adipose tissue and has attenuated systemic inflammation by decreasing circulating levels of TNFα, thereby contributing to the beneficial effects of semaglutide on liver fibrosis. Hence, semaglutide's effects in MASH are indirect, mediated through metabolic improvement rather than direct hepatic GLP-1 receptor activation, what is consistent with the known pharmacodynamic mechanism of GLP-1 receptor agonists. A direct effect of semaglutide has not been demonstrated in NASH/MASH models.

The pharmacokinetic program including the toxicokinetic analysis are considered sufficient. No major objection or any other concerns were raised.

Considering that semaglutide is an approved product, it was agreed that no further non-clinical toxicology studies were needed.

Overall, there are no objections from a non-clinical point of view to the marketing authorisation of Kayshild.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (*see section 2.4.3*).

5.1.2. Tabular overview of clinical trials

The present application is based on a clinical pharmacology study 4381, a dose-finding phase 2 trial 4296, an interim evaluation of the pivotal phase 3 trial 4553 at week 72, and a supportive trial 4492 in F4b patients.

Non-clinical and clinical information from previous clinical development programmes for semaglutide for the treatment of T2D (Ozempic) and for weight management (Wegovy) also support the present application.

Data from the cardiovascular outcomes trial (CVOT) SELECT (trial ID EX9536-4388) have also been included.

Population pharmacokinetic (PK) analysis was made based on phase 2 and phase 3 data in patients with MASH and F1 to F4 with regards to age, gender, race, and ethnicity.

There are limited data from the use of semaglutide for MASH in pregnant women.

Table 5: Clinical trials in the NN9931 programme supporting the present application

Study and MASH population	**Number of subjects** [a]	**Description**
Clinical pharmacology		
Study 4381 NAFLD (supportive)	67 subjects	72-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial investigating the effect of semaglutide s.c. 0.4 mg once daily versus placebo on liver fibrosis assessed by magnetic resonance elastography in subjects with NAFLD and increased liver stiffness.
Phase 2		
Study 4296 MASH F1-F3 (pivotal)	320 subjects, including 230 subjects with MASH F2/F3	72-week randomised, double-blind, placebo-controlled, six-arm, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. once-daily at three different doses (0.1, 0.2 or 0.4 mg) versus placebo in subjects with MASH F1-F3.

Study 4492 MASH F4c (supportive)	71 subjects	48-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial comparing the effect and safety of once-weekly semaglutide s.c. 2.4 mg with placebo in participants with MASH F4c.
Phase 3a		
Study 4553 MASH F2-F3 (pivotal)	800 subjects [b] / 1197 subjects [b]	240-week randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once-weekly versus placebo in participants with MASH F2-F3. Study 4553 has two parts with distinctive objectives: Part 1: To demonstrate that treatment with semaglutide improves liver histology compared to placebo after 72 weeks of treatment. Part 2: To demonstrate that treatment with semaglutide lowers the risk of liver-related clinical events compared to placebo after 240 weeks of treatment. The present application is based on data and results from an interim evaluation of trial 4553, i.e., on part 1.

F: fibrosis stage; F4c: compensated cirrhotic MASH (fibrosis stage F4c); SEE: substantial evidence of effectiveness.
a. number of randomised subjects.
b. According to the trial protocol, trial 4553 is planned to include a total of 1200 randomised subjects. By the data cut-off date (05 September 2024), 1197 subjects had been randomised. The present application is based on an evaluation of data from the first 800 randomised subjects with respect to efficacy-related analyses and on data from all exposed subjects (1195 subjects) by the data cut-off date with respect to safety-related evaluations.

5.2. Clinical pharmacology

5.2.1. Methods

Semaglutide was analysed in plasma using plasma protein precipitation followed by LC-MS/MS. The LC-MS/MS bioanalytical assay for semaglutide was the same as used in previous semaglutide applications. Performance of the assay in the PK analysis for the new clinical studies was satisfactory, with ISR demonstrating robustness of the assay.

Analysis of anti-semaglutide antibodies was performed using a tiered approach with screening analysis in tier 1, confirmation analysis in tier 2, and cross-reactivity to endogenous GLP-1 in tier 3. In study 4553 tier 3 also included titre determination of the confirmed antibody positive samples. The assays were validated according to current EMA guidelines. The neutralising anti-semaglutide antibody as well as the neutralising anti-GLP-1 antibody analysis were the same as used previously in the Wegovy program.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Descriptive PK data of semaglutide in subjects with metabolic dysfunction-associated steatohepatitis

(MASH) were provided, to support the use of semaglutide subcutaneous (SC) 2.4 mg once weekly (OW) as a treatment option in this population. The clinical pharmacology programme for semaglutide 2.4 mg as a treatment option for MASH builds also upon the clinical development programmes for:

- type 2 diabetes (T2D) (NN9535) with semaglutide SC 0.5, 1.0 mg (Ozempic),
- weight management (NN9536) with semaglutide 2.4 mg (Wegovy).

5.2.2.2. Evaluation and qualification of models

The popPK analysis in the MASH population was based on phase 2 studies (4296, 4492) and phase 3 study (4553) including subjects with biopsy-defined MASH and fibrosis stage (F1-F4) characterisation.

A one-compartment structural model with first-order absorption and first-order elimination was used to describe the pharmacokinetics of semaglutide. Between-subject variability was included for CL/V and V/F with a full covariance matrix. Residual variability was described by a proportional error model.

Bodyweight was included on CL/F and V/F based on previous results in clinical pharmacology studies. Other covariates (i.e. sex, age, race, ethnicity, body weight, MASH fibrosis stage, dosing device, renal function, injection site and glycaemic status) were predefined to be analysed using a "full covariate model" and assumed a power model structure. In addition to the effects of covariates investigated in the popPK model, the effects of anti-semaglutide antibody status (presence or absence of semaglutide antibodies) on the exposure were evaluated.

A reduced population pharmacokinetic model was used for simulations by omitting non-significant covariates based on backwards elimination ($p<0.001$).

The final reduced popPK model provided a good fit of the semaglutide exposure data in the 2 MASH patient phase 2 clinical Studies 4296, 4492 and phase 3 Study 4553. The model was validated by GOF and VPC plots.

The popPK parameters of the reduced popPK model are given in Table 6.

Table 6: Parameter estimates from the reduced final model of semaglutide PK

Parameter	Label	Units	Estimates	RSE (%)	95% CI	Shrinkage (%)
KA	Absorption rate constant	1/h	0.167	13.2	[0.124; 0.210]	NA
CL/F	Apparent clearance	L/h	0.0493	1.27	[0.0481; 0.0506]	NA
V/F	Apparent volume of distribution	L	13.7	3.88	[12.7; 14.7]	NA
	CL.BW		0.927	3.07	[0.872; 0.983]	NA
	CL.Mild		0.933	1.42	[0.907; 0.959]	NA
	CL.ModerateSevere		0.942	4.36	[0.862; 1.02]	NA
	CL.PDS290		1.01	2.55	[0.959; 1.06]	NA
	CL.NovoPen4		1.14	1.74	[1.10; 1.17]	NA
	CL.Non-diabetes		0.942	1.32	[0.918; 0.966]	NA
	CL.fibrosis level1		0.920	4.01	[0.848; 0.992]	NA
	CL.fibrosis level2		0.989	1 .34	[0.963; 1.02]	NA
	CL.fibrosis level4		1.02	3.35	[0.958; 1.09]	NA
	V.BW		0.714	17.7	[0.466; 0.963]	NA
CL.IIV	IIV on CL (CV%)	%	16.8	5.34	NA	16.5
V.IIV	IIV on V (CV%)	%	47.6	9.93	NA	41.8
Prop.Error	Proportional error (CV%)	%	22.3	3.07	NA	7.40

RSE: Relative standard error, CI: Confidence interval.

5.2.2.2.1. Population pharmacokinetics

Effects of prespecified covariates on semaglutide exposure were evaluated in the popPK analysis on Studies 4553, 4492 and 4296. For results on covariates see section *5.2.2.10 Special populations*.

5.2.2.3. Absorption

The maximum concentration was reached 1 to 3 days post dose. Steady state exposure was achieved following 4–5 weeks of once weekly administration. The steady state exposure of semaglutide increased proportionally with doses from 0.25 mg up to 2.4 mg once weekly. Steady state exposure was stable with time as assessed up to week 68. Similar exposure was achieved with SC administration of semaglutide in the abdomen, thigh, or upper arm. The absolute bioavailability of semaglutide was 89%. No influence of food is expected since this concerns a SC administration.

5.2.2.4. Bioequivalence

Based on findings from the Wegovy MAA, bioequivalence between the two semaglutide drug products (semaglutide dosed in the DV3396 single-dose pen-injector and a PDS290 pen-injector) was demonstrated for $AUC_{0\ 168h}$ and C_{max} at steady state, both at the 2.4 mg and 1.0 mg dose level.

5.2.2.5. Distribution

The mean volume of distribution of semaglutide following subcutaneous administration in patients with MASH was approximately 13.7 L. Semaglutide was extensively bound to plasma albumin (>99%).

5.2.2.6. Metabolism

It is known that prior to excretion, semaglutide is extensively metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) was identified as one of the active metabolic enzymes.

5.2.2.7. Elimination

The primary excretion routes of semaglutide-related material are via the urine and faeces. A small proportion, i.e., approximately 3%, of the absorbed dose was excreted in the urine as intact semaglutide. The clearance of semaglutide in patients with overweight (BMI $\geqslant$ 27 kg/m^2 to <30 kg/m^2) or obesity (BMI $\geqslant$30 kg/m^2) was approximately 0.05 L/h. With an elimination half-life of approximately 1 week, semaglutide will be present in the circulation for approximately 7 weeks after the last dose of 2.4 mg.

5.2.2.8. Dose proportionality and time dependency

Semaglutide dose-proportionality was demonstrated up to 2.4 mg upon once weekly SC administration. Further, the PK of semaglutide is not time-dependent. Steady state is reached after approximately 25 weeks, following the proposed 16-week titration schedule.

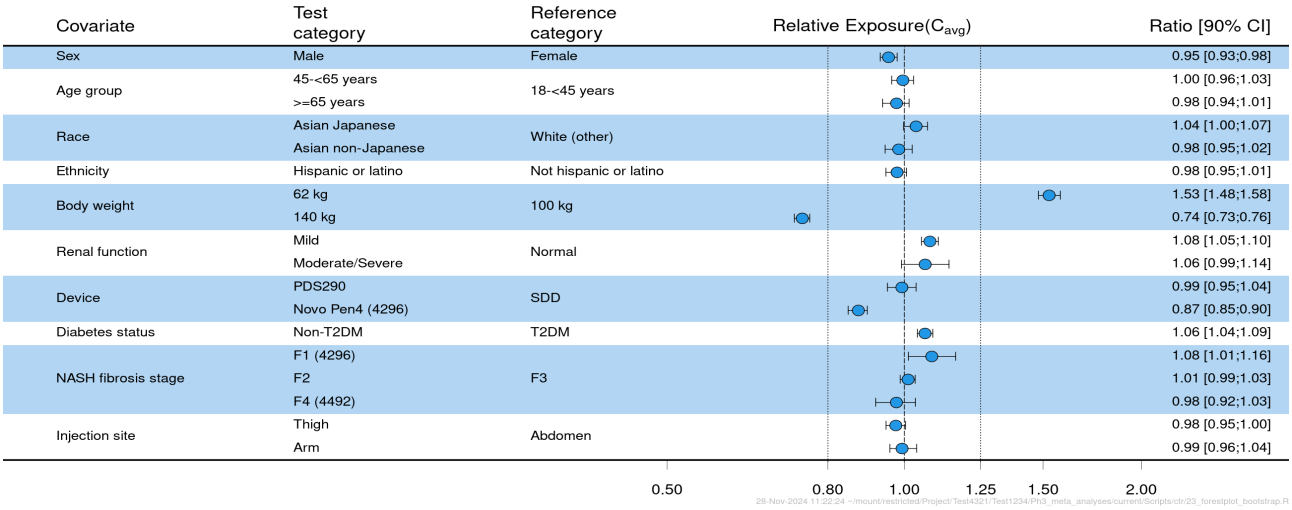
5.2.2.9. Pharmacokinetics in the target population

Based on popPK simulations, semaglutide exposure in MASH patients at a 2.4 mg dose is comparable with exposure obtained in obese subjects, either with or without T2D. Of note, a large proportion of MASH patients is obese and has T2D, and in that respect the MASH population and the obese and T2D populations for the Ozempic and Wegovy indication overlap significantly.

5.2.2.10. Special populations

Effects of prespecified covariates on semaglutide exposure were evaluated in the popPK analysis on Studies 4553, 4492 and 4296 (Figure 2).

Figure 2: Forest plot of covariate effects on the exposure (C_{avg}) of semaglutide (popPK analysis on Studies 4553, 4492 and 4296)



SDD: Single-dose device, T2D: Type 2 diabetes. Data are steady-state, dose-normalised C_{avg} relative to a reference subject profile defined as non-Hispanic or Latino, White female 18-45 years of age, with a body weight of 100 kg, with normal renal function and fibrosis stage F3, dosed with the SDD device in the abdomen and living with Type-2 diabetes. Subjects with fibrosis stage F4c were only present in study 4492 and subjects with fibrosis stage F1 were only present in study 4296. The forest plot and column to the right show means and 90% CI of relative exposure. Body weight test categories represent the 5th and 95th percentiles in the data. Vertical lines represent the [0.80; 1.25]-limits. Data from study 4553, study 4492, and study 4296.

The covariate analysis demonstrated that body weight affected semaglutide exposure; a 26% lower exposure was predicted in subjects with a high body weight (140 kg, the 95% percentile of the data set) and a 53% higher exposure was predicted in subjects with a low body weight (62 kg, the 5% percentile of the data set), relative to a subject with a prespecified reference body weight (100 kg).

Other covariates (gender, age, race, ethnicity, injection site, MASH fibrosis stage, diabetes status, device, renal and hepatic function, anti-semaglutide antibodies) had minor or no influence on the exposure of semaglutide. This is in line with conclusion in the Ozempic and Wegovy MAA patient populations. The current clinical development programme in MASH did not include any paediatric patients. This is in line with the agreed PIP.

The results of the popPK analysis on Studies 4553, 4492 and 4296 in the population of subjects with MASH are comparable with the results of the corresponding analyses performed for semaglutide 2.4 mg in subjects with overweight or obesity (see Wegovy MAA).

5.2.2.11. PK drug-drug interactions

Semaglutide is not a substrate for CYP enzymes, therefore no interactions affecting semaglutide are expected by that route.

In addition, semaglutide does not have any effect on the activity of CYP enzymes and transporters *in vitro* at clinically relevant concentrations and is therefore not expected to cause any clinically relevant drug-drug-interactions by that means. Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. However, no clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg. The proposed text for section 4.5 is identical to that for Wegovy, which was acceptable.

5.2.2.12. Interconversion and PK of metabolites

Interconversion. One semaglutide isomer P3C has been identified. The isomer is present in low concentrations (<7.7%). As P3C is a semaglutide isomer, it is considered likely that it has some activity. However, as its concentration is low (<7.7%), the contribution to the total activity is expected to be low.

PK of metabolites. All metabolites accounted for less than 10% of the total amount of semaglutide related material and are not expected to have any activity.

Consequences of genetic polymorphism. The pharmacokinetics data do not indicate any influence of polymorphisms of NEP on the pharmacokinetics of semaglutide.

Intra- and inter-individual variability. The within- and between subject of 17% and 22%, respectively, obtained in the MASH patient popPK model was comparable to that estimated in the Wegovy MAA in obese patients with or without T2D.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue with 94% homology to human GLP-1. It is classified as a GLP-1 receptor agonist (RA).

The PD properties of semaglutide are well-characterised based on findings from the Ozempic and Wegovy clinical development programmes.

The effects of semaglutide in the body are mediated via specific activation of the GLP-1 receptor and are generally well characterised. Both native GLP-1 and GLP-1 RAs reduce body weight by lowering energy intake via inducing feelings of satiety and fullness and lowering feelings of hunger. The mechanism of decreased energy intake involves GLP-1 receptors expressed in the pancreas and the brain in regions that regulates satiety and appetite. Semaglutide lowers blood glucose by a mechanism that increases insulin secretion and reduces glucagon secretion, both depending on the level of glucose in blood. Semaglutide lowered fasting triglyceride and very-low-density lipoprotein (VLDL) cholesterol blood levels. In addition, semaglutide reduced the postprandial triglyceride and VLDL cholesterol response to a high fat meal.

GLP-1 receptors are also expressed in the heart, blood vessels, as well as on kidney cells and cells of the immune system.

The GLP-1 receptor has not been detected on liver cells and the effects of semaglutide on the liver are thought to be indirect and largely mediated by improvement in metabolic factors, including body weight, blood pressure and inflammation, as well as glucose and lipid metabolism.

Any further detailed underlying mechanism for the improvement in MASH has not been described.

5.2.3.2. Primary and secondary pharmacology

The pharmacodynamics were evaluated in the phase 2 study 4381, the dose finding study 4296, and the pivotal phase 3 study 4553. The results of study 4381 are discussed below, while the results of the dose finding and pivotal study are discussed in their respective sections.

Study 4381 primary pharmacology evaluation was based on pharmacodynamic imaging (liver stiffness, liver steatosis, liver fat volume, visceral adipose tissue) and pharmacodynamic laboratory assessment (ALT, AST, GGT, several exploratory markers). Secondary pharmacology was based on pharmacodynamic laboratory assessment (hsCRP, glucose related evaluation (e.g. HbA1c), lipid profile e.g. LDL-C) and body measurements (height, body weight, BMI, and waist circumference).

<u>Primary pharmacology</u>

- Pharmacodynamic liver imaging

At week 24, 48 and 72, no statistically significant changes from baseline in liver stiffness between semaglutide 0.4 mg and placebo were found. The estimated odds of achieving an at least 15% reduction in liver stiffness did not differ statistically significantly between the semaglutide 0.4 mg and the placebo at weeks 24, 48, or 72. However, the estimated odds of achieving an at least 30% reduction in relative liver fat content were statistically significantly greater with semaglutide 0.4 mg than with placebo at weeks 24, 48, and 72 (73.5% vs 33.3% at week 72, p=0.0006).

At week 72, the reduction in liver fat content was statistically significantly greater with semaglutide 0.4 mg (- 58%; ratio to baseline of 0.42) than with placebo (-17%; ratio to baseline of 0.83) with an ETR of 0.5 [0.39; 0.66] 95%CI.

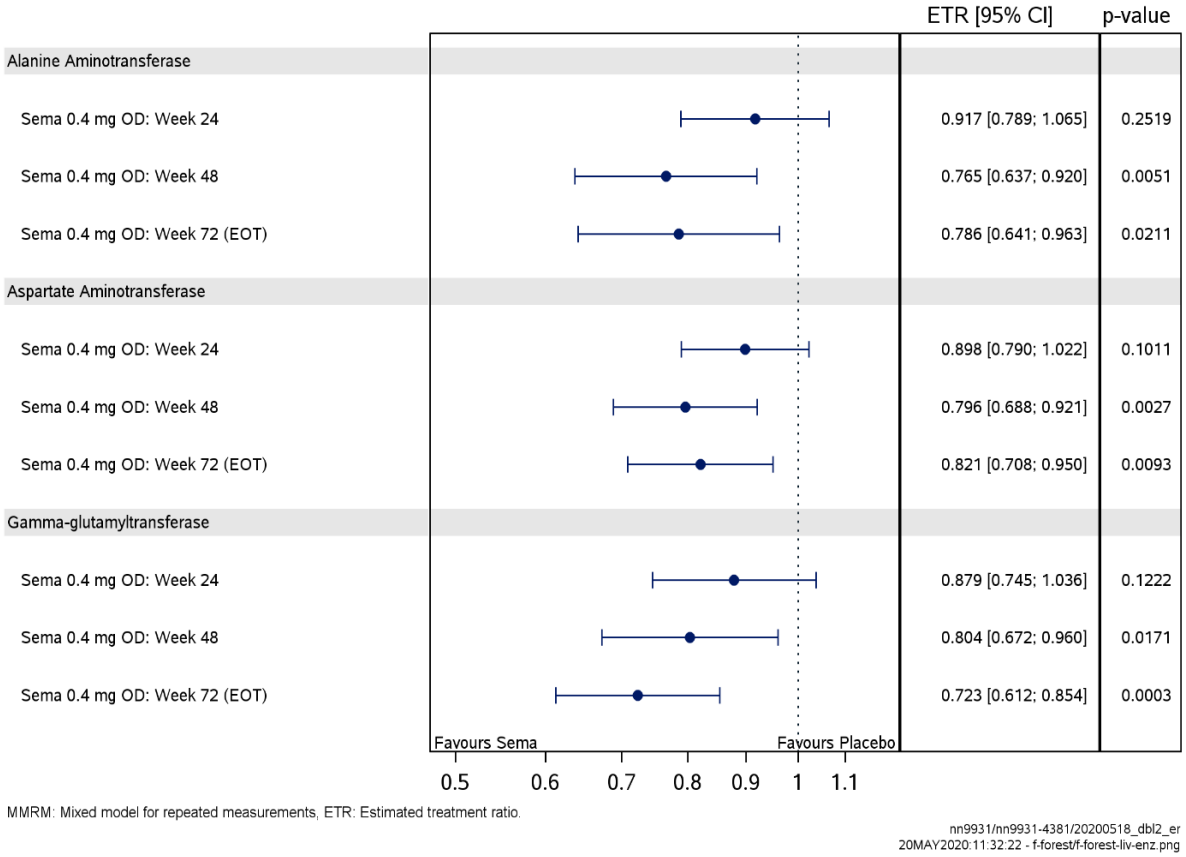
At week 72, the reduction in liver fat volume was statistically significantly greater with semaglutide 0.4 mg (-67%; ratio to baseline of 0.33) than with placebo (-20%; ratio to baseline of 0.80) with an ETR of 0.41 [0.30; 0.56] 95%CI.

At week 72, the reduction in total liver volume was statistically significantly greater with semaglutide 0.4 mg (- 21%; ratio to baseline of 0.79) than with placebo (-4%; ratio to baseline of 0.96) with an ETR of 0.82 [0.77; 0.87] 95%CI.

- Pharmacodynamic laboratory assessment

Effect on liver enzymes is provided below (Figure 3).

Figure 3: Liver enzymes - ratio to baseline – forest plot - on-treatment - full analysis set



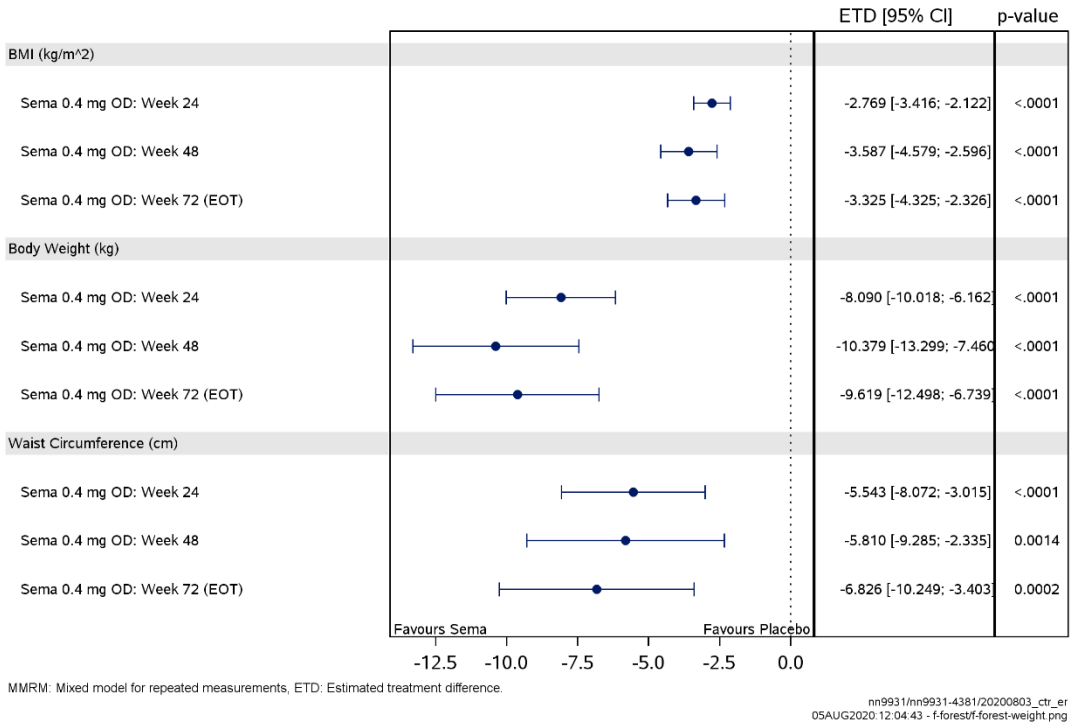
Serological biomarkers included Enhanced Liver Fibrosis (ELF) which is a non-invasive blood test that measures three direct markers of fibrosis: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). Change from baseline in ELF score between semaglutide 0.4 mg and the placebo differed statistically significantly at week 24 (ETD of - 0.44 [- 0.70; -0.19] 95%CI), but not at weeks 48 and 72.

Secondary pharmacology

- Body weight-related parameters

BMI, body weight, and waist circumference decreased statistically significantly from baseline to week 48 and remained stable to week 72 with semaglutide 0.4 mg, while with the placebo all parameters remained near baseline values (Figure 4).

Figure 4: Weight related parameters - change from baseline – forest plot - on-treatment - full analysis set



- HbA1c, FPG, Fasting glucagon and HOMA-IR in subjects with T2D

At week 72, the decrease from baseline in HbA1c was statistically significantly greater with semaglutide 0.4 mg (1.03%) than with placebo (0.03%).

At week 72, the decrease from baseline in FPG observed with semaglutide 0.4 mg (1.74 nmol/L) was statistically significantly greater than with placebo (0.28 nmol/L). At week 72, the reduction in fasting glucagon was statistically significantly greater with semaglutide 0.4 mg (- 37%; ratio to baseline of 0.63) than with placebo (-9%; ratio to baseline of 0.91). No statistically significant changes to baseline in insulin resistance (measured using the HOMA-IR index) were found.

- HbA1c, FPG, Fasting glucagon and HOMA-IR in subjects without T2D

Reduction from baseline in HbA1c was statistically significantly different between semaglutide 0.4 mg and the placebo at week 24, but not at weeks 48 and 72. At week 24, the decrease from baseline in HbA1c observed with semaglutide 0.4 mg (0.49%) was statistically significantly greater than with placebo (0.03%).

At week 74, the decrease from baseline in FPG observed with semaglutide 0.4 mg (0.69 nmol/L) was statistically significantly different from the increase observed with placebo (0.56 nmol/L). No statistically significant changes to baseline in fasting glucagon were found.

Change from baseline in insulin resistance (measured using the HOMA-IR index) was statistically significantly different at week 48, but not at weeks 24 and 72. At week 48, the decrease in insulin resistance observed with semaglutide 0.4 mg (-50%; ratio to baseline of 0.50), was statistically significantly different from the increase observed with placebo (+10%; ratio to baseline of 1.10).

- Abdominal s.c. and visceral adipose tissue (MRI)

At week 72, the reduction in abdominal s.c. adipose tissue (L) was statistically significantly greater with semaglutide 0.4 mg (-17%; ratio to baseline of 0.83) than with the placebo (-3%; ratio to baseline of 0.97) with an ETR of 0.86 [0.80; 0.92] 95%CI.

At week 72, visceral adipose tissue (L) decreased with semaglutide 0.4 mg (-25%; ratio to baseline of 0.75), while it increased with the placebo (+3%; ratio to baseline of 1.03) with an ETR of 0.72 [0.66; 0.80] 95%CI.

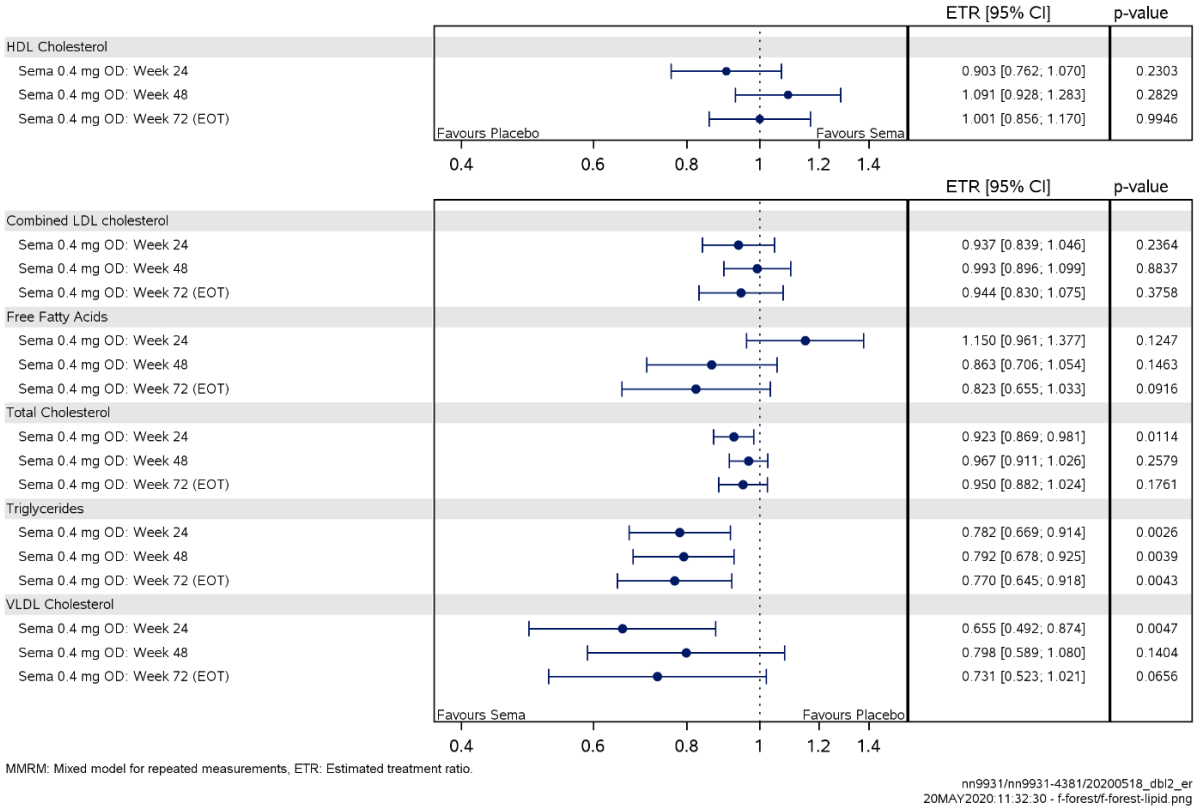
- hsCRP

Change from baseline in the inflammation marker, hsCRP, was statistically significantly different at weeks 24, 48, and 72 . At week 72, the reduction in hsCRP was statistically significantly greater with semaglutide 0.4 mg (-46%; ratio to baseline of 0.54) than with placebo (-8%; ratio to baseline of 0.92).

- Lipids

Effects on lipids is provided below (Figure 5).

Figure 5: Lipids - ratio to baseline – forest plot - on-treatment - full analysis set



MMRM: Mixed model for repeated measurements, ETR: Estimated treatment ratio.

nn9931/nn9931-4381/20200518_dbl2_er
20MAY2020:11:32:30 - f-forest/f-forest-lipid.png

- QT prolongation

As part of the Ozempic® clinical development programme, trial NN9535-3652 with semaglutide s.c. 1.5 mg once weekly demonstrated that semaglutide s.c. does not prolong the QTc interval. This conclusion was considered applicable for semaglutide 2.4 mg for weight management (Wegovy) and is also considered applicable for semaglutide 2.4 mg for MASH.

The potential effect of semaglutide on cardiac repolarisation was studied in a thorough QTc trial (NN9535-3652) in the T2D clinical development programme in healthy subjects administered doses up

to 1.5 mg semaglutide once weekly. No prolongation of the QTc interval was observed with semaglutide. Also, no relationship between the semaglutide exposure and the QTc interval was observed. The QTc study also supported the 2.4 mg dose in the weight management programme.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

N/A

5.2.3.4. Genetic differences in PD response

N/A

5.2.3.5. Immunological events

N/A

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

The effect of several covariates on the effectivity and safety parameters

- resolution of steatohepatitis and no worsening of liver fibrosis,
- improvement in liver fibrosis and no worsening of steatohepatitis,
- improvement in liver fibrosis,
- progression of liver fibrosis,
- body weight
- gastro-intestinal adverse event,
- vomiting events, and
- nausea events

was investigated. Overall, intrinsic factors like e.g., gender, baseline body weight, diabetes status and fibrosis stage did not appear to have a relevant impact on the two main efficacy or safety parameters.

Data from phase 2 Study 4296 and phase 3 Study 4553 (interim evaluation) showed an exposure-response relationship for the evaluated primary efficacy outcomes *Resolution of steatohepatitis and no worsening of liver fibrosis* and *Improvement in liver fibrosis and no worsening of steatohepatitis*, and secondary confirmatory endpoints (week 72) *Resolution of steatohepatitis and improvement in liver fibrosis* and *Change in body weight*. For all these efficacy parameters, increasing exposure was associated with increased efficacy for endpoints related to improved liver histology and body weight loss.

Further, an exposure-dependent increase in the incidence of gastrointestinal AEs, nausea and vomiting was found with increasing exposure. Results are in line with results obtained in the Wegovy MAA.

The exposure-response analyses are considered supportive for the recommended dose of semaglutide for MASH is 2.4 mg.

5.2.5. Dose selection and therapeutic window

The dosing regimen was selected based on an integrated evaluation of efficacy, safety, and exposure considerations from the phase 2 dose-finding Study 4296. The dose was also selected based upon the data from the Ozempic T2D MAA investigating semaglutide SC at doses up to 2.0 mg as well as the Wegovy weight management MAA conducted for semaglutide SC 2.4 mg.

Initially, a once daily dose of 0.1 mg, 0.2 mg, and 0.4 mg was investigated in support of the MASH indication. This once daily administration in trial 4296 was chosen based on the initial data from the Ozempic semaglutide SC T2D development programme suggesting that fluctuations in semaglutide plasma concentrations increased gastrointestinal side effects. Later data from the semaglutide SC Ozempic T2D development programme did not support the hypothesis that once daily dosing provides better gastrointestinal tolerability as compared to once weekly dosing. The proportion of participants with gastrointestinal AEs and the rates of such events were generally higher in Ozempic Study NN9535-4191 where semaglutide SC was dosed once daily compared to the phase 3a studies where semaglutide SC was dosed once weekly. Therefore, based on this sequence of information, the choice for once weekly dosing is supported (and in line with that accepted during the Ozempic and Wegovy MAA).

Dose-response evaluation based on the phase 2 Study 4296 showed a positive relationship between the dose of semaglutide and its effect on resolution of steatohepatitis and no worsening in liver fibrosis at week 72. Semaglutide 0.4 mg once daily led to the highest proportion of subjects achieving resolution of steatohepatitis and no worsening in liver fibrosis. Modelling and Simulation data further suggested levelling off the increase in gastro-intestinal effects at higher doses. The subsequent aim to target this 0.4 mg OD caused exposure with a once weekly dosing is therefore understandable. Based on popPK simulations, the C_{max} obtained by 0.4 mg once daily dosing was not passed by a once weekly dosing of 2.4 mg.

Finally, to mitigate gastro-intestinal adverse events, the dose is increased every 4 weeks. The escalation steps applied in the phase 3a Study 4553 (fixed-dose escalation regimen (0.25, 0.5, 1.0, 1.7 mg once weekly)) were identical to the escalation steps for the approved treatment of weight management (Wegovy).

It is considered that the Applicant has provided a reasonable justification for the proposed maintenance dose of 2.4 mg once weekly, to be reached by starting with a dose of 0.25 mg and escalating over a 16-week period to a maintenance dose of 2.4 mg once weekly.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Pharmacokinetics

Descriptive PK data of semaglutide in subjects with metabolic dysfunction-associated steatohepatitis (MASH) (NN9931) were provided, to support the use of semaglutide subcutaneous (SC) 2.4 mg once weekly as a treatment option in this population. The clinical pharmacology programme for semaglutide 2.4 mg as a treatment option for MASH builds also upon the clinical development programmes for:

- type 2 diabetes (T2D) (NN9535) with semaglutide SC 0.5, 1.0 mg (Ozempic),
- weight management (NN9536) with semaglutide 2.4 mg (Wegovy).

Most PK data for semaglutide have already been established based on data from the Ozempic and Wegovy MAA. The PK in MASH patients is not different from the PK observed in healthy subjects, as well as subjects with diabetes or in obese patients.

No difference was found between AUC and C_{max} following single subcutaneous dose of 0.5 mg semaglutide between individuals with normal hepatic function and those with mild, moderate, or severe hepatic impairment (classified by Child–Pugh criteria). The fraction unbound of semaglutide was less than 0.5% for all subjects but appeared to increase with increasing degree of hepatic impairment. Since the Child-Pugh classification is primarily used to assess the severity of cirrhosis (F4 fibrosis) and is not typically applied to earlier stages of fibrosis (F0, F1, F2, F3), SmPC section 4.2 distinguishes patients with preserved hepatic function (as studied in trial 4553) and those with moderate or severe hepatic impairment, for whom cautionary statements are needed.

Bioanalysis

The Applicant employed validated LC-MS/MS methods for semaglutide quantification in plasma, consistent with those used in previous submissions such as for Wegovy. These methods demonstrated acceptable performance across multiple clinical trials, with high assay acceptance rates, consistent precision and accuracy, confirmed reproducibility, and no matrix interference, including in lipemic samples.

Immunogenicity was assessed using a multi-tiered approach (screening, confirmatory, cross-reactivity, and neutralisation), also consistent with prior submissions. While the ADA and binding assays were appropriately validated, the neutralizing antibody (NAb) assay showed limited drug tolerance, detecting only high ADA levels in the presence of semaglutide concentrations well below steady-state levels (50-100 nM). This limitation was already noted in earlier regulatory assessments and has not been resolved, but clinical data suggest that detected ADAs were transient and had no apparent impact on pharmacokinetics, efficacy, or safety. Therefore, despite the NAb assay's inability to detect low-titre antibodies during treatment, the overall assay strategy was considered acceptable.

Pharmacodynamic markers

The MASH (NN9931) program incorporated a broad panel of pharmacodynamic (PD) markers across trials 4381, 4296, and 4553 to non-invasively assess hepatic steatosis, fibrosis, and features relevant to MASH, with varying sensitivity, specificity, and clinical relevance. Among imaging markers, MRI-PDFF is the most sensitive and specific for quantifying liver fat content (steatosis), with a strong correlation to histologic steatosis and established use as a surrogate endpoint; however, it does not capture inflammation or hepatocellular ballooning, limiting its ability to define steatohepatitis. Magnetic Resonance Elastography (MRE) provides a highly accurate measure of liver stiffness and is superior to transient elastography for assessing fibrosis, though stiffness may also reflect inflammation. FibroScan, using transient elastography and CAP, is less accurate than MRI-based methods, particularly in obese subjects, but remains a widely accepted tool with utility in evaluating liver stiffness and fat content. The FAST score, which combines FibroScan stiffness, CAP, and AST, provides a validated composite marker for identifying at-risk MASH and monitoring treatment response. Among blood-based markers, ALT, AST, GGT, and hsCRP provide general indicators of liver injury and inflammation but lack disease specificity. Composite indices like FIB-4 and NAFLD fibrosis score (NFS) offer non-invasive estimations of fibrosis based on clinical and biochemical data, but with moderate diagnostic accuracy. The ELF test, which directly measures fibrosis-related proteins (HA, PIIINP, TIMP-1), shows good specificity for advanced fibrosis and is associated with progression to cirrhosis; a decrease of ≥0.5 is considered clinically meaningful. Pro-C3, a marker of collagen III formation, is closely associated with active fibrogenesis in MASH and may reflect treatment impact on fibrotic activity. Exploratory biomarkers such as miR-122, FGF-21, MCP-1, and TNF-alpha may provide mechanistic insights but lack sufficient validation for use as endpoints. Overall, MRI-PDFF and MRE remain the most robust PD tools for

assessing steatosis and fibrosis respectively, while blood-based fibrosis markers (e.g. ELF, Pro-C3) and composite scores (e.g. FAST) offer supportive, clinically relevant information. However, none of these markers alone can definitively diagnose or stage MASH which still requires histologic assessment; thus, these PD tools are best interpreted as complementary measures of disease activity and treatment response in MASH and fibrosis.

popPK/PD

Efficacy evaluation is based on two pivotal studies: one phase 3a trial (study 4553) in patients with MASH F2–F3, and one phase 2 dose-finding trial (study 4296) in patients with MASH F1–F3. These are discussed in detail in the clinical efficacy section below and served as the source data for the main POP-PK/PD report. Study 4492 was excluded from the POP-PK/PD analysis due to differences in population inclusion criteria (e.g. MASH fibrosis stage). Study 4381 was excluded due to a lack of biopsy-defined MASH fibrosis stage characterisation. Nevertheless, both non-pivotal phase 2 studies (4381 and 4492) indicate a significant metabolic benefit with semaglutide but limited direct antifibrotic effect within the study duration.

Two PopPK/PD reports were submitted. They are referred to as the first (or earlier) and the second (interim) report, as they lack report numbers. The earlier report (2020) is based on phase 2 Studies 4296 and 4381. The first report included 2,266 observations from 272 subjects. The PK data set of the second interim report is based on Studies 4553, 4492, and 4296, and includes 811 subjects and 5450 PK samples while the PK/PD data set includes only data from Studies 4553, and 4296 or only 4553.

Both reports used the same computational approach and produced largely overlapping results. A one-compartment model with first-order absorption and elimination was used to describe semaglutide PK. Given the limitation of sparse sampling, this was a reasonable choice. Body weight was the most important covariate for semaglutide exposure, with higher weight resulting in lower exposure. Other covariates—sex, age, race, ethnicity, MASH fibrosis stage, dosing device, renal function, diabetes status, and injection site—were of minimal or no importance. Weight-tiered dosing is not advised, as no clear concentration–effect relationship has been established for efficacy or safety. Instead of observed C_{trough} values, model-predicted average concentrations (C_{ave}) were used to explore concentration–effect relationships. Fitted and observed C_{trough} values showed strong agreement, justifying the use of model-predicted C_{ave}.

With respect to the popPK model, a number of insignificant covariates (i.e. with 1.0 included in the 95% CI) appear still included in the reduced popPK model. The IIV and shrinkage in the full covariate model and the reduced model were very much comparable. Moreover, the point estimates of the parameter estimates were identical in the full and the reduced models. The popPK model is comparable to that developed in the Ozempic MAA. Further optimisation of the model was not requested.

With respect to the therapeutic window, the applicant argued that efficacy was demonstrated irrespective of body weight, without worsening of liver fibrosis or steatohepatitis. The applicant proposed not to define cut-off exposures leading to significantly reduced efficacy or increased safety issues for semaglutide. In that sense, the exposure-efficacy relation provided for steatohepatitis and no worsening of liver fibrosis is indicative for noticeable improvement of steatohepatitis also following lower doses with corresponding lower semaglutide exposures. It is agreed that from these data it is not feasible to define a clear exposure cut-off leading to unacceptable low efficacy. In relation to safety, it is agreed that the exposure-safety relation is relatively flat, so no marked increase in safety issues is generally noted upon increases exposure beyond a certain level, obtained with the final 2.4 mg dose. It is acknowledged that this also hinders defining a cut-off exposure which leads to unacceptable toxicity. Generally, the reason for asking a therapeutic margin to be established is that this can be used to evaluate e.g. DDI's or organ function impairment potentially affecting semaglutide. In this case, it is reassuring that no DDIs have been reported leading to markedly different semaglutide exposures.

Likewise, renal or hepatic impairment only have a minor effect on semaglutide exposures. It was agreed that there was no need for defining the therapeutic width for semaglutide.

The covariate analysis demonstrated that body weight affected semaglutide exposure; a 26% lower exposure was predicted in subjects with a high body weight (140 kg, the 95% percentile of the data set) and a 53% higher exposure was predicted in subjects with a low body weight (62 kg, the 5% percentile of the data set), relative to a subject with a prespecified reference body weight (100 kg). Also because an E-R was noted on the MASH efficacy endpoints, the applicant was requested to show that also for the MASH indication the fixed 2.4 mg weekly dose of semaglutide provides an adequate systemic exposure over the body weight range of 42.7−206.0 kg. The applicant provided an evaluation of the weight-response analysis for the primary endpoints steatohepatitis and no worsening of liver fibrosis and liver fibrosis and no worsening of steatohepatitis across subpopulations stratified by baseline body weight (<80 kg; ≥80 kg to <100kg; ≥100 kg). In this analysis, efficacy in the highest weight category, with expectedly the lowest exposure, was not significantly different from efficacy reached in lower weight categories with expected higher exposure. The provided information is considered sufficient to conclude that exposure in all weight categories is adequate to obtain efficacy.

PK/PD results (Study 4296 and 4553)

The two primary categorical composite endpoints—(1) resolution of steatohepatitis with no worsening of fibrosis, and (2) improvement in fibrosis with no worsening of steatohepatitis—were modelled using logistic E_{max} and linear regression models, respectively, corresponding to the primary clinical endpoints.

There were noticeable differences between the concentration–response curves from Studies 4296 and 4553. These differences theoretically suggest potential variations in efficacy based on dosing frequency—daily dosing in Study 4296 versus weekly dosing in Study 4553. Specifically, semaglutide demonstrated greater effectiveness in resolving steatohepatitis in Study 4553, whereas it was more effective for fibrosis improvement in Study 4296. However, the difference was statistically significant only for fibrosis improvement and was primarily attributed to varying placebo responses across the two studies.

Notably, no clear concentration-dependent effect was observed when assessing fibrosis progression independently. This discrepancy highlights the inherent limitations of composite endpoints, as statistical significance may arise even if improvement occurs predominantly in only one component (e.g., steatohepatitis resolution). Given the relatively short duration of these studies, definitive conclusions regarding semaglutides impact on fibrosis progression are premature. The *CHMP Reflection Paper (EMA/CHMP/111529/2024)* recommends a study duration of two years prior to interim analysis but provides flexibility dependent on phase 2 data, study size, patient characteristics, and statistical considerations. Further analysis of the exposure–response relationship for liver stiffness (measured by FibroScan) may offer valuable additional insights. Unlike histological evaluations, liver stiffness was assessed at multiple time points (baseline, weeks 24 [Study 4296 only], 48, and 72), which could enhance understanding despite technical limitations. Developing a robust PK/PD model that integrates both concentration and temporal factors could facilitate better prediction of clinical outcomes for Study 4553. The results so far suggest that liver stiffness does not evolve fully in parallel with fibrosis but may serve as a controlling or intermediate factor in disease progression. Under a discrete model framework, liver stiffness could represent a transitional state influencing the probability of progression to the next fibrosis stage. These assumptions are reasonable, but at present no firm conclusions can be drawn regarding the clinical relevance of these markers until on-going trials are completed. Nevertheless, if liver stiffness proves to be a valid biomarker for fibrosis, then the applicant has demonstrated a clear, dose-dependent, and statistically significant effect of semaglutide.

The concentration dependence of adverse effects such as vomiting was modelled using logistic regression without incorporating time.

Pharmacodynamics

The applicant has briefly discussed the pharmacodynamic effects of semaglutide as previous characterised from the Ozempic and Wegovy dossiers.

In study 4381, treatment related effects could be observed on relative percentage liver fat content (and subject with a minimum of 30% reduction in liver fat content), liver fat volume, and total liver volume, as measured by MRI. However, no effect could be observed on liver stiffness by MRE (or subjects achieving a minimum of 15% reduction in liver stiffness), liver stiffness by Fibroscan, and on liver synthesis function (albumin, INR). While a treatment effect on the exploratory marker of liver steatosis by Fibroscan could be observed. All these markers examine the effect on associated clinical signs of MASH and on some clinical liver impairment markers. None examine the underlying mechanism of semaglutide.

Effects on metabolic markers have previously been described including on glucose homeostasis, weight reduction (and adipose tissue reduction), lipid profile, and inflammation (hsCRP). Especially, improvement of glucose homeostasis and weight reduction are known pharmacological mechanisms of Ozempic and Wegovy and they constituted the basis of the approval of these medicinal products. In the current dossier, also positive effects on HbA1c were noticed in patients without T2DM for all timepoints of study 4381. Further, clear improvement in weight related parameters were seen for all timepoints evaluated in study 4381. Improvement in lipid profile and inflammation have also already been described. Most notable effects are seen for TG reduction and VLDL, while being less clear for other parameters including LDL-C and HDL-C. For hsCRP, a clear reduction was seen for all timepoints evaluated in study 4381.

Further data on several of these markers and other PD markers have been generated in the dose finding study and the main study which are discussed under efficacy, and generally show improvement in these markers, thereby supporting the primary evaluation.

However, the exact underlying mechanism for the improvement in MASH is not described. For instance, it has been described that GLP-1 is dysregulated in MASH, which triggers multiple pathways including e.g. fibroblast growth factor (FGF)-21 signalling.

Although changes in non-invasive fibrosis biomarkers such as ELF score, Pro-C3, and Fib-4 were reported, these markers do not directly confirm hepatic target engagement. There appears to be an absence of GLP-1 receptor expression on hepatocytes, but the exact mechanism could not be fully elucidated.

Any potential for a pro-arrhythmic effect has previously been studies in the diabetes MAA dossier, and it was concluded that any pro-arrhythmic effect would be unlikely. Extrapolation to the current population was considered reasonable, as there is no substantial deviation to the pro-arrhythmic risk from the existing target populations.

With 3 patients, the number of antibody formation was considered low and no relevant impact on PK was seen.

5.2.6.2. Conclusions

Overall, the PK of semaglutide is sufficiently investigated, and the proposed dose is supported from clinical pharmacological point of view. PK in MASH patients is largely comparable to the known PK in patients with T2D or in obese patients, as known from the Ozempic and Wegovy MAA.

Indirect evidence is generated based on liver associated PD markers and more general (cardio)metabolic markers in the phase 1 study, the dose finding study and the pivotal study, generally supporting the pivotal evaluation in the phase 3 study. The applicant has also elaborated on the possible mechanism of action.

The results of the refinement of exposure–response modelling for fibrosis based on stiffness suggest that liver stiffness does not evolve fully in parallel with fibrosis but may serve as a controlling or intermediate factor in disease progression and could represent a transitional state influencing the probability of progression to the next fibrosis stage. However, at present no firm conclusions can be drawn regarding the clinical relevance of these markers until on-going trials are completed.

Section 4.2 of the SmPC provides a clear distinction between patients with preserved hepatic function (as studied in trial 4553) and those with moderate or severe hepatic impairment, reassuring prescribers regarding the safety of semaglutide in patients with NASH/MASH and preserved hepatic function, while maintaining cautionary statements for patients with more advanced hepatic impairment.

5.3. Clinical efficacy

5.3.1. Dose response study

The dosing regimen was selected based on an integrated evaluation of efficacy, safety, and exposure considerations from the phase 2 dose-finding Study 4296. The dose was also selected based upon the data from the Ozempic T2D MAA investigating semaglutide SC at doses up to 2.0 mg as well as the Wegovy weight management MAA conducted for semaglutide SC 2.4 mg. See also section 5.2.5.

Study 4296

- General design

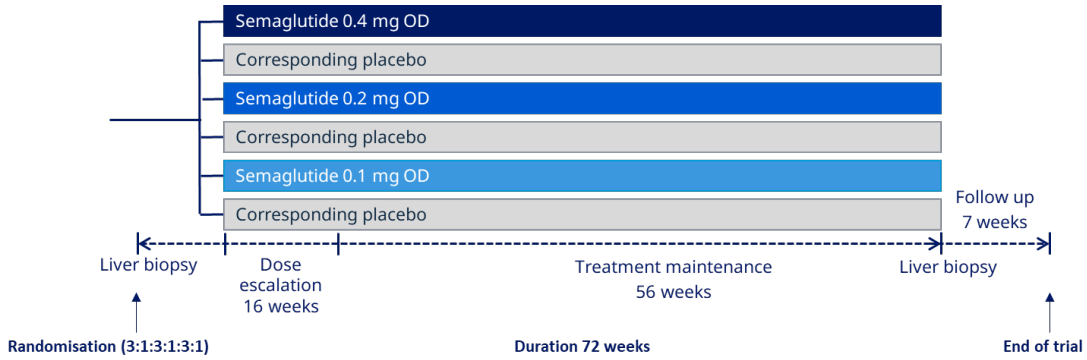
Study 4296 was a 72-week, multinational, multicentre, randomised, double-blind, six-armed, parallel-group, placebo controlled, multiple-dose trial comparing the efficacy and safety of semaglutide s.c. 0.1 mg, 0.2 mg and 0.4 mg once daily (OD) versus placebo in subjects with MASH. The diagnosis of MASH was confirmed by histological evaluation of liver biopsy samples prior to randomisation.

The total maximum trial duration for the individual subject was 85 weeks, comprising a 6-week screening period, followed by the 72-week randomised treatment period and a follow-up period of 7 weeks. Subjects were randomised in a 3:3:3:1:1:1 ratio to semaglutide s.c. 0.1 mg, 0.2 mg, 0.4 mg OD, or to the corresponding injection volumes of placebo.

After randomisation, the subjects entered a dose-escalation period, with increases in dose every 4 weeks until the target dose was reached. The trial was double-blinded within dose levels but not between dose levels because of the different dose escalation schemes and volumes administered. Subjects who prematurely discontinued trial product were to continue with the originally scheduled site visits/contacts and final assessments (including performing a liver biopsy) until 72 weeks after randomisation. Randomisation was stratified in five groups based on region (Japanese or non-Japanese) and, within the non-Japanese group, based on diabetes status at screening (with or without type 2 diabetes (T2D)) and fibrosis stage of baseline liver biopsy (F1/F2 or F3).

Subjects in all treatment groups, including subjects who prematurely discontinued trial product, received nutritional and physical activity counselling throughout the trial.

Figure 6: Trial design - trial 4296



- Included patients

Patients with histologic evidence of MASH based on central pathologist evaluation of a liver biopsy obtained up to 21 weeks before screening; Histological NAFLD activity score (NAS) > 4 with a score of 1 or more in each sub-component of the score based on central pathologist evaluation; MASH fibrosis stage F1, F2 or F3 based on central pathologist evaluation.

- Study objectives

The primary objective was to compare the effect of semaglutide s.c. once daily versus placebo on histological resolution of MASH.

Secondary objectives included investigation of the dose-response relationship of three dose levels of semaglutide s.c. once daily (0.1 mg/day, 0.2 mg/day and 0.4 mg/day) on histological resolution of MASH, effects on liver-related histological parameters and biomarkers of MASH disease, weight related parameters, glucose metabolism, cardiovascular risk factors, patient reported outcomes, and to evaluate the safety and tolerability of three dose levels of semaglutide s.c. once daily in subjects with MASH.

- Study endpoints

The primary endpoint was MASH resolution without worsening of fibrosis after 72 weeks (yes/no)

The most important secondary endpoint was at least one stage of liver fibrosis improvement with no worsening of MASH after 72 weeks. This endpoint was defined as supportive in the protocol and as confirmatory in the Statistical Analysis Plan (SAP) issued before unblinding of the trial.

- Statistical considerations

The SAP was finalised prior to unblinding the trial. The main revisions to the analyses specified in the protocol were:

1. The secondary endpoint *fibrosis improvement with no worsening of MASH* was added to the confirmatory test procedure and, thus, became a confirmatory secondary endpoint.

2. The population for the confirmatory tests was restricted to only consist of subjects with fibrosis stage 2 or 3 at baseline (that is, excluding subjects with baseline fibrosis stage 1)

- Results

A total of 288 subjects were planned for randomisation; 1227 were screened and 320 were randomised. In total, 302 (94.4%) of the randomised subjects completed the trial and 277 subjects (>86%) had an evaluable biopsy at week 72 (Table 7).

Table 7: Table Baseline characteristics

DEMOGRAPHY OF TRIAL POPULATION

	Semaglutide 0.1 mg N (%)	Semaglutide 0.2 mg N (%)	Semaglutide 0.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	80	78	82	80	320
Sex					
Female	51 (63.8)	52 (66.7)	47 (57.3)	44 (55.0)	194 (60.6)
Male	29 (36.3)	26 (33.3)	35 (42.7)	36 (45.0)	126 (39.4)
Age group (years)					
18 <= to < 65	64 (80.0)	58 (74.4)	70 (85.4)	70 (87.5)	262 (81.9)
65 <= to < 75	15 (18.8)	19 (24.4)	11 (13.4)	10 (12.5)	55 (17.2)
75 <=	1 (1.3)	1 (1.3)	1 (1.2)	0 (0.0)	3 (0.9)
Race					
White	65 (81.3)	59 (75.6)	62 (75.6)	62 (77.5)	248 (77.5)
Black or African American	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)
Asian	10 (12.5)	12 (15.4)	14 (17.1)	12 (15.0)	48 (15.0)
American Indian or Alaska Native	0 (0.0)	1 (1.3)	2 (2.4)	0 (0.0)	3 (0.9)
Other	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.3)	2 (0.6)
N/A	4 (5.0)	5 (6.4)	3 (3.7)	5 (6.3)	17 (5.3)
Region					
Europe*	44 (55.0)	42 (53.8)	41 (50.0)	36 (45.0)	163 (50.9)
North America	26 (32.5)	27 (34.6)	29 (35.4)	34 (42.5)	116 (36.3)
Japan	10 (12.5)	9 (11.5)	12 (14.6)	10 (12.5)	41 (12.8)
BMI group(kg/m^2)					
<25	1 (1.3)	0 (0.0)	2 (2.4)	1 (1.3)	4 (1.3)
25<= to <30	15 (18.8)	18 (23.1)	17 (20.7)	14 (17.5)	64 (20.0)
30<= to <35	20 (25.0)	21 (26.9)	25 (30.5)	21 (26.3)	87 (27.2)
35<=	44 (55.0)	39 (50.0)	38 (46.3)	44 (55.0)	165 (51.6)
Type 2 diabetes					
Yes	49 (61.3)	51 (65.4)	49 (59.8)	50 (62.5)	199 (62.2)
No	31 (38.8)	27 (34.6)	33 (40.2)	30 (37.5)	121 (37.8)
Fibrosis stage (0-4)					
1	23 (28.8)	19 (24.4)	26 (31.7)	22 (27.5)	90 (28.1)
2	18 (22.5)	18 (23.1)	14 (17.1)	22 (27.5)	72 (22.5)
3	39 (48.8)	41 (52.6)	42 (51.2)	36 (45.0)	158 (49.4)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total NAS (0-8)					
4	29 (36.3)	30 (38.5)	37 (45.1)	37 (46.3)	133 (41.6)
5	34 (42.5)	29 (37.2)	31 (37.8)	20 (25.0)	114 (35.6)
6	15 (18.8)	14 (17.9)	11 (13.4)	19 (23.8)	59 (18.4)
7	1 (1.3)	5 (6.4)	2 (2.4)	4 (5.0)	12 (3.8)
8	1 (1.3)	0 (0.0)	1 (1.2)	0 (0.0)	2 (0.6)

*Region Europe included 4 subjects randomised in Australia.

continues

continued

	Semaglutide 0.1 mg Mean (SD)	Semaglutide 0.2 mg Mean (SD)	Semaglutide 0.4 mg Mean (SD)	Placebo Mean (SD)	Total Mean (SD)
Age, years	55.2 (10.9)	58.1 (9.9)	54.3 (10.2)	52.4 (10.8)	55.0 (10.6)
Body weight, kg	98.4 (21.1)	97.1 (22.0)	96.6 (20.1)	101.3 (23.3)	98.4 (21.7)
BMI, kg/m^2	36.1 (6.4)	35.6 (6.1)	35.2 (6.6)	36.1 (6.6)	35.8 (6.4)
HbA1c, % - T2D	7.4 (1.3)	7.2 (1.0)	7.2 (1.2)	7.3 (1.2)	7.3 (1.2)
HbA1c, % - non T2D	5.8 (0.5)	5.8 (0.5)	5.7 (0.4)	5.8 (0.7)	5.8 (0.5)
FPG, mmol/L - T2D	8.87(2.72)	7.87(2.12)	8.05(2.56)	8.39(2.36)	8.29(2.46)
FPG, mmol/L - non T2D	5.73(1.50)	5.93(1.17)	5.73(0.66)	5.91(1.41)	5.82(1.21)
NAS	4.9 (0.8)	4.9 (0.9)	4.8 (0.9)	4.9 (0.9)	4.9 (0.9)
ELF	9.8 (1.0)	9.8 (0.9)	9.9 (1.0)	9.6 (0.9)	9.8 (0.9)

N: number of subjects, %: proportion of subjects, SD: standard deviation

- Hierarchical testing of the primary endpoint (1) and secondary endpoints (2 on forward) (Table 8)

Table 8: Hierarchical testing of the primary and secondary endpoints

Endpoint Contrast	Estimate (95% CI)	One-sided p-value	One-sided alpha	Alternative hypothesis	Conclusion
1. Resolution of steatohepatitis and no worsening in liver fibrosis at week 72					
Sema 0.4 mg/ Placebo	6.87 [2.60; 17.63]	<.0001	0.025	Superiority	**Confirmed**
2. Improvement in liver fibrosis and no worsening in steatohepatitis at week 72					
Sema 0.4 mg/ Placebo	1.42 [0.62; 3.28]	0.2407	0.025	Superiority	Not confirmed
3. Resolution of steatohepatitis and no worsening in liver fibrosis at week 72					
Sema 0.2 mg/ Placebo	2.71 [1.06; 7.56]	0.0180	0	Superiority	Not confirmed
4. Improvement in liver fibrosis and no worsening in steatohepatitis at week 72					
Sema 0.2 mg/ Placebo	1.00 [0.43; 2.32]	0.5780	0	Superiority	Not confirmed
5. Resolution of steatohepatitis and no worsening in liver fibrosis at week 72					
Sema 0.1 mg/ Placebo	3.36 [1.29; 8.86]	0.0050	0	Superiority	Not confirmed
6. Improvement in liver fibrosis and no worsening in steatohepatitis at week 72					
Sema 0.1 mg/ Placebo	1.96 [0.86; 4.51]	0.0577	0	Superiority	Not confirmed

It was concluded that semaglutide 0.4 mg was superior over placebo regarding the proportion of subjects who achieved resolution of steatohepatitis and no worsening in liver fibrosis at week 72, and no further conclusion could be made.

- Other secondary endpoints

A summary of liver-related histological parameters is provided in Table 9 (0.4 mg OD only).

Table 9: Other liver-related histological parameters

	Improvement	No change	Missing	Worsening
Fibrosis stage to week 72 (Kleiner fibrosis classification)				
0.4 mg OD	42.7	36.6	15.9	4.9
Placebo	31.3	37.5	12.5	18.8
Steatosis to week 72				
0.4 mg OD	63.4	20.7	12.2	3.7
Placebo	26.3	46.3	12.5	15.0

Lobular inflammation				
0.4 mg OD	37.8	43.9	12.2	6.1
Placebo	26.3	45.0	11.3	17.5
Hepatocyte ballooning				
0.4 mg OD	74.4	12.2	12.2	1.2
Placebo	38.8	46.3	12.5	2.5
Total NAS				
0.4 mg OD	82.9	1.2	12.2	3.7
Placebo	43.8	27.5	12.5	16.3
Activity component of SAF score				
0.4 mg OD	72.0	14.6	12.2	1.2
Placebo	42.5	33.8	12.5	11.3

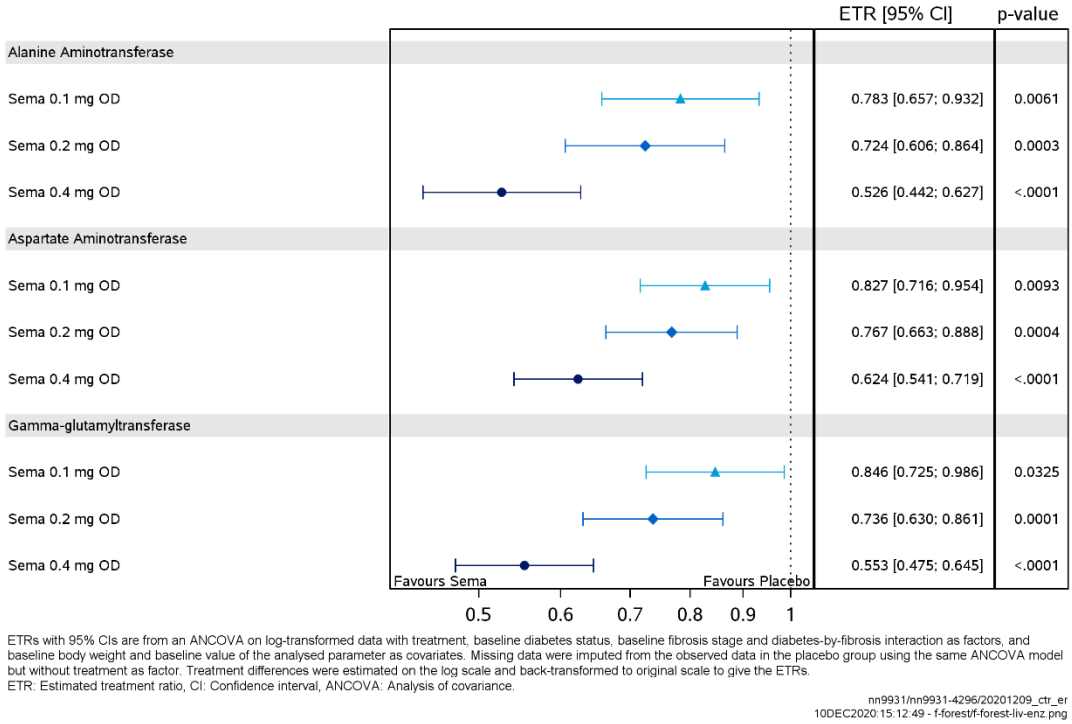
Table 10: Imaging biomarkers of MASH and - ratio to baseline at 72 weeks (0.4 mg OD only)

		0.4 mg OD	**Placebo**
Liver stiffness by FibroScan	Ratio to baseline	0.72	1.02
	Vs placebo	0.71 (0.59; 0.85)	
Liver steatosis by FibroScan	Ratio to baseline	-39.13	-17.73
	Vs placebo	21.41 (-45.54; 2.73) p=0.0821	

- Blood samples of liver tests

Results on liver enzymes are provided below. Also, numerical improvements in liver synthesis function of albumin and INR were seen.

Figure 7: Liver enzymes - ratio to baseline at 72 weeks - forest plot - in-trial - FAS



ETRs with 95% CIs are from an ANCOVA on log-transformed data with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline body weight and baseline value of the analysed parameter as covariates. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor. Treatment differences were estimated on the log scale and back-transformed to original scale to give the ETRs.
ETR: Estimated treatment ratio, CI: Confidence interval, ANCOVA: Analysis of covariance.

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- Indirect marker of weight effects (Table 11)

Table 11: Weight effects

		0.1 mg OD	0.2 mg OD	0.4 mg OD	Placebo
Body weight loss	Relative change from baseline	-4.84	-8.91	-12.51	-0.61
	Vs placebo	-4.23 (-6.58; -1.88) p=0.0004	-8.29 (-10.67; -5.92) p <0.001	-11.90 (-14.25; -9.54)	
BWL > 10%	Ratio to baseline	17.7	38.6	60.1	2.5
	Vs placebo	P=0.0072	P<0.001	P<0.001	
BWL > 5%	Ratio to baseline	44.8	64.8	78.4	17.0
	Vs placebo	P=0.0003	P<0.001	P<0.001	
BMI	Change from baseline	-1.68	-3.22	-4.40	-0.24
	Vs placebo	-1.44 (-2.30; =0.57) p=0.0012	-2.98 (-3.85; -2.10) p<0.001	-4.16 (-5.03; -3.29) p<0.001	
Waist circumference	Change from baseline	-3.85	-6.58	-11.04	-1.31

	Vs placebo	-2.54 (-5.00; -0.09) p=0.0423	-5.27 (-7.77; -2.77) p<0.001	-9.73 (-12.18; -7.27) p<0.001

- Diabetes markers

Table 12: Diabetes markers

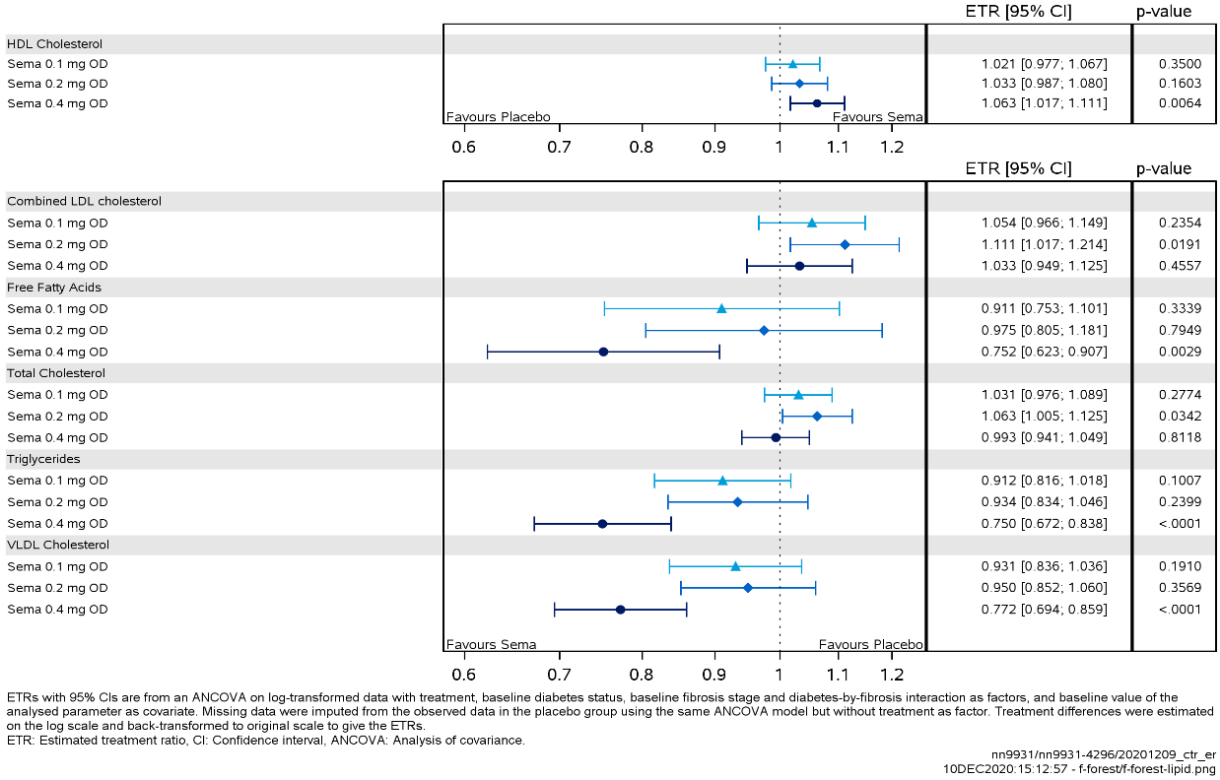
		0.1 mg OD	0.2 mg OD	0.4 mg OD	Placebo
HbA1c-with diabetes	Change from baseline	-0.63	-1.07	-1.15	-0.01
	Vs placebo	P=0.0013	P<0.001	P<0.001	
Fasting plasma glucose -with diabetes	Change from baseline	-0.99	-2.27	-2.13	-0.28
	Vs placebo	P=0.0775	P<0.001	P<0.001	
Fasting glucagon-with diabetes	Ratio to baseline	0.79	0.69	0.63	1.02
	Vs placebo	P=0.0878	P=0.0078	P=0.0010	
HOMA-IR – subjects with diabetes	Ratio to baseline	0.79	0.58	0.56	0.88
	Vs placebo	P=0.5110	P=0.0130	P=0.0057	

- Blood pressure

Numerical improvements in SBP were observed greatest with the 0.4 mg OD dose (SBP -4 mmHg difference, p=0.0523), while less clear for DBP (0.8 to -1.0 mmHg difference).

- Lipids

Figure 8: Effects on the lipid profile



ETRs with 95% CIs are from an ANCOVA on log-transformed data with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline value of the analysed parameter as covariate. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor. Treatment differences were estimated on the log scale and back-transformed to original scale to give the ETRs.
ETR: Estimated treatment ratio, CI: Confidence interval, ANCOVA: Analysis of covariance.

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- Other markers

Table 13: Inflammation marker (hsCRP)

		0.1 mg OD	0.2 mg OD	0.4 mg OD	Placebo
hsCRP	Ratio to baseline	0.79	0.52	0.43	0.92
	Vs placebo	P=0.255	P<0.001	P<0.001	

5.3.2. Main study

5.3.2.1. NN9931-4553

5.3.2.1.1. Study title

The effect of semaglutide in subjects with non-cirrhotic non-alcoholic steatohepatitis

5.3.2.1.2. Study design

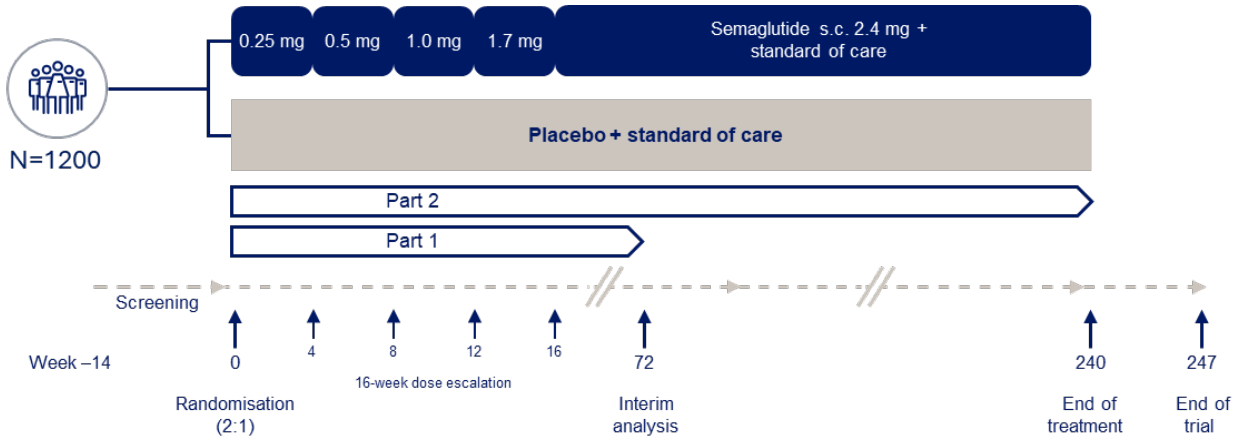
General design

Trial 4553 is a 240-week randomised, multicentre, double-blind, parallel-group phase 3 trial comparing semaglutide s.c. 2.4 mg once weekly versus placebo s.c. once weekly in subjects with MASH and F2 or F3 (recruitment cap of approximately 20% for subjects with F2). The trial design is outlined in Figure 9.

The trial has two parts, with distinctive objectives and endpoints. The objective in part 1 was to demonstrate that semaglutide s.c. 2.4 mg in addition to standard of care improves liver histology after 72 weeks of treatment. The objective in the ongoing part 2 is to demonstrate that semaglutide 2.4 mg in addition to standard of care lowers the risk of liver-related clinical events after 240 weeks of treatment.

The present application is based on an interim evaluation of part 1.

Figure 9: Trial design – trial 4553



N: protocol-specified planned total trial population; s.c. subcutaneous.

Treatment

The treatment period includes a 16-week dose escalation phase from 0.25 mg to 2.4 mg once weekly, followed by maintenance treatment. Due to the lack of pharmacological treatment options for patients with MASH, placebo was chosen as the comparator on top of standard of care. Two different pen-injectors were provided in this trial: the DV3396 single-dose pen-injector (for all countries except China) and the PDS290 pen-injector (for all countries).

Randomisation

All subjects were screened and centrally randomised using an IWRS (interactive web response system) and assigned to the next available treatment according to randomisation schedule. Eligible subjects were randomised 2:1 to receive either semaglutide or placebo s.c. Randomisation was stratified based on the presence of T2D at screening (yes or no; T2D defined as a medical history of T2D and/or HbA1c ≥ 48 mmol/mol (≥ 6.5%)), fibrosis stage (F2 or F3) and region (Japan, East Asia excluding Japan, or rest of the world). The IWRS is used for blind-breaking.

Blinding

During the entire trial conduct, trial subjects, investigators, and Novo Nordisk personnel actively involved in the trial conduct were blinded to individual treatment assignments. To preserve the blinding of the trial, a minimum number of Novo Nordisk personnel were able to see the randomisation table and treatment assignments before the trial was complete to conduct the interim analysis. The responsibilities and procedures under which the unblinded team and other personnel would operate to

prepare the documentation for regulatory and other filings based on the interim evaluation were described in an interim evaluation charter. As specified in detail in an interim evaluation charter, personnel who had had access to unblinded subject-level data will not be involved in the conduct of the ongoing trial until the end of part 2.

According to standard pharmacovigilance procedures, specific members of the Novo Nordisk A/S Global Safety department were not blinded to SUSARs (for reporting purposes), whereas the clinical trial group and the investigator remained blinded throughout the trial.

Two investigators were designated as signatory investigators for both part 1 and part 2 of the 4553 trial. To avoid unblinding of the signatory investigators towards part 2 of trial 4553, Novo Nordisk as the sponsor of the trial appointed an internal medical specialist as the responsible party for reviewing and approving the interim CTR.

Histological evaluation

The eligibility biopsies were later re-read along with the week-72 biopsies by one of the pathologist teams to serve as the baseline for the derivation of the histology-related efficacy endpoints. The pathologists were blinded towards subject ID as well as biopsy type (baseline or week 72).

Patient population

Before randomisation

All subjects needed either a historical liver biopsy or a trial-related liver biopsy performed before randomisation. To reduce the screen failure rate in subjects undergoing a trial-related biopsy, subjects had to fulfil at least 1 pre-qualification criterion to confirm the likelihood of MASH and significant fibrosis before proceeding to a trial-related liver biopsy.
Pre-qualification criteria were as follows:

- Liver biopsy performed within 180 days prior to V1 which can be sent to central evaluation.
- History of any of the following:
    - ELF ≥9.8
    - FibroScan® ≥9.1 kPa
    - MRE ≥3.2 kPa
    - FAST ≥0.67
    - Biopsy consistent with MASH and presence of fibrosis stage 2 or 3
- FIB-4 ≥1.3 measured at V1.

All subjects underwent a liver biopsy at week 72 (end of part 1), unless they had had a confirmed liver-related clinical event prior to week 72.

Key inclusion criteria

Subjects were eligible to be included in the trial only if all of the following criteria applied: Informed consent and age above or equal to 18 years at the time of signing informed consent; Histological evidence of MASH based on a central pathologist evaluation of the baseline liver biopsy, of fibrosis stage 2 or stage 3 according to the MASH CRN classification, and NAS ≥ 4 with a score of 1 or more in steatosis, lobular inflammation and hepatocyte ballooning . The baseline liver biopsy can be a historical biopsy obtained within 180 days prior to screening visit (V1).

Key exclusion criteria

Subjects were excluded from the trial if any of the following relevant criteria applied (in addition to standard exclusion criteria):

- Liver related

Documented causes of chronic liver disease other than NAFLD; Positive HBsAg, positive anti-HIV, positive HCV RNA at screening (V2A) or any known presence of HCV RNA or HBsAg within 2 years of screening (V2A); Presence or history of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis or liver transplantation at randomisation; ALT or AST > 5 times ULN at screening (V2A), doubling of ALT or AST level between V1 and V2A deemed clinically significant in the opinion of the investigator, total bilirubin > 1.5 mg/dL at screening (V2A) (Total bilirubin level > 1.5 mg/dL is allowed if conjugated bilirubin is within normal range), alkaline phosphatase levels > 2 x ULN at screening (V2A), INR of prothrombin time ≥ 1.35 at screening (V2A); MELD score > 12 points at screening (V2A).

- Concomitant therapy

Known or suspected excessive consumption of alcohol (> 20 g/day for women or > 30 g/day for men) or alcohol dependence (assessed by the Alcohol Use Disorders Identification Test [AUDIT questionnaire]); Treatment with vitamin E (at doses ≥ 800 IU/day) or pioglitazone or medications approved for treatment of MASH which has not been at a stable dose in the period from 90 days prior to the screening visit (V2A). Treatment with GLP-1 RAs in the period from 90 days prior to the screening visit (V2A); Treatment with glucose-lowering agent(s) (other than GLP-1 RAs), lipid-lowering medication or weight loss medication not stable in the opinion of the investigator in the period from 90 days prior to the screening visit (V2A); Previous or planned (during the trial period) obesity treatment with surgery or a weight loss device.

- Carcinoma

Presence or history of hepatocellular carcinoma at randomisation; Presence or history within the past 5 years prior to screening (V2A) of malignant neoplasms other than hepatocellular carcinoma. Basal and squamous cell skin cancer and any carcinoma in-situ are allowed; Personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.

- Diabetes related

HbA1c > 80 mmol/mol (9.5%) at screening (V2A); For subjects with T2D: Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. History or presence of type 1 diabetes.

- CV related

Any of the following: myocardial infarction, stroke, classification of heart failure New York Heart Association (NYHA) Class IV, hospitalisation for unstable angina pectoris or transient ischaemic attack within the past 90 days prior to the day of screening (V2A) and between screening and randomisation.

- Body weight related

Unstable body weight defined as more than 5% self-reported change in body weight in the period from 90 days prior to the screening visit (V1); Any subject where a substantial weight loss in the investigator’s opinion might jeopardise subject’s safety.

- Others

eGFR < 30 mL/min/1.73 m^2 (CKDEPI) at screening (V2A); Thrombocyte count less than 150,000 per microliter of blood (V2A), unless it reflects the patient's habitual thrombocytes level and there is no presence of portal hypertension in the opinion of the investigator; Presence of acute pancreatitis within the past 180 days prior to screening (V2A); History or presence of chronic pancreatitis at screening (V2A); Any condition which, in the investigator’s opinion might jeopardise subject’s safety or compliance with the protocol.

Countries

The trial is expected to be conducted in 39 countries. For Part 1 (in scope for the current interim CTR), 334 sites enrolled 1197 subjects in 38 countries.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective for Part 1 is to demonstrate that treatment with semaglutide s.c. 2.4 mg improves liver histology compared to placebo in subjects with MASH and fibrosis stage 2 or 3.

Estimand for the primary objective

Table 14: Estimand for the primary objective

Population	Patients with MASH F2-F3
Treatment condition	Assignment to semaglutide s.c. 2.4 mg once weekly, regardless of discontinuation and initiation of ancillary therapy possibly modifying MASH, compared to assignment to placebo, regardless of discontinuation and initiation of ancillary therapy possibly modifying MASH
Endpoint (variable)	Primary endpoints: • Resolution of steatohepatitis and no worsening of liver fibrosis[a] (Yes/No) • Improvement in liver fibrosis and no worsening of steatohepatitis[b] (Yes/No) For both endpoints, liver-induced MELD score ≥15, hepatic decompensation events, unplanned biopsy showing progression to cirrhosis, liver transplantation and death will be counted as a negative response.
Population-level summary	Absolute difference in proportion between treatments in achieving the endpoint
Intercurrent events and strategy to handle them	
Premature treatment discontinuation	Treatment policy
Initiation of ancillary therapy possibly modifying MASH	Treatment policy
Liver-induced MELD score ⩾15	Composite endpoint (negative response)
Hepatic decompensation events	Composite endpoint (negative response)
Unplanned biopsy showing progression to cirrhosis	Composite endpoint (negative response)
Liver transplantation	Composite endpoint (negative response)
Death	Composite endpoint (negative response)

[a)] Resolution of steatohepatitis is defined as an NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (According to NASH CRN7). Fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4.

[b)] Improvement in fibrosis is defined as $\geqslant$ 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis.

Statistical methods for estimation and sensitivity analysis on primary estimands

General considerations

The "in-trial" observation period was defined as the time period where the subject was to be be followed in the trial. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive):

- follow-up visit (end-of-trial visit);
- withdrawal of consent;
- last contact with subject (for subjects lost to follow-up);
- death.

In the case that the part 1 interim was based on the first 800 randomised trial subjects, the primary data cut for efficacy evaluations was based on the analysis set "FAS (interim)" and the in-trial observation period truncated at week 72. Otherwise, the primary data cut was based on the analysis set "FAS (interim, all randomised subjects)" and the in-trial observation period truncated at week 72. In either case, supplementary efficacy evaluations were made based on the analysis set "FAS (interim, all randomised subjects)" and the in-trial observation period. For both FAS (interim) and FAS (interim, all randomised subjects), subjects were analysed according to the trial product they were randomised to receive.

The safety evaluations were based on the analysis set "SAS (interim)" and on-treatment observation period as the primary safety data cut. All subjects assigned to trial treatment and who take at least 1 dose of trial product. Subjects were analysed according to the trial product they received. The in-trial observation period was used for selected safety areas.

For confirmatory endpoints controlled for multiplicity, one-sided p-values were used for test of superiority. For reporting of results, the estimated treatment effect and the 95% confidence interval was accompanied by the two-sided p-value.

Vital status, non-fatal events and other assessments were not systematically collected after withdrawal of consent, lost-to-follow-up, or after end-of-trial. For this reason, any event occurring, or data ascertained after the in-trial observation period that were reported in the trial database, were be included in analyses, unless otherwise stated.

If not otherwise specified, the baseline measurement was defined as the latest available eligible measurement at or prior to the randomisation visit. For the analysis of continuous statistical data, subjects with no available baseline assessment were omitted.

Baseline diabetes status and baseline fibrosis stage were used as stratification variables for the randomisation and were consequently included as factors in the statistical analyses. The diabetes status factor was based on medical history. The fibrosis stage factor was defined by the histological evaluation that was used for determining eligibility. The randomisation was also stratified based on region; however, including all three stratification variables in the analyses may create too small strata and lead to unreliable estimates. The factors in the analyses have therefore been restricted to the two that were considered most relevant.

For deriving the histological endpoints, the baseline biopsies were re-read twice; one time for the week 72 analysis and one time for the week 240 analysis. The endpoints were derived by comparing the

reading of the in-trial biopsy (week 72/week 240) with the corresponding re-read baseline biopsy. For the analyses of liver histology at week 72 and week 240, only biopsies with ascertainment dates within a visit window of minus/plus 180 days around 72 weeks and 240 weeks from baseline, respectively, were included.

For adjudicated events, the onset date was defined based on the outcome of the evaluation of the event as defined by the EAC.

Co-participation in COVID-19 trials was handled like an intercurrent event. In line with the pre-specified treatment policy estimand including the handling of intercurrent events, co-participation were regarded as an integrated part of the treatment regimen.

Primary estimands

The two primary endpoints, "Resolution of steatohepatitis and no worsening in liver fibrosis at 72 weeks", and "Improvement in liver fibrosis and no worsening in steatohepatitis at 72 weeks", as well as the confirmatory secondary endpoint "Resolution of steatohepatitis and improvement in liver fibrosis" were analysed using a Cochran-Mantel-Haenszel (CMH) test stratified into four strata defined by baseline diabetes status (with or without T2D) and baseline fibrosis stage (F2 or F3). Missing data was handled by reference-based imputation, i.e. a method of multiple imputation that is informed by data from subjects in the placebo group. It is thereby assumed that subjects in either treatment group without an observed outcome have the same chances of meeting the endpoint as subjects in the placebo group with an observed outcome. Subjects who have had a liver-related clinical event before the week 72 visit will be handled as non-responders, i.e. these subjects were not considered to have met the endpoint.

Inference on the below statistical procedure for the confirmatory endpoints was adjusted for the group sequential design. Adjustment of estimates, p-values and two-sided 95% confidence intervals were calculated using stage-wise ordering. The adjustment procedure used the available information defined as the reciprocal of the squared standard error from the corresponding analysis as specified below. Note that analysis results were estimated and reported at either intermediate stage or final stage for all part 1 endpoints regardless of at which stage superiority was established as per the look-back approach by Örhn.

A two-way tipping point sensitivity analysis was conducted to investigate the impact of the assumptions underlying the imputation procedure on the conclusion. Testing of superiority followed the same approach as the main analytical approach; however, instead of sampling missing data from the observed data in the placebo group, a prespecified range of responder proportions was used to draw responses in each arm from which multiple complete data sets are generated. The grid used for responder rates in each arm was given by 1% to 99% by increments of 1%-point.

The handling of missing data in the main analytical approach was aligned with a treatment policy strategy. As a sensitivity analysis, all subjects with missing data were alternatively classified as non-responders according to a composite strategy. The analysis was performed as a CMH test stratified by baseline fibrosis stage and baseline diabetes status in the same way as in the main analytical approach using a single imputation only.

The main analyses of binary liver histology endpoints were supplemented by evaluating the relative risk as treatment effect estimate. Specifically, the Mantel-Haenszel estimate of the common relative risk in responder proportions was used with the corresponding Greenland and Robins estimate of the variance. Estimates and standard errors from multiple imputed data were pooled using Rubin's rule analogous with main approach.

To complement the interpretation of liver histology, a different clinical question was targeted in a

supplementary analysis. In this analysis, a hypothetical strategy was used to handle the two intercurrent events of (i) premature trial product discontinuations and (ii) initiation of ancillary therapy, possibly modifying MASH. The analysis of the primary part 1 endpoints was targeting a treatment effect that quantifies the effect of taking the randomised trial product as planned.

Operationally, this means that data collected after the occurrence of an intercurrent event of these types are set to missing and instead imputed according to the hypothetical strategy. The statistical analysis was identical to the primary part 1 analysis, with the exception that missing data was imputed differently. In line with the hypothetical strategy, missing data, regardless of the reason, was handled by multiple imputation informed by observed data from study subjects within their own treatment arm.

Secondary objectives

The secondary objectives are as follows:

- To demonstrate that treatment with semaglutide s.c. 2.4 mg lowers body weight compared to placebo in subjects with NASH and fibrosis stages 2 or 3.
- To demonstrate that treatment with semaglutide s.c. 2.4 mg improves patient-reported outcomes compared to placebo in subjects with MASH and fibrosis stages 2 or 3.
- To compare the effects of semaglutide s.c. 2.4 mg versus placebo on cardiovascular disease and cardio-metabolic factors in subjects with MASH and fibrosis stages 2 or 3.
- To compare the effect of semaglutide s.c. 2.4 mg versus placebo on biomarkers related to fibrosis in subjects with MASH and fibrosis stages 2 or 3.

Estimand for the secondary objectives

Endpoints for secondary objectives were split between confirmatory and supportive. Estimands were only described for the former.

The population and treatment attributes of the estimand for secondary objectives were the same as for primary objectives.

The endpoint (and respective population-level summary) for confirmatory secondary objectives was defined as follows:

- Change in body weight from randomisation (week 0) to week 72 (absolute difference in percentage between treatments);
- Resolution of steatohepatitis and improvement in liver fibrosis from randomisation (week 0) to week 72 [a, b] (absolute difference in proportion between treatments in achieving both);
    - a. Resolution of steatohepatitis is defined as an NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (according to NASH CRN2);
    - b. Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale;
- Change in SF-36 bodily pain from randomisation (week 0) to week 72 (absolute difference in score points between treatments);
- Change in body weight from randomisation (week 0) to week 240 (absolute difference in percentage between treatments)

Intercurrent currents of premature treatment discontinuation and initiation of ancillary therapy possibly modifying MASH were handled for confirmatory secondary objectives as for primary objectives, with a treatment policy strategy.

The intercurrent events of liver-induced MELD score ⩾15, hepatic decompensation events, unplanned

biopsy showing progression to cirrhosis, liver transplantation and death were handled for confirmatory secondary objectives as for primary objectives for resolution of steatohepatitis and improvement in liver fibrosis because it is a binary variable: each event will be counted as a negative response.

For other endpoints (change in body weight and change in SF-36 bodily pain), the estimand strategy was not provided for these five intercurrent events.

Supportive secondary endpoints are listed in the following table.

Table 15: Table of supportive secondary endpoints and summary measures

Endpoint title	Time frame	Unit
Improvement in steatohepatitis with at least a 2-point reduction in NAS[a] and no worsening of fibrosis (Yes/No)	From randomisation (week 0) to week 72	Count of subject
Change in histology-assessed liver collagen proportionate area	From randomisation (week 0) to week 72	Ratio to baseline
Worsening in steatohepatitis[b] (Yes/No)	From randomisation (week 0) to week 72	Count of subject
Improvement in histology-assessed ballooning (Yes/No)	From randomisation (week 0) to week 72	Count of subject
Improvement in histology-assessed inflammation (Yes/No)	From randomisation (week 0) to week 72	Count of subject
Improvement in histology-assessed steatosis (Yes/No)	From randomisation (week 0) to week 72	Count of subject
NASH resolution (ballooning of 0, inflammation of 0-1) and ≥2point NAS[a] reduction with no worsening of fibrosis	From randomisation (week 0) to week 72	Count of subject
Progression of liver fibrosis in patients with F2 at baseline (Yes/No)	From randomisation (week 0) to week 72	Count of subject
Progression of liver fibrosis	From randomisation (week 0) to week 72	Count of subject
Resolution of steatohepatitis and no worsening of liver fibrosis (Yes/No)	From randomisation (week 0) to week 240	Count of subject
Improvement in liver fibrosis and no worsening of steatohepatitis (Yes/No)	From randomisation (week 0) to week 240	Count of subject
Changes in liver stiffness values assessed by transient elastography (FibroScan®[f])	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in ELF score	From randomisation (week 0) to week 72 and week 240	Logarithm
Change in ALT	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in AST	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in CAP values assessed by transient elastography (FibroScan)	From randomisation (week 0) to week 72 and week 240	Absolute change
Change in FAST score	From randomisation (week 0) to week 72 and week 240	Probability (absolute change)
Change in Pro-C3	From randomisation (week 0) to week 72 and week 240	Logarithm
Change in inflammation assessed by hsCRP	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in HbA_{1c}[c]	From randomisation (week 0) to week 72 and week 240	%-points (absolute change)

Endpoint title	Time frame	Unit
Change in triglyceride	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in free fatty acids	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in LDL cholesterol	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in HDL cholesterol	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Time to first MACE (composite endpoint)[d]	From randomisation (week 0) to week 240	Days
Major cardio-hepatic event-free survival (Yes/No)[e]	From randomisation (week 0) to week 240	Count of subject
Changes in SF-36 Physical Component Summary	From randomisation (week 0) to week 72 and week 240	Score points
Changes in SF-36 Mental Component Summary	From randomisation (week 0) to week 72 and week 240	Score points
Change in SF-36 Bodily Pain	From randomisation (week 0) to week 240	Score points
Changes in NASH-CHECK Abdominal Pain	From randomisation (week 0) to week 72 and week 240	Score points

a) The 2-point reduction needs to include at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning

b) Defined as increase in NAS for ballooning, inflammation, or steatosis

c) For subjects with type 2 diabetes

d) The MACE composite endpoint consists of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke

e) Major cardio-hepatic event-free survival corresponds to not having experienced one of the following major cardio-hepatic events: MACE, death (any cause), histological progression to cirrhosis, liver-induced MELD score ≥15, liver transplant or hepatic decompensation event

f) FibroScan® will only be assessed at sites that has the equipment available

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAP = Controlled Attenuation Parameter; ELF = Enhanced Liver Fibrosis; FAST= FibroScan-AST; HDL = high density lipoprotein; hsCRP = high sensitivity C-reactive protein; LDL = low density lipoprotein; MACE = major adverse cardiovascular event; MELD = Model for End-stage Liver Disease; NAS = Non-alcoholic fatty liver disease Activity Score; Pro-C3= pro-peptide of type III collagen, SF-36 = Short Form 36.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Change in body weight from baseline to at 72 weeks and change in SF-36 bodily pain from baseline to 72 weeks was analysed using an analysis of covariance model (ANCOVA) with missing data and data non-ascertainable due to death handled by unconditional reference-based imputation, i.e. imputation of missing data was to be informed by data from subjects in the placebo group.

Subjects with any missing baseline assessment used in the model available were omitted. The analysis was performed in the following steps:

1. An ANCOVA model with baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline body weight (kg) as a covariate was fitted to the placebo data week 72 only.
2. Five hundred sets of estimates of the model parameters are drawn from the posterior distribution. For each replicated set of parameter estimates, the model was used to generate a

complete dataset by imputing missing data based on subjects' baseline diabetes status, baseline fibrosis stage and baseline body weight.

3. Each complete data set was analysed separately using an ANCOVA model with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline body weight as a covariate. The estimated treatment differences and standard errors were then pooled using Rubin's rule to draw inference.

Resolution of steatohepatitis and improvement in liver fibrosis at 72 weeks were analysed using the same CMH test and multiple imputation of missing data as for the primary binary endpoints. Like the primary binary endpoints, both the absolute treatment difference and the relative treatment difference were estimated.

For the continuous confirmatory secondary endpoints, a tipping point analysis was carried out. A penalty term was added to the imputed values from the main analysis at week 72. The approach was to explore a range of penalties for both treatment groups, and the impact these would have on the trial conclusions. This sensitivity analysis evaluated the robustness of the superiority conclusions to departures from the observed change in the continuous confirmatory secondary endpoint in both treatment groups. The grid of the penalty terms for the tipping point analysis of body weight is -30 to 30 by increments of 1, the penalty term was to be added as %-points. For SF-36 bodily pain the grid for the tipping point analysis is -15 to 15 by increments of 1, the penalty term was added as absolute change.

For the binary confirmatory secondary endpoint, if superiority was confirmed, a two-way tipping point analysis similar to the analysis for the primary endpoints was carried out.

Secondary binary endpoints were analysed using the same CMH test and handling of missing data as for the primary binary endpoints. Secondary continuous endpoints were analysed using the same type of ANCOVA with multiple imputation as for change in body weight.

Tertiary objectives

The tertiary objectives are as follows:

- To compare the effect of semaglutide s.c. 2.4 mg versus placebo on insulin sensitivity in subjects with MASH and fibrosis stages 2 or 3.
- To compare the effect of semaglutide s.c. 2.4 mg versus placebo on cognitive function in subjects with MASH and fibrosis stages 2 or 3.

Estimands for the tertiary objectives

Table 16: Tertiary endpoints and summary measures

Endpoint title	Time frame	Unit
Change in insulin sensitivity (assessed by HOMA-IR)[a]	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in cognitive function[b]	From randomisation (week 0) to week 240	Various
Change in TNF-alpha	From randomisation (week 0) to week 72 and week 240	Ratio to baseline
Change in Il-1 RA	From randomisation (week 0) to week 72 and week 240	Ratio to baseline

a) Only for subjects not being treated with insulin at baseline

b) Assessed by Stroop Color and Word Test and The Portosystemic Encephalopathy Syndrome Test (PSE Syndrome Test)

Abbreviations: HOMA-IR = homeostatic model assessment – insulin resistance, TNF-alpha = Tumour necrosis factor alpha, Il-1 RA = Interleukin-1 receptor agonist protein

Estimands are not defined for these endpoints.

Statistical methods for estimation and sensitivity analysis on the tertiary estimands

Exploratory continuous endpoints were analysed using the same type of ANCOVA with multiple imputation as for change in body weight. The model included treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, baseline body weight and baseline value of the endpoint as covariates. Continuous endpoints which were analysed as a ratio to baseline would be logarithmically transformed for the statistical analysis, together with their baseline value. The estimated treatment differences were back-transformed to the original scale and expressed as treatment ratios.

5.3.2.1.4. Results

Participant flow and numbers analysed

Table 17: Subject disposition - overview at week 72 - full analysis set (interim)

	Sema 2.4 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Screened					7600	
Randomised	802		395		1197	
Full analysis set (interim)	534		266		800	
Exposed	533	(99.8)	266	(100.0)	799	(99.9)
Part 1 trial completer	501	(93.8)	245	(92.1)	746	(93.3)
On-treatment at visit 13 (week 72)	468	(87.6)	214	(80.5)	682	(85.3)
Biopsy at visit 13 (week 72)	474	(88.8)	227	(85.3)	701	(87.6)
With a consensus result for at least one parameter	472	(88.4)	225	(84.6)	697	(87.1)
Without a consensus result	2	(0.4)	2	(0.8)	4	(0.5)
Biopsy with a consensus result for at least one parameter at visit 13 (week 72)	472	(88.4)	225	(84.6)	697	(87.1)
Part 1 trial completer	471	(88.2)	224	(84.2)	695	(86.9)
Part 1 non-trial completer	1	(0.2)	1	(0.4)	2	(0.3)
On-treatment at time of biopsy sampling	458	(85.8)	213	(80.1)	671	(83.9)
Off-treatment at time of biopsy sampling	14	(2.6)	12	(4.5)	26	(3.3)

%: Proportion of full analysis set, N: Number of subjects. A trial completer for part 1 is defined as a subject that either attended the week 72 visit or died before the visit.
Eligibility window for biopsy endpoints is minus/plus 180 days. A biopsy is classified as
on-treatment if it is sampled before last dose of trial product + 49 days (included).

	Sema 2.4 mg	Placebo	Total
	N (%)	N (%)	N (%)
Screened			7600
Screening failures			5284 (69.5)
Withdrawn before randomisation			1119 (14.7)
Randomised	802	395	1197
Exposed	800 (99.8)	395 (100.0)	1195 (99.8)
Full analysis set (interim, all randomised subjects)	802 (100.0)	395 (100.0)	1197 (100.0)
Safety analysis set (interim)	800 (99.8)	395 (100.0)	1195 (99.8)
Exposed at cut-off date	729 (90.9)	320 (81.0)	1049 (87.6)
Premature trial product discontinuation	54 (6.7)	73 (18.5)	127 (10.6)
Adverse event(s)	23 (2.9)	15 (3.8)	38 (3.2)
Protocol deviation	3 (0.4)	4 (1.0)	7 (0.6)
Lost to follow-up	5 (0.6)	4 (1.0)	9 (0.8)
At the discretion of the investigator	1 (0.1)	4 (1.0)	5 (0.4)
Site closure	0 (0.0)	2 (0.5)	2 (0.2)
Epidemic/Pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Other	22 (2.7)	44 (11.1)	66 (5.5)
Withdrawal from trial	31 (3.9)	35 (8.9)	66 (5.5)
Withdrawal by subject	22 (2.7)	26 (6.6)	48 (4.0)
Lost to follow-up	2 (0.2)	1 (0.3)	3 (0.3)
Physician decision	3 (0.4)	2 (0.5)	5 (0.4)
Site closure	1 (0.1)	0 (0.0)	1 (0.1)
Epidemic/Pandemic	0 (0.0)	0 (0.0)	0 (0.0)
Death	3 (0.4)	6 (1.5)	9 (0.8)
Other	0 (0.0)	0 (0.0)	0 (0.0)

%: Percentage of subjects, N: Number of subjects.

Deviations from study plan

In total, 1163 important protocol deviations were reported before interim DBL (7 were trial-level deviations, no country-level deviations, 137 were site-level deviations, 1019 were subject-level deviations) but were not likely to have affected the statistical inferences, analyses, subject safety, or conclusions presented in this report.

Baseline data

Baseline data are summarised below (Table 18, Table 19).

Table 18: Demographics and baseline characteristics for categorical variables – summary – FAS (interim, all randomised subjects) – trial 4553

	Sema 2.4 mg		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	802		395		1197	
Age group (years)						
18<= to <45	120	(15.0)	83	(21.0)	203	(17.0)
45<= to <65	470	(58.6)	213	(53.9)	683	(57.1)
65<=	212	(26.4)	99	(25.1)	311	(26.0)
Sex						
Female	453	(56.5)	215	(54.4)	668	(55.8)
Male	349	(43.5)	180	(45.6)	529	(44.2)
Race						
American Indian or Alaska Native	6	(0.7)	1	(0.3)	7	(0.6)
Asian	215	(26.8)	111	(28.1)	326	(27.2)
Black or African American	8	(1.0)	3	(0.8)	11	(0.9)
Native Hawaiian or Other Pacific Islander	0	(0.0)	0	(0.0)	0	(0.0)
White	531	(66.2)	261	(66.1)	792	(66.2)
Other	34	(4.2)	17	(4.3)	51	(4.3)
Missing	8	(1.0)	2	(0.5)	10	(0.8)
Ethnicity						
Hispanic or Latino	145	(18.1)	76	(19.2)	221	(18.5)
Not Hispanic or Latino	627	(78.2)	309	(8.2)	936	(78.2)
Not Reported	25	(3.1)	8	(2.0)	33	(2.8)
Missing	5	(0.6)	2	(0.5)	7	(0.6)
Region						
Asia	200	(24.9)	103	(26.1)	303	(25.3)
Europe	217	(27.1)	86	(21.8)	303	(25.3)
North America	261	(32.5)	145	(36.7)	406	(33.9)
South America	73	(9.1)	34	(8.6)	107	(8.9)
Other	51	(6.4)	27	(6.8)	78	(6.5)
BMI group (kg/m^2)						
<25	52	(6.5)	24	(6.1)	76	(6.3)
25<= to <30	177	(22.1)	73	(18.5)	250	(20.9)
30<= to <35	249	(31.0)	114	(28.9)	363	(30.3)
35<=	323	(40.3)	183	(46.3)	506	(42.3)
Missing	1	(0.1)	1	(0.3)	2	(0.2)
Type 2 diabetes						
Yes	447	(55.7)	222	(56.2)	669	(55.9)
No	355	(44.3)	173	(43.8)	528	(44.1)
Trial product pen-injector						
DV3396	520	(64.8)	252	(63.8)	772	(64.5)
PDS290	280	(34.9)	143	(36.2)	423	(35.3)
Childbearing potential (only females)						
Yes	75	(9.4)	41	(10.4)	116	(9.7)
No	378	(47.1)	174	(44.1)	552	(46.1)

Classification of eGFR-CKD (mL/min/1.73m2)			
<30	*	*	1 (0.1)
30<= to <60	38 (4.7)	7 (1.8)	45 (3.8)
60<= to <90	204 (25.4)	103 (26.1)	307 (25.6)
90<=	557 (69.5)	284 (71.9)	841 (70.3)
Missing	*	*	3 (0.3)
Fibrosis stage (0-4)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	174 (21.7)	82 (20.8)	256 (21.4)
3	628 (78.3)	313 (79.2)	941 (78.6)
4	0 (0.0)	0 (0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase			
<= 1xULN	377 (47.0)	182 (46.1)	559 (46.7)
> 1xULN to <=3xULN	398 (49.6)	197 (49.9)	595 (49.7)
> 3xULN to <=5xULN	26 (3.2)	16 (4.1)	42 (3.5)
> 5xULN	0 (0.0)	0 (0.0)	0 (0.0)
Missing	*	*	1 (0.1)
Aspartate aminotransferase			
<= 1xULN	202 (25.2)	89 (22.5)	291 (24.3)
> 1xULN to <=3xULN	542 (67.6)	273 (69.1)	815 (68.1)
> 3xULN to <=5xULN	57 (7.1)	32 (8.1)	89 (7.4)
> 5xULN	*	*	1 (0.1)
Missing	*	*	1 (0.1)
Alkaline phosphatase			
<= 1xULN	773 (96.4)	377 (95.4)	1150 (96.1)
> 1xULN to <=2xULN	27 (3.4)	18 (4.6)	45 (3.8)
> 2xULN	*	*	1 (0.1)
Missing	*	*	1 (0.1)

—

N: Number of subjects, %: Percentage of subjects, BMI: Body mass index, eGFR: Estimated glomerular filtration rate.

* information removed to avoid unblinding

Table 19: Relevant concomitant medication at randomisation according to ATC code – Trial 4553

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects (FAS)	534	266	800
Anti-obesity preparations (A08)			
• Phentemine	*	*	1 (0.1)
• Orlistat	*	*	1 (0.1)
Drugs used in diabetes (A10)			
• Insulins and analogues (A10A)	39 (7.3)	21 (7.9)	60 (7.5)
• Blood glucose lowering drugs, excl. insulins (A10B)			
• Biguanides (A10BA)	226 (42.3)	106 (39.8)	332 (41.5)
• Sulfonylureas (A10BB)	56 (10.5)	21 (7.9)	77 (9.6)
• Combinations of oral blood glucose lowering drugs (A10BD)	16 (3.0)	12 (4.5)	28 (3.5)
• Alpha glucosidase inhibitors (A10BF)	1 (0.2)	1 (0.4)	2 (0.3)
• Thiazolidinediones (A10BG)	19 (3.6)	7 (2.6)	26 (3.3)
• Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH)	60 (11.2)	23 (8.6)	83 (10.4)
• Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)	53 (9.9)	32 (12.0)	85 (10.6)

• Other blood glucose lowering drugs, excl. insulins (A10BX)	3 (0.6)	1 (0.4)	4 (0.5)
Antihypertensives (C02)	8 (1.5)	5 (1.9)	13 (1.6)
Diuretics (C03)	103 (19.3)	50 (18.8)	153 (19.1)
Beta blocking agents (C07)	84 (15.7)	56 (21.1)	140 (17.5)
Calcium channel blockers (C08)	111 (20.8)	51 (19.2)	162 (20.3)
Agents acting on the renin-angiotensin system (C09)	252 (47.2)	131 (49.2)	383 (47.9)
Lipid modifying agents (C10)			
• Lipid modifying agents, plain (C10A)	278 (52.1)	151 (56.8)	429 (53.6)
• Statins (C10AA)	196 (36.7)	104 (39.1)	300 (37.5)
• Lipid modifying agents, combination (C10B)	6 (1.1)	1 (0.4)	7 (0.9)
Antithrombotic agents (B01A)	37 (6.9)	24 (9.0)	61 (7.6)

* information removed to avoid unblinding

After randomisation 0 vs 18 (6.8%) started semaglutide treatment.

Patients with a BMI < 25 kg/m^2 and BMI 25-30 kg/m^2 were older (mean 65 (10.3) and 59 (10.4)), more women (77% and 59%) and more Asian (77% and 45%) vs White, and less from Europe (9.4% and 23%) compared to the entire study population. Other baseline characteristics were more or less comparable for these subgroups compared to the entire study population.

Outcomes and estimation

Primary and Secondary endpoints under hierarchical testing

The primary and secondary endpoints which were analysed under hierarchical testing are displayed in Table 20.

Table 20: Overview of confirmatory tests - statistical analysis - full analysis set (interim)

Endpoint	Estimate of difference in proportions	p-value[a]	Nominal significance level	Responder rates	Conclusion
Primary endpoint					
Resolution of steatohepatitis and no worsening in liver fibrosis at week 72[b]					
Sema 2.4 mg Placebo	28.65 [21.09; 36.21]	<0.0001	0.00225	62.9% (336 of 534 subjects) 34.3% (91 of 266 subjects)	Superiority confirmed
Primary endpoint					
Improvement in liver fibrosis and no worsening of steatohepatitis at week 72[c]					
Sema 2.4 mg Placebo	14.39 [7.51; 21.27]	<0.0001	0.00225	36.8% (197 of 534 subjects) 22.4% (59 of 266 subjects)	Superiority confirmed
Confirmatory secondary endpoint					
Change in body weight (%) at week 72					
Sema 2.4 mg Placebo	-8.46 [-9.55; -7.38]	<0.0001	0.0045	-	Superiority confirmed
Confirmatory secondary endpoint					
Resolution of steatohepatitis and improvement in liver fibrosis at week 72[d, e]					

Endpoint	Estimate of difference in proportions	p-value[a]	Nominal significance level	Responder rates	Conclusion
Sema 2.4 mg Placebo	16.54 [10.24; 22.83]	<0.0001	0.0045	32.7% (175 of 234 subjects) 16.1% (43 of 266 subjects)	Superiority confirmed
Confirmatory secondary endpoint					
Change in SF-36 bodily Pain					
Sema 2.4 mg Placebo	1.34 [0.01; 2.67]	0.0244	0.0045	-	Superiority not confirmed

[a]One-sided P-values were compared with the corresponding nominal significance level as per the statistical testing strategy to draw conclusions.
[b]Resolution of steatohepatitis is defined as a NAFLD Activity Score (NAS) of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (according to NASH CRN[21]). Fibrosis is graded on the NASH CRN fibrosis scale from 0 to 4.
[c]Improvement in fibrosis is defined as ≥ 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation, or steatosis.
[d]Resolution of steatohepatitis is defined as an NAS of 0–1 for inflammation, 0 for ballooning, and any value for steatosis (according to NASH CRN[21]).

A tipping point sensitivity analysis was performed evaluating the robustness of the assumptions about the missing data. Additionally, a sensitivity analysis was performed where all subjects with missing data were alternatively classified as non-responders. The tipping point analysis and sensitivity analyses for the primary endpoints supported the conclusions for the main analytical approach.

The hierarchical testing was violated at the Change in SF-36 bodily Pain endpoint.

At week 72, the estimated mean change from week baseline in body weight was -10.51 kg vs -2.04 kg. At week 72, the estimated change from week baseline in SF-36 Bodily pain was 0.86 vs -0.47.

Exploratory secondary endpoints

The exploratory secondary endpoints related to liver histology and liver imaging are displayed in Table 21 and Table 22.

Table 21: Trial 4553 (part 1 Supportive secondary endpoints related to liver histology

	Subjects meeting the endpoint at week 72 (responders)		
Endpoint	Semaglutide 2.4 mg	Placebo	Treatment difference [a]
Improvement of steatohepatitis with at least a 2-point reduction in NAS and no worsening of liver fibrosis	50.1% (267 of 534 subjects)	25.0% of subjects (67 of 266 subjects)	25.34 %-points [18.23; 32.45]; p<0.0001
MASH resolution (ballooning of 0, hepatocyte inflammation of 0-1) and ≥2-point NAS reduction with no worsening of liver fibrosis	43.5% (232 of 534 subjects)	18.8% (50 of 266 subjects)	24.75 %-points [18.07; 31.43]; p<0.0001
Worsening in steatohepatitis	13.7% (73 of 534 subjects)	31.1% (83 of 266 subjects)	-17.53 %-points [-24.35; -10.72]; p<0.0001
Improvement in histology-assessed steatosis	70.0% (374 of 534 subjects)	42.3% (113 of 266 subjects)	27.70 %-points [20.09; 35.31]; p<0.0001

	Subjects meeting the endpoint at week 72 (responders)		
Improvement in histology-assessed inflammation	36.0% (192 of 534 subjects)	20.6% (55 of 266 subjects)	15.67 %-points [8.99; 22.34]; p<0.0001
Improvement in histology-assessed ballooning	58.3% (311 of 534 subjects)	40.1% (107 of 266 subjects)	18.40 %-points [10.76; 26.03]; p<0.0001

Results are estimates for subjects in 'FAS (interim)'.
a. Estimated difference (semaglutide – placebo) in responder proportions [95%CI]; p-value is 2-sided.

Table 22: Trial 4553 (part 1) Supportive secondary endpoints related to liver imaging – week 72

Endpoint	Semaglutide	Placebo	Treatment contrast [a]
Liver stiffness [b]			
Change from baseline	-31.10%	-13.48%	-20.37% [-25.92; -14.41]; p<0.0001
Liver steatosis [c]			
Change from baseline	-43.40 dB/m	-13.07 dB/m	-30.33 dB/m [-39.33; -21.33]; p<0.0001
FAST (FibroScan-AST) score	-0.28	-0.10	-0.18 ([-0.22; -0.14]; p<0.0001

Results are estimates for subjects in 'FAS (interim)' (trial 4553; semaglutide 2.4 mg). Details on the statistical methodology used in the analyses of the endpoints are provided in Summary 2.7.3, Section 1.3.6.
a. Estimated treatment contrast (semaglutide vs placebo) [95%CI] in responder proportions or in absolute or relative change from baseline; p-value is 2-sided.
b. Assessed by transient elastography (FibroScan®).
c. Assessed by transient elastography (FibroScan®) using CAP (Controlled Attenuation Parameter).

At week 0, the observed geometric mean (CV) liver stiffness assessed by FibroScan was 11.46 (47.47) kPa vs 11.58 (45.55) kPa, and for transient elastography (FibroScan) 329 (45) dB/m vs 330 (49) dB/m, and FAST 0.59 (0.23) vs 0.58 (0.22).

Change in ELF score (Enhanced Liver Fibrosis score)

At baseline, the estimated mean (SD) in ELF was 10.0 (0.9) vs 10.0 (1.0) with an ETD to week 72 of -0.57 [-0.68; -0.47]95% CI; p-value <0.0001.

Liver enzymes

Table 23: Trial 4553 (part 1)- ALT and AST – change from baseline at week 72

	Semaglutide	Placebo	Treatment contrast [a]
ALT	-52.14%	-22.24%	-38.45% [-43.38; -33.10]; p<0.0001
AST	-44.89%	-17.07%	-33.54% [-37.86; -28.93]; p<0.0001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval.
Results are estimates for subjects in 'FAS (interim)' (trial 4553; semaglutide 2.4 mg).
a. Estimated treatment contrast (semaglutide vs placebo) [95%CI] in relative change from baseline; p-value is 2-sided.

Pro-C3

At week 72, the observed mean (SD) ratio of pro-C3 to baseline was 0.8 (0.3) vs 1.0 (0.5) with week 72 ETF of 0.83 [0.78; 0.88]95% CI; p-value <0.0001.

Cardiometabolic effects (other than body weight)

Lipid profile

Table 24: Blood lipids – change from baseline at week 72 – trial 4553 (part 1)

	Semaglutide 2.4 mg	Placebo	Treatment contrast [a]
Total cholesterol	-6.03%	-3.19%	-2.93% [-5.60; -0.19]; p=0.0364
LDL cholesterol	-6.07%	-4.11%	-2.04% [-6.35; 2.46]; p=0.3680
HDL cholesterol	2.62%	-1.95%	4.66% [2.12; 7.26]; p=0.0003
Free fatty acids	-13.55%	-4.62%	-9.37% [-16.02; -2.18]; p=0.0115
Triglycerides	-16.77%	-0.27%	-16.54% [-21.02; -11.81]; p<0.0001

HDL: high-density lipoprotein; LDL: low-density lipoprotein.
Results are estimates for subjects in 'FAS (interim)'. Details on the statistical methodology used in the analyses of the endpoints are provided in Summary 2.7.3, Section 1.3.6.

Inflammation markers

At baseline, the observed geometric mean (CV) inflammation assessed by hsCRP was 3.25 (145.60) mg/L vs 3.12 (160.57) mg/L (Table 25).

Table 25: Effects on inflammation markers

		Semaglutide	Placebo
hsCRP (secondary)	Ratio from baseline	0.46	0.80
	Vs placebo	0.58 [0.50; 0.66]95% CI; p-value <0.0001	
TNF-alpha (exploratory)	Ratio from baseline	0.91	1.00
	Vs placebo	0.92 [0.86; 0.97]95% CI; p-value =0.0037	
IL-1R antagonist (exploratory)	Ratio from baseline	0.71	0.92
	Vs placebo	0.76 [0.69; 0.84]95% CI; p-value <0.0001	

Change in HbA1c

- Diabetes markers (Table 26)

Table 26: Diabetes markers

		With diabetes		Without diabetes	
		Semaglutide	Placebo	Semaglutide	Placebo
HbA1c (secondary)	Change from baseline	-1.08 %	-0.00 %	-0.42 %	0.11 %

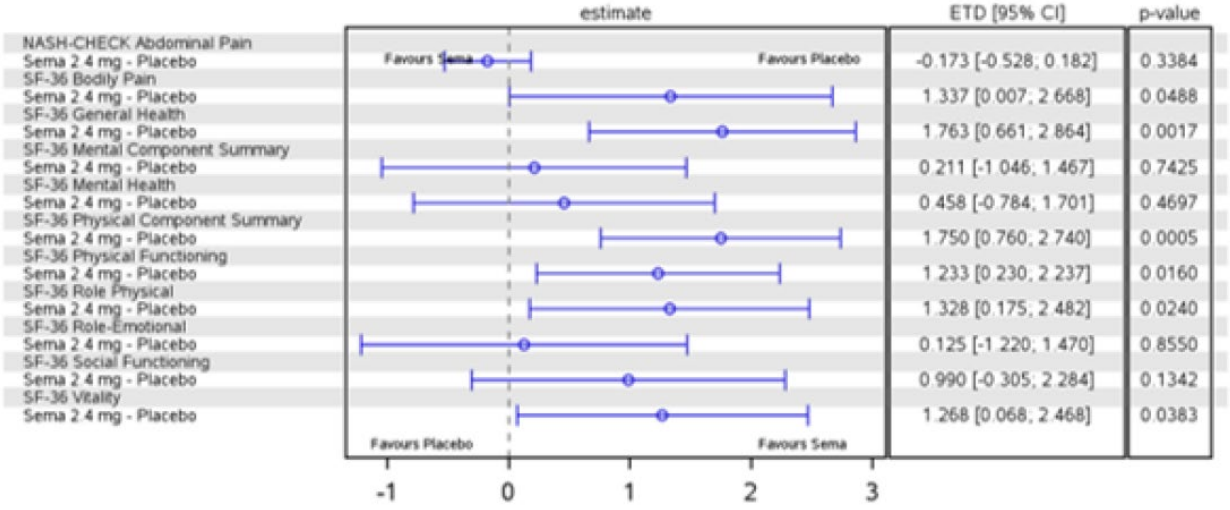
	Vs placebo	-1.08 [-1.27; -0.89]95% CI; p-value <0.0001		-0.53 [-0.61; -0.44]95% CI; p-value <0.0001	
HOMA-IR (exploratory)	Ratio to baseline	0.6 (101.4)	0.9 (86.7)	0.6 (79.3)	1.0 (67.8)
	Vs placebo	0.65 [0.56; 0.77]95% CI; p-value =0.0001 (TFL 8.2.153)		0.68 [0.58; 0.79]95% CI; p-value =0.0001	

Patient reported outcomes (other than SF-36 Physical bodily Pain)

At week 0 (baseline), the observed mean (SD) SF-36 Physical Component was 47.1 (8.7) for subjects in the semaglutide 2.4 mg treatment group and 45.8 (9.5) for subjects in the placebo treatment group.

At week 0 (baseline), the observed mean (SD) SF-36 Mental Component was 49.5 (10.4) for subjects in the semaglutide 2.4 mg treatment group and 50.3 (10.2) for subjects in the placebo treatment group.

Figure 10: Patient reported outcomes - change from baseline - forest plot - in-trial (72 weeks) - full analysis set (interim)

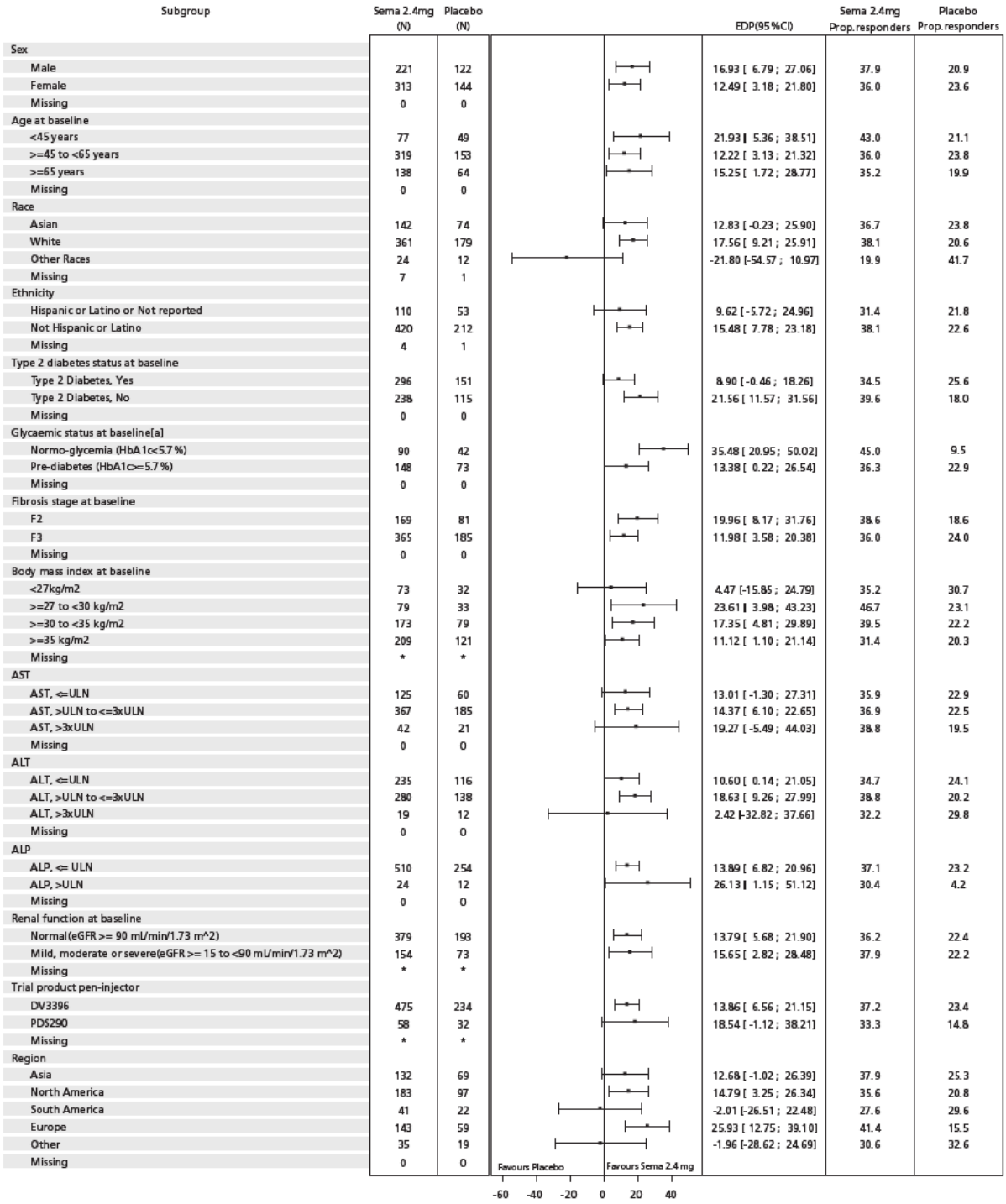


ANCOVA: Analysis of Covariance, CI: Confidence interval, ETD: Estimated treatment difference, SF-36: Short Form 36 v2.0 acute. ETDs with 95% CIs are from an ANCOVA with treatment, baseline diabetes status, baseline fibrosis stage and diabetes-by-fibrosis interaction as factors, and baseline body weight and baseline value of analysed parameter as covariate. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor.

Pre-defined and post-hoc subgroup analyses

No relevant differences for both primary endpoints of clinically relevant subpopulations by demographic and disease-related factors were observed as displayed below (Figure 11).

Figure 11: Improvement in liver fibrosis and no worsening of steatohepatitis by subgroups Absolute difference - MI based on unconditional reference - forest plot in-trial (72 weeks) - full analysis set (interim) - Trial 4553



Subgroup	Sema 2.4mg (N)	Placebo (N)	EDP(95%CI)	Sema 2.4mg Prop.responders	Placebo Prop.responders
Sex					
Male	221	122	16.93 [6.79 ; 27.06]	37.9	20.9
Female	313	144	12.49 [3.18 ; 21.80]	36.0	23.6
Missing	0	0			
Age at baseline					
<45 years	77	49	21.93 [5.36 ; 38.51]	43.0	21.1
>=45 to <65 years	319	153	12.22 [3.13 ; 21.32]	36.0	23.8
>=65 years	138	64	15.25 [1.72 ; 28.77]	35.2	19.9
Missing	0	0			
Race					
Asian	142	74	12.83 [-0.23 ; 25.90]	36.7	23.8
White	361	179	17.56 [9.21 ; 25.91]	38.1	20.6
Other Races	24	12	-21.80 [-54.57 ; 10.97]	19.9	41.7
Missing	7	1			
Ethnicity					
Hispanic or Latino or Not reported	110	53	9.62 [-5.72 ; 24.96]	31.4	21.8
Not Hispanic or Latino	420	212	15.48 [7.78 ; 23.18]	38.1	22.6
Missing	4	1			
Type 2 diabetes status at baseline					
Type 2 Diabetes, Yes	296	151	8.90 [-0.46 ; 18.26]	34.5	25.6
Type 2 Diabetes, No	238	115	21.56 [11.57 ; 31.56]	39.6	18.0
Missing	0	0			
Glycaemic status at baseline[a]					
Normo-glycemia (HbA1c<5.7 %)	90	42	35.48 [20.95 ; 50.02]	45.0	9.5
Pre-diabetes (HbA1c>=5.7 %)	148	73	13.38 [0.22 ; 26.54]	36.3	22.9
Missing	0	0			
Fibrosis stage at baseline					
F2	169	81	19.96 [8.17 ; 31.76]	38.6	18.6
F3	365	185	11.98 [3.58 ; 20.38]	36.0	24.0
Missing	0	0			
Body mass index at baseline					
<27kg/m2	73	32	4.47 [-15.85 ; 24.79]	35.2	30.7
>=27 to <30 kg/m2	79	33	23.61 [3.98 ; 43.23]	46.7	23.1
>=30 to <35 kg/m2	173	79	17.35 [4.81 ; 29.89]	39.5	22.2
>=35 kg/m2	209	121	11.12 [1.10 ; 21.14]	31.4	20.3
Missing	*	*			
AST					
AST, <=ULN	125	60	13.01 [-1.30 ; 27.31]	35.9	22.9
AST, >ULN to <=3xULN	367	185	14.37 [6.10 ; 22.65]	36.9	22.5
AST, >3xULN	42	21	19.27 [-5.49 ; 44.03]	38.8	19.5
Missing	0	0			
ALT					
ALT, <=ULN	235	116	10.60 [0.14 ; 21.05]	34.7	24.1
ALT, >ULN to <=3xULN	280	138	18.63 [9.26 ; 27.99]	38.8	20.2
ALT, >3xULN	19	12	2.42 [-32.82 ; 37.66]	32.2	29.8
Missing	0	0			
ALP					
ALP, <= ULN	510	254	13.89 [6.82 ; 20.96]	37.1	23.2
ALP, >ULN	24	12	26.13 [1.15 ; 51.12]	30.4	4.2
Missing	0	0			
Renal function at baseline					
Normal(eGFR >= 90 mL/min/1.73 m^2)	379	193	13.79 [5.68 ; 21.90]	36.2	22.4
Mild, moderate or severe(eGFR >= 15 to <90 mL/min/1.73 m^2)	154	73	15.65 [2.82 ; 28.48]	37.9	22.2
Missing	*	*			
Trial product pen-injector					
DV3396	475	234	13.86 [6.56 ; 21.15]	37.2	23.4
PDS290	58	32	18.54 [-1.12 ; 38.21]	33.3	14.8
Missing	*	*			
Region					
Asia	132	69	12.68 [-1.02 ; 26.39]	37.9	25.3
North America	183	97	14.79 [3.25 ; 26.34]	35.6	20.8
South America	41	22	-2.01 [-26.51 ; 22.48]	27.6	29.6
Europe	143	59	25.93 [12.75 ; 39.10]	41.4	15.5
Other	35	19	-1.96 [-28.62 ; 24.69]	30.6	32.6
Missing	0	0			

a: The analyses included those without T2D at baseline. Unstratified CMH test. Missing data in any treatment group will be handled by MI that is informed by data from placebo subjects. Subjects who experience a liver-related clinical event before the week 72 visit will be handled as non-responders. Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. CI: Confidence interval, CMH: Cochran-Mantel-Haenszel, EDP: Estimated difference in responder proportions, N: Number of subjects, Prop. Responders %: proportion of responders in percentage. AST: Aspartate Aminotransferase. ALT: Alanine Aminotransferase.

ALP: Alkaline Phosphatase, T2D: type 2 diabetes.

* information was redacted to avoid unblinding

Pre-defined and post-hoc sensitivity analyses

See primary endpoints results.

5.3.3. Clinical studies in special populations

Table 27: Clinical studies in special populations

	Controlled Trials
Renal impairment* patients (Subjects number /total number)	1
Hepatic impairment** patients (Subjects number /total number)	-
Paediatric patients <18 years (Subjects number /total number)	-
Older patients; Age 65-74 (Subjects number /total number)	182
Age 75-84 (Subjects number /total number)	20
Age 85+ (Subjects number /total number)	0
Other (Subjects number /total number)	-

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C
Numbers in the phase 3 trial (n=1197)

The number of patients over 75 years of age included in the clinical trials is low.

5.3.4. In vitro biomarker test for patient selection for efficacy

Not applicable

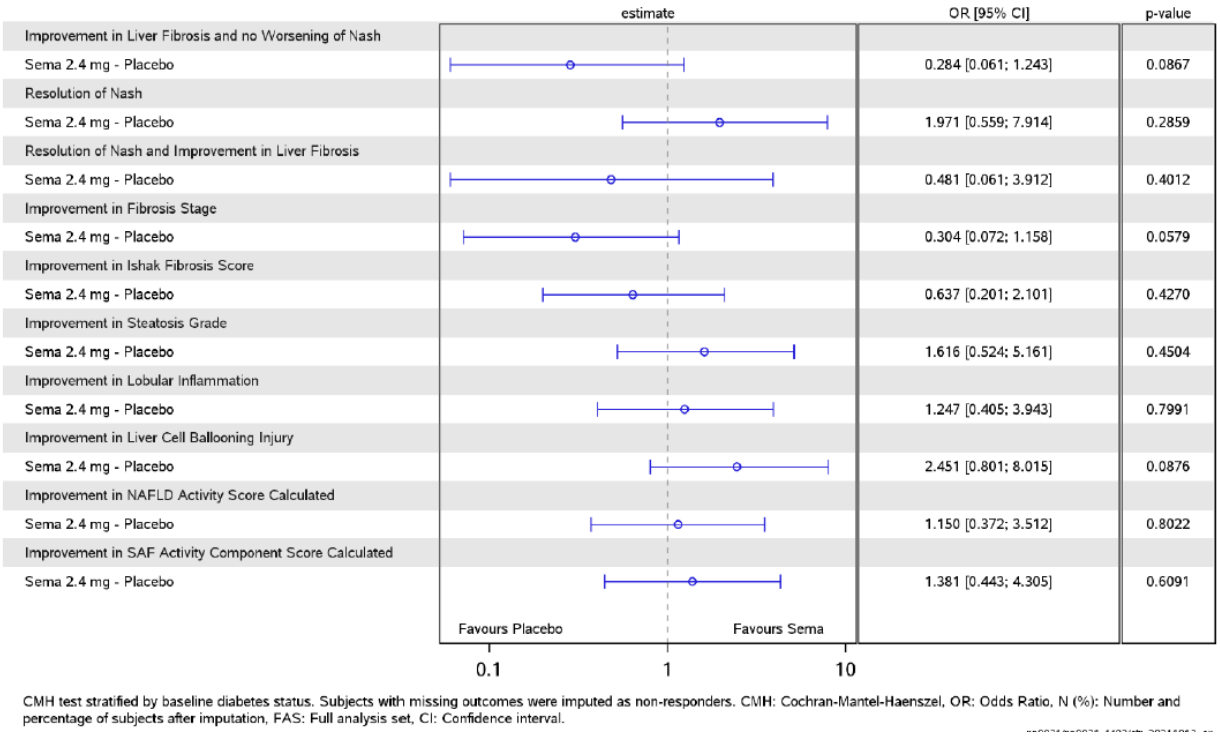
5.3.5. Supportive studies

Study 4492

This was a 48-week randomised, double-blind, placebo-controlled, parallel group, multi-centre trial in 72 patients with histologic evidence of MASH and fibrosis stage 4, a histological NAFLD activity score (NAS) ≥ 3, and a Body mass index ≥27 kg/m^2. There was a 6-weeks screening period followed by a randomisation visit and a 48-week treatment period. The treatment period was divided into a dose escalation period of 16 weeks and a maintenance period of 32 weeks. The follow-up period was 7 weeks. Total trial duration was approximately 61 weeks. Subjects were randomised in a 2:1 ratio to receive either: semaglutide s.c. 2.4 mg once-weekly or semaglutide placebo s.c. once-weekly as an adjunct to a reduced-calorie diet and increased physical activity. To mitigate the risk of GI side effects, the trial included an initial 16-week dose-escalation period during which the dose was gradually increased to the maintenance dose of 2.4 mg once weekly.

The proportion of subjects achieving the primary endpoint of liver fibrosis improvement with no worsening of MASH at week 48 was 10.6% in the semaglutide group and 29.2% in the placebo group and was not significantly different (OR: 0.28 [0.06 – 1.24], p = 0.0867).

Figure 12: Biomarkers of MASH disease - Liver-related histological paraments

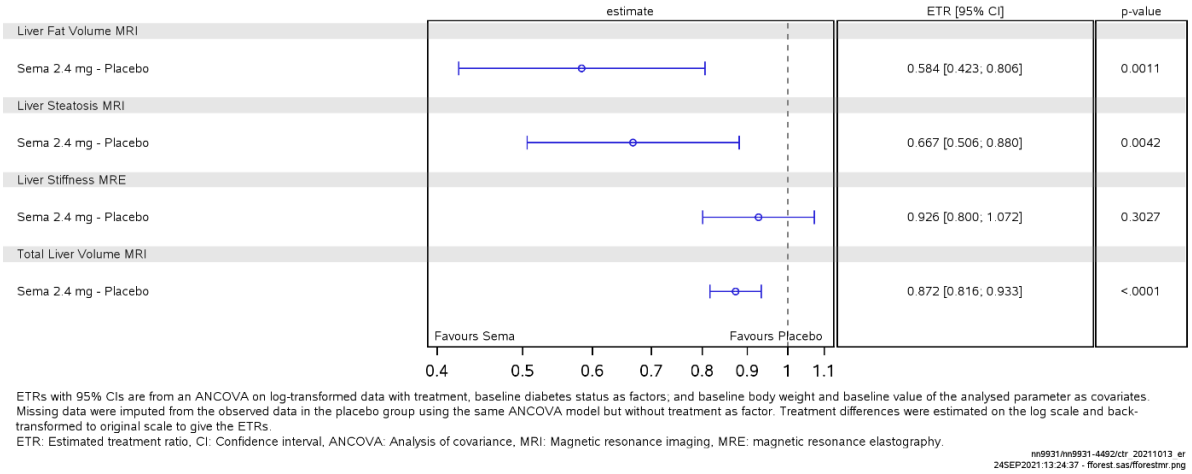


CMH test stratified by baseline diabetes status. Subjects with missing outcomes were imputed as non-responders. CMH: Cochran-Mantel-Haenszel, OR: Odds Ratio, N (%): Number and percentage of subjects after imputation, FAS: Full analysis set, CI: Confidence interval.

Other endpoints including the proportions of subjects in the semaglutide group achieving 'Resolution of MASH' (semaglutide: 34.0%, placebo: 20.8%) or 'Resolution of MASH and improvement in liver fibrosis' (semaglutide: 6.4%, placebo: 12.5%) at Week 48 were not statistically significantly different from that in the placebo group.

At week 48, reductions in liver fat volume (assessed by MRI), liver steatosis (assessed by MRI-PDFF) and total liver volume were significantly greater in the semaglutide group than in the placebo group. Reductions in liver stiffness were not significantly different between treatment groups (Figure 13).

Figure 13: Liver imaging – changes in MRI/MRE assessments



ETRs with 95% CIs are from an ANCOVA on log-transformed data with treatment, baseline diabetes status as factors; and baseline body weight and baseline value of the analysed parameter as covariates. Missing data were imputed from the observed data in the placebo group using the same ANCOVA model but without treatment as factor. Treatment differences were estimated on the log scale and back-transformed to original scale to give the ETRs.
ETR: Estimated treatment ratio, CI: Confidence interval, ANCOVA: Analysis of covariance, MRI: Magnetic resonance imaging, MRE: magnetic resonance elastography.

nn9931/nn9931-4492/ctr 20211013 er 24SEP2021:13:24:37 - fforest.sas/fforestmr.png

At week 48, the liver enzymes ALT, AST and GGT all decreased (improved) significantly more in the semaglutide group versus placebo.

Trial EX9536-4388

Trial EX9536-4388 was a randomised and placebo-controlled phase 3b CVOT that in a confirmatory analysis demonstrated that Wegovy reduces the risk of major adverse cardiovascular events (MACE; a composite outcome comprising cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight. Results from SELECT have been assessed by CHMP under Wegovy and are reflected in the current SmPC for Wegovy.

The effect of semaglutide 2.4 mg on the risk of MACE was assessed based on analyses of clinically relevant subpopulations of subjects at risk of MASH in trial EX9536-4388, identified using baseline levels of the FIB-4 biomarker.

From the full population of 17,604 subjects in SELECT, a subpopulation of 6,442 subjects was identified as being at risk of MASH based on the FIB-4 threshold of 1.3, exclusion of other causes of chronic liver disease as pre-specified in the SAP. Hereafter, this subpopulation will be referred to as 'subjects at risk of MASH' and will be the primary subpopulation in the evaluation of efficacy. This cut-off of FIB-4⩾1.3 regardless of age was pre-specified prior to the database lock of trials ESSENCE and SELECT and followed the European guidelines available at the time of trial execution.

Additionally, two supplemental analyses were conducted to assess consistency. The subpopulation at "age-adjusted risk of MASH" was defined to consider recent clinical evidence and new guidelines from 2024. Lastly, a subpopulation of subjects "at increased risk of MASH" was defined based on a high FIB-4 cut-off.

In the pre-specified subpopulation of subjects from EX9536-4388 at risk of MASH, semaglutide 2.4 mg was associated with a reduction in the risk of first event adjudication committee (EAC)-confirmed MACE of 26%, HR: 0.74 [0.63; 0.88]95% CI, thus confirming superiority. This was supported by the analysis in the subpopulation of subjects at age-adjusted risk of MASH, were the risk reduction of first EAC-confirmed MACE was 21% with a 95% CI. In the subpopulation of subjects at increased risk of MASH, the risk reduction of first EAC-confirmed MACE was 36%.

Regarding the individual subcomponents of the composite MACE-endpoint, the outcomes of CV death and non-fatal myocardial infarction (MI) attained similar benefits across the EX9536-4388 subpopulations at risk of MASH, age-adjusted and at increased risk of MASH, respectively. Similar to

the EX9536-4388 main population, the overall reduction in MACE was mainly driven by a reduction in CV-death and non-fatal MI. Like the total EX9536-4388 population, the all-cause death was equally reduced through all three subpopulations. Overall, the tendency was clear, the risk of MACE was lower in individuals at risk of MASH as well as age-adjusted risk of MASH when treated with semaglutide 2.4 mg.

In summary, the prespecified analysis of the subpopulation at risk of MASH showed a reduction in the risk of first EAC-confirmed MACE events. This was further supported by the additional analysis of the age-adjusted subpopulation and the subpopulation with an increased risk of MASH.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable. No analysis across clinical trials has been performed.

5.3.7. Observational data/Data from registries

Not applicable

5.3.8. Patient experience data (PED)

Not applicable

5.3.9. Healthcare professional engagement

Not applicable

5.3.10. Overall discussion and conclusions on clinical efficacy

5.3.10.1. Discussion

Dose finding

The dose selection was primarily based on the study results of the dose response phase 2 study 4296 and the experience as derived from previous studies including T2DM and weight management, which have been part of the respective MAAs. An important learning from these previous studies was that a weekly dosing is associated with less GI symptoms than once daily dose. Further, dose escalation has been shown to be associated with less GI symptoms and greater tolerability, which would support the 16 weeks intended dose escalation.

The design of the phase 2 study of a 72-week, multinational, multicentre, randomised, double-blind, six-armed, parallel-group, placebo controlled, multiple-dose trial comparing the efficacy and safety of semaglutide s.c. 0.1 mg, 0.2 mg and 0.4 mg once daily (OD) versus placebo in 302 subjects with MASH, is considered appropriate to evaluate different doses in the treatment of MASH. In the phase 2 study, MASH was diagnosed appropriately as based on central pathologist evaluation of a recent liver biopsy including NAFLD activity score (NAS) > 4 and fibrosis staging F1-3, resulting in inclusion of patients with a mean age of 55, cardiometabolic indicators (BMI mean 36 kg/m^2, T2DM 62%) and fibrosis indicators (NAS >4, F1-F3 28% to 49% across categories).

According to the hierarchical testing in the dose response study 4296, a statistical significant effect was only found for the 0.4 mg OD dosing for the primary endpoint of *resolution of steatohepatitis and no worsening of fibrosis* (59% vs 17%, ratio 6.87 [2.60;17,63], p<0.001), while no statistical significant was found for the confirmatory secondary endpoint of *improvement in liver fibrosis and no worsening of steatohepatitis (43% vs 33%; ratio 1.42 [0.62;3.28], p=0.2407).* Only numerical improvements were observed for the other doses, for the respective endpoints. A *post hoc* exposure-response analysis suggests an exposure-related effect on the primary endpoint, with a less clear relation for the confirmatory secondary endpoint. A limitation is that the primary endpoint only aligns with one of the primary endpoints of the phase 3 study, while the secondary endpoint meeting one of the primary endpoints of the pivotal could not demonstrate significance.

A dose-dependent effect for some of the supportive liver-related histological parameters and cardiometabolic markers was observed

It is mentioned that GI events level of at a dose of 0.1-0.2 mg. This would conclude that the highest 0.4 mg OD dose would be the most appropriate dose, and a dose of 2.4 mg once weekly would closest meet the 0.4 mg OD dose.

Based on these considerations, it is considered reasonable to select the 2.4 mg once daily dosing as a maintenance dose with dose escalation to maintenance dose when starting therapy, as the selected dose strategy for the confirmatory pivotal study, although the primary endpoint for the phase 3 deviates from the dose finding study.

Design and conduct of the clinical studies

In support of the current application, an on-going pivotal phase 3 study provided histological efficacy evidence during the 72 weeks interim period. in 800 subjects with NASH and F2 or F3 (recruitment cap of approximately 20% for subjects with F2).

The general study design of a randomised, placebo-controlled, blinded study was considered appropriate to address the main estimand of the study, to demonstrate that treatment with semaglutide s.c. 2.4 mg improves liver histology compared to placebo in subjects with MASH and fibrosis stage 2 or 3. The co-primary endpoints are *Resolution of steatohepatitis and no worsening of liver fibrosis*, and *Improvement in liver fibrosis and no worsening of steatohepatitis*, which complied with those defined in the EMA Reflection Paper on MASH (*EMA reflection paper of on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (MASH)* (EMA/CHMP/111529/2024)) and the EMA scientific advice. The objective of Part 2 to demonstrate that treatment with semaglutide s.c. 2.4 mg lowers the risk of liver-related clinical events compared to placebo in subjects with MASH and fibrosis stage 2 or 3 is considered important to confirm the potential benefits of the currently presented Part 1 interim. However, the large timeframe between Part 1 data and the second part of the study may pose a risk for study integrity.

For the (alpha controlled) key secondary objectives some issues were identified. Resolution of steatohepatitis and improvement in liver fibrosis as a secondary estimand is likely to highly overlap with one component of the co-primary endpoint/estimand, and in that sense may be of limited value. Further, lowering of body weight is a known effect of semaglutide while there are also other cardiometabolic markers of interest. However, comparing the treatment effects on cardio-metabolic risk factors in subjects with MASH and fibrosis stages 2 or 3 might not support the primary objective evaluation, since it can only show an indirect benefit. A demonstration that treatment with semaglutide s.c. 2.4 mg improves patient-reported outcomes could be of direct interest to the patient. However, the general nature of the instrument of Change in SF-36 Bodily Pain does not entirely discriminate whether the changes in score from baseline to 72 weeks may be due to an effect on MASH or due to other related factors, such as reduction in BMI.

Strategies are the same for primary and secondary estimands, except for the continuous outcomes of body weight and SF-36. Here, the intercurrent events of MELD score ≥15, hepatic decompensation events, unplanned biopsy showing progression to cirrhosis, liver transplantation and death were assigned a treatment policy strategy. Although a composite strategy would be better aligned with the primary endpoint, implementation of a composite strategy in continuous endpoints is not straightforward. Considering the relatively low amount of liver-related intercurrent events, the difference between the strategies is likely small and the choice was accepted. It also allows comparison with the endpoints in the weight reduction program.

The intermediate stage of part 1 was set to be based on a fixed number of participants, the first 800 randomised participants. Trial integrity was ensured by using a statistical service provider that was independent of trial conduct and external to the trial sponsor and MAH.

Primary endpoints were analysed with a CMH test, stratifying for the stratification factors. Data handling for the statistical analysis is line with estimand strategies defined above. Missing data was handled by reference-based imputation, which is deemed as conservative for a superiority hypothesis.

Missing data handling was tested using a tipping point analysis, which did not raise any concern about the primary analysis. Nor did a sensitivity analysis using non-response imputation in case of missing data, although this analysis is considered less suitable as it is not conservative when missing data is more prevalent in the comparator arm.

Secondary endpoints measures on a continuous scale were analysed using an ANCOVA, adjusting for the stratification factors.

In the sample size calculation sections, assumptions for treatment difference are specified for the primary and the most important secondary endpoints (so-called confirmatory secondary).

The results of the statistical analyses for the secondary endpoints are agreed.

Strict control of type I error was achieved for all part 1 estimands and the procedure is well described.

Blinding and randomisation were standard and meet general requirements. To meet current general blinding and study conduct criteria, a data monitoring committee independently adjudicate events in a blinded manner following the charter for interim evaluation. According to the DMC charter, the DMC was instructed to recommend unblinding the Novo Nordisk interim team (SIT) to support global regulatory filing when superiority of either one or both primary endpoints was confirmed. The DMC was provided efficacy outputs by an external statistical vendor after the clinical data cut-off. Inclusion of an external event adjudication committee is considered appropriate for a proper evaluation of safety issues. Histological evaluation including central evaluation by a team of two expert histologists and a third when consensus was not reached, is considered rigorous and acceptable.

Inclusion criteria are considered appropriate for selection of the appropriate patient population of informed consented adult patients with stage F2 or F3 MASH. As patients had to have biopsy within 180 days with confirmed stage F2 or F3, and a NAS ≥ 4 with a score of 1 or more in steatosis, lobular inflammation and hepatocyte ballooning, as based on a central pathologist evaluation.

Exclusion criteria are generally considered appropriate. Especially, exclusion of patients with excessive alcohol consumption, meeting any of the defined clinical endpoints, with other possible causes of liver disease, highly elevated liver enzyme, and liver infected diseases, is acceptable. Further, exclusion criteria that could importantly affect study outcome, such as concomitant therapy (GLP-1, vitamin E, pioglitazone), or unstable treatment of associated medication (LLT, glucose lowering medication), signs of uncontrolled diabetes (according to several criteria), and interventions associated with significant obesity change, have been defined. Further, generally known exclusion criteria that potentially could jeopardise study success have appropriately been defined.

Both diabetic and non-diabetic patients were included in the study. During the screening period (V1–V2), only HbA1c was measured. From the point of randomisation (V3) onward, HbA1c, fasting plasma glucose (FPG), insulin, glucagon, and HOMA-IR were assessed. The applicant has clarified that the above parameters (HbA1c, FPG, insulin, glucagon, and HOMA-IR) were measured systematically in all participants, irrespective of whether a diagnosis of T2D had been established at screening or diagnosed during trial conduct.

Different injectors have been used in the study, including a single dose and multiple dose injector. These injectors are the same as used for the other indications and bioequivalence between both has been demonstrated. It has been accepted through scientific advice that no additional human factor validation studies were needed for current target population as the target population was considered equally suitable as the T2D and obesity populations.

Efficacy data and additional analyses

Important protocol deviations were observed, although these were overall comparable between both arms. It was considered that this did not substantially impact study outcome.

A high number of patients (69.5%) were screening failures and 14.7% already withdrew before treatment. Screening failures typically included those not meeting the fibrosis criteria, and uncontrolled diabetes (HbA_{1c} too high). Further, withdrawals consisted of consent by subject, recruitment cap of stage 2 fibrosis, and some others. Of those patients randomised, only a small proportion of patients discontinued, and this was larger in the placebo arm (6.7% vs 18.5%). Semaglutide appears to be well tolerated with only 2.9% vs 3.8% discontinuing due to adverse events, although 12.4% vs 19.5% were not on treatment at the interim Week 72.

Of the 501 (93.8%) semaglutide and 245 (92.1%) placebo patients, only 472 (88.4%) and 225 (84.6%) of the overall population had a biopsy. The applicant has provided details on those with missing biopsies at 72 weeks, which included valid reasons with missing with protocol deviations as most mentioned reason. Among these, subject refusal, and different types of safety concerns, and physician decision of non-improvement were mentioned as examples. Since these were counted as non-responders in the sensitivity analyses, this is considered conservative. Sensitivity analyses and tipping point analyses did not provide different conclusions as to the main findings.

With fairly comparable percentages across important baseline characteristics, randomisation has been successful. A population with certain cardiometabolic disease characteristics has been included in the study with a mean BMI of 35 kg/m^2 and 56% of type 2 diabetes. Weight related disease comorbidities with a large proportion of patients with dysglycemia, hypertension and/or dyslipidemia were noticed. These parameters were reasonably well balanced across the randomised groups. All patients were categorised with Fibrosis stage 2 (21%) or stage 3 (79%) in accordance with baseline inclusion requirements. Moderate enzyme elevation was seen for AST and ALT for about 49% and 68%, respectively, but not for AP (3%). There is sufficient representation of an EU population with 25% of the overall population included. Only 6.3% had a BMI < 25 kg/m^2 and 20.9% with a BMI of 25 to 30 kg/m^2. The applicant provided baseline characteristics for the subgroup of patients with BMI < 25 kg/m^2, BMI < 27 kg/m^2 and BMI 25-30 kg/m^2. For those patients with a BMI < 25 kg/m^2, these patients were older, more women and more Asian vs White, and less from Europe. This also applies to the BMI 25-30 kg/m^2, while other baseline characteristics were more or less comparable for these subgroups compared to the entire study population.

Despite the fact that inclusion criteria for the current pivotal study are primarily based on MASH associated criteria and not those as used for approved indications of semaglutide e.g. diabetes and obesity criteria, evidence of efficacy and safety for the population not covered by current approved

indications could further support a separate indication of MASH for semaglutide. For the patients with a BMI < 27 kg/m^2, post-hoc analyses show that weight reduction is also achieved in this subpopulation, as well as for other secondary liver related effects as evaluated in this trial. Any further evidence showing that other factors than weight loss contributed to the treatment effect have not been demonstrated. Nevertheless, a study in China and Taiwan (STEP12) shows in a limited number of 80 patients with a BMI of 24-30 (mean 28 kg/m^2) that the greatest reduction was achieved on fat mass instead of lean body mass. These data could also be of support for the EU population with absence of influence on exposure for race and region as derived from phase 3 studies as previously evaluated.

The use of concomitant medication was fairly similar between treatment groups. For some medicinal products this was slightly increased for the placebo-arm, however, not believed to favourably impact the semaglutide arm. 6.8% of the placebo arm patients were treated with semaglutide during the study. All these patients were discontinued study treatment according to protocol but remained in the study for ITT analyses. Reasons for starting this treated were based on prescribed by a physician or suspicion of placebo or lack of effect.

Semaglutide was superior to placebo on both the EMA guideline required intermediate histological endpoints at the pre-planned Week 72 interim of resolution of steatohepatitis and no worsening of liver fibrosis (62.9% vs 34.4%; 28.65 %-points [21.09; 36.21]95% CI; p-value <0.0001), and improvement in liver fibrosis and no worsening of steatohepatitis (36.8% vs 22.4%; 14.39 %-points [7.51; 21.27]95% CI; p-value <0.0001). Missing data due to study discontinuation occurred more often in the placebo arm but the number of patients was low. Other reasons for missing data were balanced between study arms. Missing data was handled by reference-based imputation, this will likely have led to a more conservative treatment estimate and therefore does not raise a concern. Sensitivity and supplementary analyses, and consistency across important subgroups of both endpoints, confirmed the robustness of these findings. Especially, consistent findings were observed for the F2 and F3 subgroups, and consistent smaller subgroups of BMI <25 kg/m^2 and 25-30 kg/m^2, likely not covering populations that fall under the currently already approved indications, in comparison to higher BMIs. Efficacy according to subgroups of < 70 years of age did not reveal important differences with regard to PK, efficacy and safety, while any further subgroup according to age categories of 75-85 and >85 years of age appears not useful due to the low number of patients). Furthermore, as MASH is a slow progressing disease, the relevance of treating patients at older age may be questioned, which has sufficiently addressed in the SmPC.

Hierarchical testing demonstrated statistical significant effect of change in body weight (-10.51 kg vs -2.04 kg; -8.46 %-points [-9.55; -7.38]95%CI; p-value < 0.0001), resolution of steatohepatitis and improvement in liver fibrosis (32.7% vs 16.1%; 16.54 [10.24; 22.83]95%CI; p-value <0.0001), however not for SF-36 Bodily pain (0.86 vs -0.47; 1.34 [0.01; 2.67]95% CI; p-value =0.0488). However, these secondary endpoints may have limitations in support for the primary evaluation as previously discussed.

Of importance for the future assessment of part 2 results, the hypothesis test for SF-36 Bodily plain was not rejected thus no statistical significance can be carried over from part 1 to part 2 of the study.

Nevertheless, also some further support for efficacy based on numerical statistical improvement could be derived from other (exploratory) secondary endpoints of MASH/liver related endpoints including steatohepatitis with at least a 2-point reduction in NAS and no worsening of fibrosis, histology-assessed liver collagen proportionate area, worsening in steatohepatitis, improvement in histology-assessed ballooning, improvement in histology-assessed inflammation, improvement in histology-assessed steatosis, MASH resolution (ballooning of 0, inflammation of 0-1) and ≥2-point NAS reduction with no worsening of fibrosis, progression of liver fibrosis in patients with F2, and progression of liver fibrosis. Further, imaging-based endpoints also provided some suggestion for efficacy based on

numerical statistical improvements in liver stiffness assessed by FibroScan, CAP values assessed by transient elastography (FibroScan), and FibroScan-AST score. Also, efficacy based on numerical statistical improvements was observed for liver enzymes including ALT and AST, although these were only moderately elevated for about half of the patients. Other blood biomarkers of type-iii collagen through Pro-C3 score and Enhanced Liver Fibrosis score also showed numerical improvements.

Several other cardiometabolic makers other than body weight reduction and known to be associated with semaglutide treatment have been evaluated including diabetes markers, lipid markers, and inflammation markers. In line with known mechanisms of semaglutide, numerical improvements were observed for HbA1c and on the exploratory marker of insulin sensitivity (through HOMA-IR), in diabetic patients but also the non-diabetic patients. While the lipid profile was close to the normal range, slight numerical improvements could be seen for semaglutide vs placebo for changes in triglycerides, free fatty acids, LDL-C, and HDL-C. Suggestion for inflammation reduction could be observed for hsCRP, and on exploratory markers including TNF-alpha and IL-1R antagonist. Still, the clinical meaning of these observations is considered not entirely clear. Discontinuation based solely on weight reduction is likely not appropriate considering that other factors also contribute to the overall treatment effect.

The impact on patient reported outcome is somewhat unclear. While patient reported outcome of the hierarchical tested secondary endpoint of SF-36 Bodily pain could not demonstrate significance, and NASH-CHECK abdominal pain was not numerically improved, some suggestion for efficacy based on numerical improvement could be observed for the SF-36 Physical Component, SF-36 Mental Component.

With regard to immunogenicity findings, three patients developed detectable ADA responses, with antibody titres ranging from 15 to 120 and a median titre of 30.

The subjects did not exhibit extreme obesity or atypical metabolic characteristics, and their baseline profiles were comparable to the general study population, excluding any identifiable metabolic or phenotypic factors contributing to altered immunogenicity. The description that no clinical, pharmacokinetic, or pharmacodynamic impact was observed further supports the lack of clinical relevance of these antibody findings.

Overall, the available evidence would support a conditional marketing authorisation in accordance with the EMA reflection paper of on regulatory requirements for the development of medicinal products for MASH (EMA/CHMP/111529/2024). Interim findings on intermediate histological endpoints and some other markers possible associated with liver disease should ultimately show to translate into clinical improvement. Therefore, evidence on clinical endpoints should be delivered as a specific obligation, as currently planned with the conduct of the second part of the on-going pivotal study. Clinical evidence is currently defined based on a combined endpoint of histological progression to cirrhosis, all cause death, liver induced MELD score ≥ 15, liver transplantation, or hepatic decompensation events.

5.3.10.2. Conclusions on the clinical efficacy

In the pivotal study including patients with biopsy confirmed MASH and fibrosis stage 2 and 3, semaglutide demonstrated a significant beneficial effect at 72 weeks on the interim co-primary endpoints of resolution of steatohepatitis and no worsening of liver fibrosis (62.9% vs 34.4%; 28.65 %-points [21.09; 36.21]95% CI; p-value <0.0001), and improvement in liver fibrosis and no worsening of steatohepatitis (36.8% vs 22.4%; 14.39 %-points [7.51; 21.27]95% CI; p-value <0.0001) compared to placebo. Hierarchical tested secondary endpoints of change in body weight, resolution of steatohepatitis and improvement in liver fibrosis showed beneficial effects, however, this was not the case for the patient reported SF-36 Bodily pain endpoint. Further, support of these endpoints for the primary endpoint may be limited. Nevertheless, other histological, imaging, plasma

derived liver markers, cardiometabolic markers, and inflammation markers generally support the beneficial effect of semaglutide.

However, clinical endpoint evaluation is still needed to confirm the interim histological benefits, which are intended to be gathered with the on-going study to obtain full approval.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse drug reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The clinical development programme for semaglutide 2.4 mg for MASH includes 4 trials, pivotal phase 3a trial 4553 (ESSENCE) in a population with biopsy-confirmed MASH F2–F3, and 3 supportive studies, phase 2 dose finding trial 4296 in a population with MASH F1–F3, phase 2 trial 4492 in a population of subjects with biopsy-defined MASH and compensated cirrhosis (F4c) and one clinical pharmacology trial 4381 in a population of subjects with NAFLD and increased liver stiffness (Table 29).

The safety data from on-going study 4553 are based on a predefined interim analysis set on subject #800 reaching the week-72 visit window, as per the data cut-off date of 05 September 2024. Because the trials are heterogeneous with respect to treatment regimen (dose levels and dosing frequency), trial populations, and duration of exposure for subjects contributing to the safety-related evaluations, data from each trial are evaluated and presented separately.

Table 28: Clinical trials supporting the present application – NN9931

Trial NASH population	Number of subjects	Description Hyperlink to CSR
Clinical pharmacology		
Trial 4381 NAFLD (supportive)	FAS: 67 subjects SAS: 66 subjects	72-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial investigating the effect of semaglutide s.c. 0.4 mg once daily versus placebo on liver fibrosis assessed by magnetic resonance elastography in subjects with NAFLD and increased liver stiffness.
Phase 2		
Trial 4296 NASH F1–F3 (pivotal)	FAS: 320 subjects, including 230 subjects with NASH F2/F3 SAS: 319 subjects	72-week randomised, double-blind, placebo-controlled, six-arm, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. once-daily at three different doses (0.1, 0.2 or 0.4 mg) versus placebo in subjects with NASH F1–F3.
Trial 4492 NASH F4c (supportive)	FAS: 71 subjects SAS: 71 subjects	48-week randomised, double-blind, placebo-controlled, parallel-group, multicentre trial comparing the effect and safety of once-weekly semaglutide s.c. 2.4 mg with placebo in subjects with NASH F4c.
Phase 3a		
Trial 4553 NASH F2–F3 (pivotal)	FAS (interim) [a]: 800 subjects FAS (interim, all randomised subjects): 1197 subjects [a] SAS (interim) [a]: 1195 subjects	240-week randomised, double-blind, placebo-controlled, parallel-group, multicentre, multinational trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly versus placebo in subjects with NASH F2 or F3. Trial 4553 has two parts with distinctive objectives: • Part 1: To demonstrate that treatment with semaglutide improves liver histology compared to placebo after 72 weeks of treatment. • Part 2: To demonstrate that treatment with semaglutide lowers the risk of liver-related clinical events compared to placebo after 240 weeks of treatment. The present application is based on data and results from an interim evaluation of trial 4553 (part 1). The SAS (interim) includes all subjects exposed to a least one dose of trial product up until the interim data cut-off date.

F: fibrosis stage; F4c: compensated cirrhotic NASH (fibrosis stage F4); FAS: full analysis set; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic fatty liver disease; SAS: safety analysis set; SEE: substantial evidence of effectiveness; s.c.: subcutaneous; CSR: clinical study report.

a. According to the trial protocol, trial 4553 is planned to include a total of 1200 randomised subjects. By the data cut-off date (05 September 2024), 1197 subjects had been randomised. The present application is based on an evaluation of data from the first 800 randomised subjects (FAS [interim]) with respect to efficacy-related analyses and on data from all exposed subjects (1195 subjects) by the data cut-off date with respect to safety-related evaluations (SAS [interim]).

The safety evaluation of semaglutide 2.4 mg in subjects with MASH presented in this summary builds upon the compiled knowledge of safety with semaglutide from earlier development programmes, as well as post-marketing data. At the time of data-cut off, post marketing data covered approximately 20 million patients treated for the approved indications for Ozempic, Rybelsus and Wegovy.

Safety data analysis methodology

Safety analysis dataset

The SAS includes all subjects who have been exposed to at least one dose of trial product.

Observations periods

- The in-trial observation period is defined as the time period where the subject is followed in the trial and ends at the first of the following dates, end-of-trial visit for completed trials; follow-up visit for subjects who have withdrawn, last visit prior to the interim data cut-off date (trial 4553 only), last contact with subject (for subjects lost to follow-up), or death.
- The on-treatment observation period is defined as the time period where the subject is treated with trial product. The on-treatment period begins on the date of first dose of trial product and ends after a follow-up period following the last dose, of 7 weeks for AEs, adjudicated events and hypoglycaemic episodes, and of 1 week (7 days) for laboratory assessments, and physical examination.

The aggregated duration of the in-trial and on-treatment observation periods are given in patient years of observation (PYO) and patient years of exposure (PYE), respectively. Additionally, in trial 4553, the patient years at risk of incident event (PYI) is used for safety evaluations, where time at risk is defined as the duration from randomisation until the first event or the end of the observation period, whichever comes first.

In general, safety evaluations will be based SAS (interim) or SAS and the on-treatment period as the primary safety data cut. The in-trial observation period is used for safety areas concerning "use in pregnancy and during lactation" (pre-defined MedDRA searches on neonatal exposures via breast milk, and fertility disorders with potential long latency between onset and diagnosis). Safety focus areas will be summarised for both the in-trial and on-treatment observation periods.

Safety assessments and data collection

For trial 4553, the schedule of safety (AE) visits was every 2 weeks the first four weeks, thereafter every fourth week up to week 16 and increasingly longer visit windows from week 16. For trials 4296, 4492 and 4381, the schedule of safety (AE) visits were every 2 weeks for at least 12 weeks and thereafter every 4-12 weeks until end-of trial.

AEs were collected via investigator reporting. Adverse events (AEs) will be summarised by the number of subjects with at least one event, proportion of subjects with at least one event, number of events, event rate based on exposure or observation time (number of events per 100 person-years of exposure or observation (PYE/PYO)), and incidence based on time at risk (number of events per 100 person-years at risk (PYI)).

In trials 4553 and 4296, blinded adjudication of selected event types was performed on an ongoing basis by an independent, external event adjudication committee (EAC). In both trials, types of AEs to be sent for adjudication were pre-specified, as presented in Table 29.

Table 29: AEs in scope for adjudication – trials 4553 and 4296

Events for adjudication	Trial 4553	Trial 4296
Death/Fatal event	X	X
Acute coronary syndrome	X	X
Cerebrovascular event (stroke and transient ischemic attack)	X	X
Heart failure requiring hospitalisation and urgent outpatient clinic visits due to heart failure	X	X
Hepatic decompensation	X	
Liver-induced MELD score ≥ 15[a]	X	
Hepatic event (potential DILI) [b]	X	
Acute pancreatitis		X

AE: adverse event; MELD: Model for End-stage Liver Disease; DILI: drug-induced liver injury.

a: Liver-induced MELD score ≥ 15 confirmed by central laboratory, not in scope for subjects treated with Vitamin K antagonists. b: Based on clinically significant laboratory assessments, as defined in Protocol.

Safety focus areas

Based on the therapeutic experience with GLP-1 RAs and regulatory feedback and requirements, safety focus areas were pre-defined as being of special interest in the evaluation of the safety of semaglutide 2.4 mg for MASH: Gastrointestinal disorders, Hepatic disorders, Gallbladder-related disorders, Acute pancreatitis, Cardiovascular disorders, Neoplasms, Acute renal failure, Hypoglycaemia, Retinal disorders, Immunogenicity, Psychiatric disorders, Rare events, Medication errors, drug abuse or misuse, and overdose, Suspected transmission of an infectious agent via trial product, COVID-19.

5.4.2. Patient exposure

An overview of patient exposure is indicated in Table 30.

Table 30: Patient exposure- – safety analysis sets trials 4553 (interim), 4296, 4492 and 4381 (05 September 2024)

	Study	Patients enrolled (semaglutide vs placebo)	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	Study 4553 (interim; F2-F3)	1195	800	800	643
	Study 4492 (F4c)	71 (47 vs 24)	47	47	46
	Study 4296 (F1-F3)	319 (239 vs 80)	239	0	221
	Study 4381 (NAFLD with increased liver stiffness)	66 (33 vs 33)	33	0	33
Blinded studies (active -controlled)	N/A				

	Study	Patients enrolled (semaglutide vs placebo)	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Open studies	N/A				
Post marketing	N/A				
Compassionate use	N/A				

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

An overview of total exposure and the number of subjects exposed to semaglutide in the phase 2 and phase 3a trials in the clinical development programme for semaglutide 2.4 mg for MASH is provided in Table 31. In the phase 2 and phase 3a trials (trials 4296, 4492 and 4553 [interim]), a total of 1585 subjects were exposed to trial product: 1086 subjects to semaglutide and 499 subjects to placebo. The total exposure to semaglutide in the on-treatment observation period was 1716.6 PYE.

Table 31: Total exposure and subject disposition – safety analysis sets trials 4296, 4492 and 4553 (interim)

	Sema 0.1 mg OD		Sema 0.2 mg OD		Sema 0.4 mg OD		Sema 2.4 mg		Total Sema		Placebo		Total
	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE	N	PYE	N
PYE													
Total exposed	80	115.4	78	105.8	81	114.2	847	1381.2	1086	1716.6	499	765.3	1585
4198.5													
Trial													
NN9931-4296 (phase 2, F1-F3)	80	115.4	78	105.8	81	114.2	0	0.0	239	335.4	80	113.7	319
784.4													
NN9931-4492 (phase 2, F4c)	0	0.0	0	0.0	0	0.0	47	46.0	47	46.0	24	24.6	71
116.6													
NN9931-4553 (phase 3, F2-F3)	0	0.0	0	0.0	0	0.0	800	1335.3	800	1335.3	395	627.0	1195
3297.5													

N: Number of subjects, OD: Once daily, OW: Once weekly, PYE: Person-years of exposure; F: fibrosis stage (F1-F4); F4c: compensated cirrhotic NASH (fibrosis stage F4); SAS: safety analysis set.

Data from trial 4553 are based on SAS (interim).

Study 4553
A total of 1195 subjects were randomised to receive semaglutide 2.4 mg once weekly (n=800) or placebo (n=395). At the time of the interim evaluation, 800 subjects were treated with semaglutide, with 643 subjects treated for at least 6 months, and a total of 542 subjects treated for at least 12 months. At time of the interim evaluation, the mean (SD) exposure time for subjects in SAS (interim) was 85.7 (50.4) weeks for the on-treatment observation period, 87.1 (50.7) weeks on semaglutide, and 82.8 (49.9) weeks on placebo.

Supportive studies

Study 4296 A total of 320 subjects were randomised to receive semaglutide 0.1 mg (80 subjects), semaglutide 0.2 mg (78 subjects), semaglutide 0.4 mg (82 subjects), or placebo (80 subjects). All randomised subjects except one (in the semaglutide 0.4 mg group) were exposed to trial product. The total exposure time in the treatment groups ranged from 105.8 years to 115.4 years (on-treatment period) and the total observation time ranged from 112.2 years to 119.6 years (in-trial period), with the lowest values in the semaglutide 0.2 mg group (both periods).

Study 4492 A total of 71 subjects were randomised to receive semaglutide 2.4 mg (47 subjects) or placebo (24 subjects). The total on-treatment patient years of exposure (PYE) in the semaglutide group (46.0 years) and the placebo group (24.6 years) reflected the 2:1 randomisation ratio.

Study 4381 A total of 66 subjects were exposed to trial product, of these 33 subjects were exposed to semaglutide 0.4 mg once daily, following dose escalation from 0.05 mg/day up to 0.4 mg mg/day. The total mean (SD) on-treatment observation period was 73.0 (16.8) weeks. The mean (SD) number of treatment weeks per subject in the semaglutide arm was 71.9 (17.6) and 74.0 (16.1) in the placebo arm.

5.4.3. Adverse events

Overall incidence of Adverse Events

Study 4553
Overall, the proportions of subjects who experienced AEs, as well as the event rates, were higher with semaglutide 2.4 mg (86.3%, 407.1 events per 100 PYE) than with placebo (78.7%; 303.0 events per 100 PYE). This treatment difference was largely driven by the higher proportions of subjects with gastrointestinal AEs (mainly nausea, diarrhoea, constipation and vomiting) in the semaglutide 2.4 mg group (Table 33).

The majority of AEs were non-serious, and mild or moderate in severity across both treatment groups. The subjects reporting events were primarily reported as recovered or not recovered at the time of the interim evaluation. AEs leading to premature discontinuation of trial product were reported by a low proportion of subjects, with comparable proportion of subjects between semaglutide 2.4 mg and placebo.

The majority of events were assessed as unlikely related to trial product in both treatment groups. A higher proportion of subjects reported events assessed as probably or possibly related to trial product with semaglutide 2.4 mg compared to placebo, this was driven by gastrointestinal AEs.

Table 32: Adverse events overview on treatment SAS (interim) – trial 4553

	Sema 2.4 mg						Placebo						Total					
	N	(%)	PYI	I	E	R	N	(%)	PYI	I	E	R	N	(%)	PYI	I	E	R
Number of subjects	800						395						1195					
PYE	1335.26						627.03						1962.28					
Events	690	(86.3)	219.6	314.2	5436	407.1	311	(78.7)	177.0	175.7	1900	303.0	1001	(83.8)	396.6	252.4	7336	373.8
Serious																		
Yes	104	(13.0)	1219.0	8.5	159	11.9	51	(12.9)	580.7	8.8	77	12.2	155	(13.0)	1799.6	8.6	236	12.0
No	684	(85.5)	221.9	308.3	5277	395.2	304	(77.0)	183.6	165.6	1823	290.7	988	(82.7)	405.4	243.7	7100	361.8
Severity																		
Severe	71	(8.9)	1257.4	5.6	103	7.7	33	(8.4)	599.0	5.5	46	7.3	104	(8.7)	1856.4	5.6	149	7.5
Moderate	382	(47.8)	792.8	48.2	1199	89.8	169	(42.8)	412.4	41.0	473	75.4	551	(46.1)	1205.2	45.7	1672	85.2
Mild	642	(80.3)	278.8	230.3	4134	309.6	286	(72.4)	214.3	133.5	1381	220.2	928	(77.7)	493.1	188.2	5515	281.0
Relationship to trial product																		
Probable	363	(45.4)	758.2	47.9	1569	117.5	84	(21.3)	520.8	16.1	191	30.4	447	(37.4)	1279.1	34.9	1760	89.6
Possible	386	(48.3)	762.8	50.6	1162	87.0	116	(29.4)	482.9	24.0	257	40.9	502	(42.0)	1245.7	40.3	1419	72.3
Unlikely	575	(71.9)	452.2	127.2	2675	200.3	286	(72.4)	220.6	129.7	1444	230.2	861	(72.1)	672.7	128.0	4119	209.9
Related to technical complaint																		
Yes	7	(0.9)	1323.2	0.5	7	0.5	2	(0.5)	623.3	0.3	3	0.4	9	(0.8)	1946.5	0.5	10	0.5

No	688	(86.0)	221.2	311.0	5398	404.2	311	(78.7)	177.9	174.8	1889	301.2	999	(83.6)	399.2	250.3	7287	371.3

%: Percentage of subjects with at least one event, E: Number of events, I: Incidence (number of incident events per 100 PYI), N: Number of subjects with at least one event, PYE: Person-years of exposure, PYI : Person-years at risk of incident event, where time at risk is the duration until the first event or the end of the period, whichever comes first, R: Event rate (number of events per 100 PYE/PYO). MedDRA version 27.0.

Adverse events - overview - on-treatment - safety analysis set (interim)

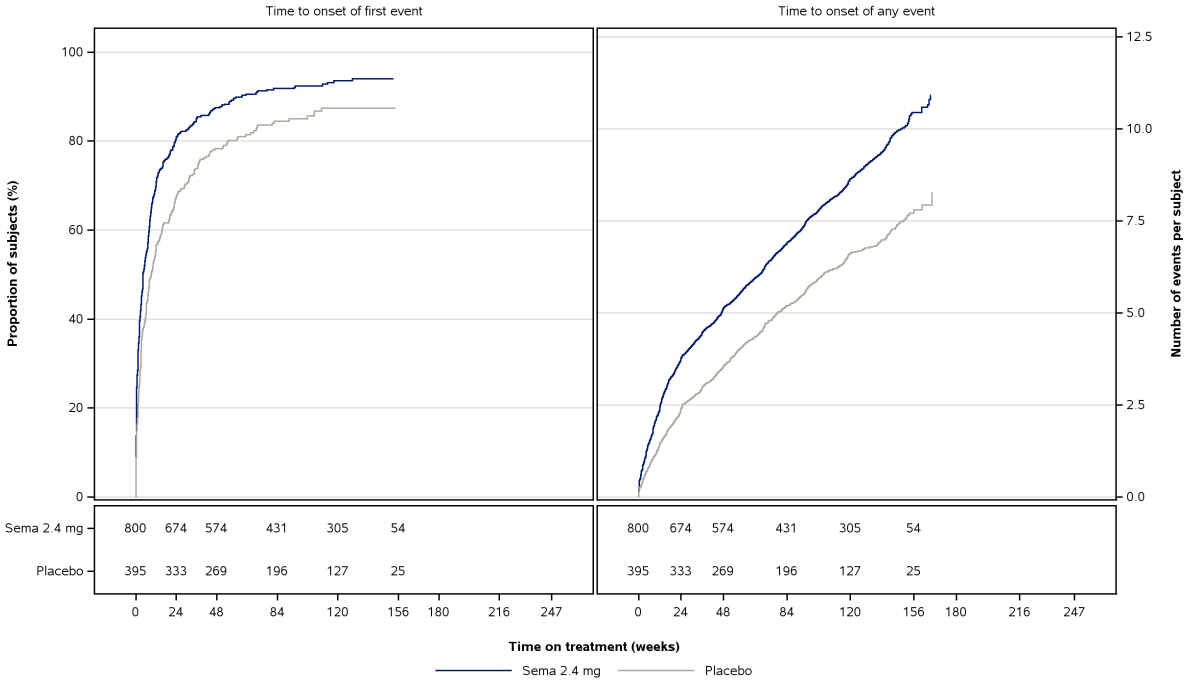
	Sema 2.4 mg						Placebo						Total					
	N	(%)	PYI	I	E	R	N	(%)	PYI	I	E	R	N	(%)	PYI	I	E	R
Action taken to trial product																		
Drug interrupted	96	(12.0)	1224.4	7.8	176	13.1	27	(6.8)	595.6	4.5	47	7.5	123	(10.3)	1820.0	6.8	223	11.3
Drug withdrawn	21	(2.6)	1328.6	1.6	32	2.4	13	(3.3)	623.3	2.1	16	2.5	34	(2.8)	1951.9	1.7	48	2.4
Dose reduced	80	(10.0)	1225.1	6.5	157	11.7	8	(2.0)	615.9	1.3	11	1.7	88	(7.4)	1841.0	4.8	168	8.5
Dose increased	15	(1.9)	1320.2	1.1	20	1.5	1	(0.3)	624.8	0.2	1	0.1	16	(1.3)	1945.1	0.8	21	1.0
Dose not changed	664	(83.0)	245.5	270.5	4992	373.8	305	(77.2)	186.2	163.8	1802	287.3	969	(81.1)	431.7	224.4	6794	346.2
Unknown	*	*	*	*	*	*	*		*	*	*	*	1	(0.1)	1961.0	0.1	1	0.0
Not applicable	13	(1.6)	1329.6	1.0	28	2.1	12	(3.0)	625.9	1.9	15	2.3	25	(2.1)	1955.5	1.3	43	2.1
Outcome																		

Fatal	3 (0.4)	1335.1	0.2	3	0.2	5 (1.3)	625.6	0.8	7	1.1	8 (0.7)	1960.7	0.4	10	0.5
Not recovered	488 (61.0)	689.6	70.8	1405	105.2	211 (53.4)	377.3	55.9	597	95.2	699 (58.5)	1066.8	65.5	2002	102.0
Recovered with sequelae	* *	*	*	*	*	*	*	*	*	*	11 (0.9)	1949.1	0.6	13	0.6
Recovering	89 (11.1)	1232.6	7.2	175	13.1	32 (8.1)	593.6	5.4	41	6.5	121 (10.1)	1826.2	6.6	216	11.0
Recovered	632 (79.0)	304.2	207.7	3836	287.2	274 (69.4)	210.2	130.3	1250	199.3	906 (75.8)	514.4	176.1	5086	259.1
Unknown	2 (0.3)	1334.4	0.1	4	0.3	1 (0.3)	625.6	0.2	5	0.8	3 (0.3)	1960.0	0.2	9	0.4

%: Percentage of subjects with at least one event, E: Number of events, I: Incidence (number of incident events per 100 PYI), N: Number of
subjects with at least one event, PYE: Person-years of exposure, PYI : Person-years at risk of incident event, where time at risk is the
duration until the first event or the end of the period, whichever comes first, R: Event rate (number of events per 100 PYE/PYO).
MedDRAversion 27.0.
* information removed to avoid unblinding

In the semaglutide 2.4 mg group, around 80% of the subjects reported their first event within the dose-escalation period; however, AEs were reported throughout the trial in both treatment groups (4).

Figure 14: AEs – plot over time – on treatment – SAS (interim) – trial 4553



Left panel: Kaplan-Meier estimator. Numbers in the lower panels are number of subjects at risk. Plot includes events with onset at or before the scheduled follow-up visit. Right Panel: Mean Cumulative Function. Subjects are considered to be at risk until their first adverse event. Proportion of subjects with at least one adverse event and mean number of adverse events.

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Supportive studies

Study 4296 The proportions of subjects who experienced AEs, as well as the event rates, were higher in each of the semaglutide groups (90.0%-97.4%; 447.6-545.4 events per 100 PYE) than in the placebo group (83.8%; 391.4 events per 100 PYE). The highest proportion of subjects who experienced AEs, as well as the event rates, were seen in the semaglutide 0.2 mg group. The difference in the proportions of subjects with AEs between the semaglutide groups and the placebo group appeared to be largely driven by the higher proportions of subjects with gastrointestinal AEs (mainly nausea, constipation, diarrhoea, vomiting, and abdominal pain) in the semaglutide groups. Across treatment groups, the majority of AEs were non-serious, mild in severity and with the outcome resolved.

The proportion of subjects with AEs leading to premature treatment discontinuation was higher in the semaglutide 0.2 mg group (12.8%) than in the other treatment groups including placebo (ranging between 3.8% and 5.0%). Gastrointestinal disorders were the most common reason for discontinuation among subjects who received semaglutide (1.3%-7.7% of the subjects); no subjects in the placebo group discontinued because of gastrointestinal disorders.

A larger percentage of AEs in the semaglutide groups (approximately 31% to 46% of all AEs) than in the placebo group (20% of all AEs) were judged by the investigator as possibly or probably related to trial product, driven by gastrointestinal AEs.

AEs were reported throughout the trial in all treatment groups, however, in the semaglutide groups, 80% or more of the subjects had their first event within the first 24 weeks of treatment.

Study 4492 AEs were reported by 89.4% of subjects in the semaglutide group treated with 2.4 mg once weekly (630.5 events per 100 PYE) compared to 79.2% of the subjects in the placebo group (345.1 events per 100 PYE). Event rates in the semaglutide group were primarily driven by gastrointestinal AEs. The majority of the AEs in the two treatment groups were of mild or moderate severity. Slightly more severe AEs were seen in the semaglutide group compared to placebo, though based on low numbers, in 17% versus 4.2 % of subjects. SAEs were reported by 12.8% (corresponding to 6 subjects) in the semaglutide group and 8.3% (corresponding to 2 subjects) in the placebo group.

Study 4381 AEs were reported by 93.9% of subjects in the semaglutide group (464.0 events per 100 PYE) compared to 87.9% of the subjects in the placebo group (303.3 events per 100 PYE). Proportions and event rates in the semaglutide group appeared to be largely driven by gastrointestinal AEs. The majority of the AEs in the two treatment groups were of mild or moderate severity, and severe AEs were reported in 12.1% versus 9.1%. Study drug was withdrawn in 1(3.0%) subject on semaglutide, and dose was reduced in 2 (6.1%), and outcome was reported as recovered in 93.9% of subjects. More SAEs were reported in the semaglutide s.c. 0.4 mg arm (12.1%, 6 events in 4 subjects) than in the placebo arm (9.1%, 3 events in 3 subjects).

Semaglutide 2.4 mg for weight management

Overall, the AE reporting was similar between trial 4553 (interim evaluation) and the clinical development programme for Wegovy (see SmPC).

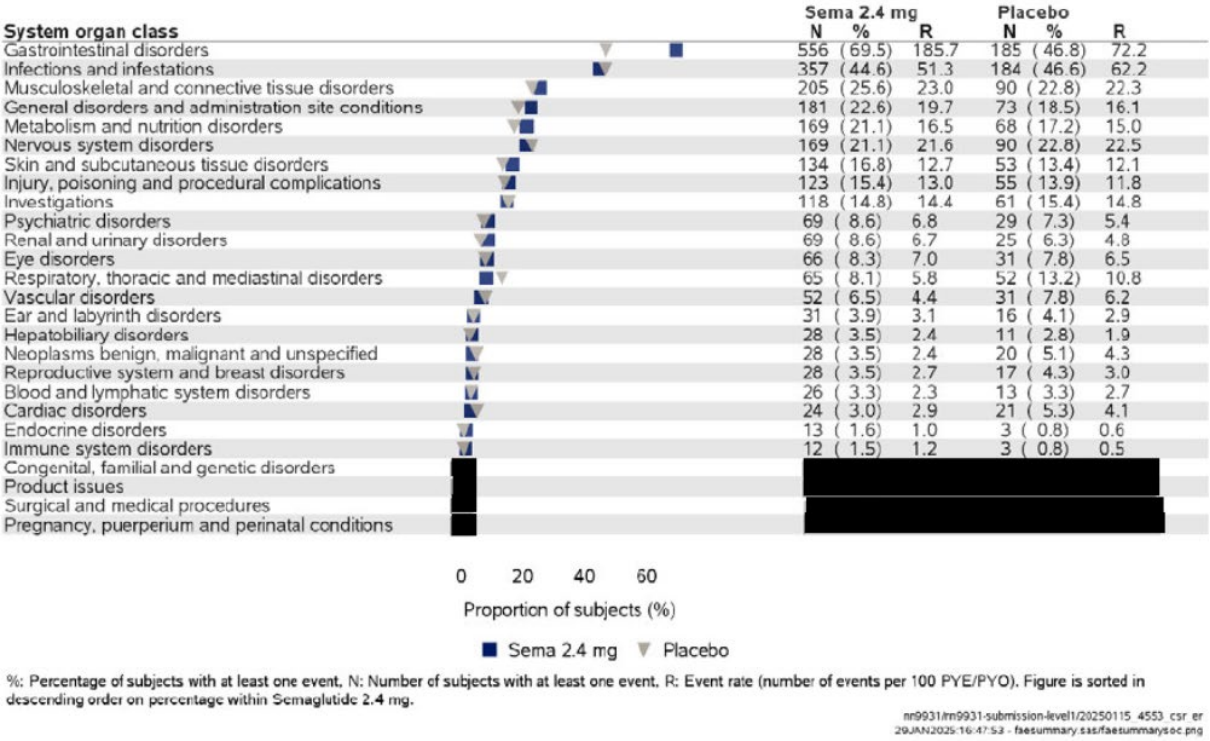
Common adverse events

Study 4553

The most frequently reported AEs belonged to the SOC Gastrointestinal disorders with a higher proportion of subjects with semaglutide 2.4 mg reporting gastrointestinal AEs compared to placebo (69.5% versus 46.8%). AEs within the SOCs Infections and infestations, Musculoskeletal and connective tissue disorders, General disorders and administration site conditions, Metabolism and nutrition disorders and Nervous system disorders were also frequently reported (by at least 20% of the subjects in any treatment group).

With the exception of Gastrointestinal disorders, the proportion of subjects reporting AEs within the different SOCs were generally comparable across treatment groups (Figure 15).

Figure 15: Adverse events by system organ class on treatment – SAS (interim) – trial 4553



%: Percentage of subjects with at least one event, N: Number of subjects with at least one event, R: Event rate (number of events per 100 PYE/PYO). Figure is sorted in descending order on percentage within Semaglutide 2.4 mg.

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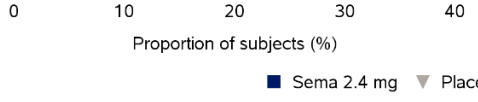
* information was redacted to avoid unblinding

An overview of the **most frequently reported AEs** by PT reported by ≥10% of the subjects in any treatment group is provided in 6.

Figure 16: AEs by PT – most frequent (⩾10%) – on treatment – SAS (interim) – trial 4553

Preferred term	Sema 2.4 mg N	%	R	Placebo N	%	R
Nausea	289	(36.1)	57.0	49	(12.4)	12.8
Diarrhoea	214	(26.8)	25.3	48	(12.2)	9.7
Constipation	177	(22.1)	16.0	31	(7.8)	5.9
Vomiting	148	(18.5)	16.3	22	(5.6)	4.0
COVID-19	132	(16.5)	10.8	74	(18.7)	12.8
Decreased appetite	112	(14.0)	9.9	10	(2.5)	1.6



%: Percentage of subjects with at least one event, N: Number of subjects with at least one event, R: Event rate (number of events per 100 PYE/PYO). Figure is sorted in descending order on percentage within Semaglutide 2.4 mg.

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Among the most frequently reported AEs, nausea, diarrhoea, constipation and vomiting belonging to the SOC Gastrointestinal disorders were all more frequently reported in the semaglutide 2.4 mg group compared to the placebo group (18.5%-36.1% versus 5.6%-12.4%). These types of events are well known for semaglutide and for the GLP-1 RA class in general. The PT decreased appetite belonging to the SOC Metabolism and nutrition disorders was reported more often with semaglutide 2.4 mg compared to placebo (14.0% versus 2.5%).

AEs reported by ⩾5% and by a higher proportion of subjects with semaglutide 2.4 mg compared to placebo are: Dyspepsia: 7.6 % versus 2.8%; Abdominal distension: 7.5% versus 3.5%; Gastro-oesophageal reflux disease: 7.4% versus 1.5%; Eructation: 5.3% versus 0.8%; Back pain: 6.1% versus 4.1%; Headache: 8.0% versus 6.3%; and Fatigue: 8.9% versus 5.3%. The majority of events were non-serious and all mild or moderate in severity. Most events were unlikely related to trial product, did not lead to premature trial product discontinuation and approximately half resolved. There was 1 SAE of back pain (worsening). The event did not lead to any changes in dose, resolved and was assessed as unlikely related to trial product.

AEs reported by ⩾2% and by a higher proportion of subjects with semaglutide 2.4 mg compared to placebo are: Flatulence: 3.6% versus 2.5%; Alopecia: 3.0% versus 0.5%; Lipase increased: 2.5% versus 1.0%; Weight decreased: 4.4% versus 0.8%; Gastroenteritis: 4.0% versus 1.8%; Muscle spasms: 2.5% versus 1.0%; Insomnia: 4.1% versus 1.8%; Fall: 2.1% versus 0.8%. All events were non-serious, and mild or moderate in severity except one SAE of PT fall that led to treatment discontinuation and none led to treatment discontinuation. Most of the events were resolved at time of the interim evaluation of trial 4553 and assessed as unlikely related to trial product.

Supportive studies

Study 4296 The most frequently reported AEs in all treatment groups belonged to the SOC Gastrointestinal disorders with the highest proportions of subjects reporting gastrointestinal AEs in the semaglutide groups (63.8%−76.9% versus 45.0% in the placebo group). AEs within the SOCs Infections and infestations, Nervous system disorders, Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, General disorders and administration site conditions, Injury, poisoning and procedural complications, and Investigations were also frequently reported in all treatment groups (by at least 20% of the subjects in any treatment group), and by overall similar proportions of subjects across treatment groups.
A higher proportion of subjects in the semaglutide groups than in the placebo group reported AEs within the SOC Skin and subcutaneous tissue disorders (12.3%−21.8% versus 7.5%) and the SOC Neoplasms, benign, malignant and unspecified (6.3%−7.4% versus 2.5%). AEs related to neoplasms were mostly benign, non-serious and mild in severity. A total of 3 malignant neoplasms in the semaglutide 0.1 mg and 0.2 mg groups were reported. These affected different organs and were all assessed by the investigator as unlikely related to trial product. A lower proportion of subjects in the semaglutide groups than in the placebo group reported AEs within the SOC Renal and urinary disorders (7.4%−8.8% versus 15.0%).
An overview of the **most frequently reported AEs by PT** reported by ≥10% of the subjects in any treatment group is provided in Figure 17. Among the most frequently reported AEs, nausea, constipation, decreased appetite, diarrhoea, vomiting and abdominal pain (SOCs Gastrointestinal disorders and Metabolism and nutrition disorders) were all more frequently reported in the semaglutide groups than in the placebo group. Other frequently reported AEs, back pain, nasopharyngitis, arthralgia, and fatigue – were reported by comparable proportions of subjects across treatment groups, without noteworthy differences between the treatment groups.

Figure 17: AEs by PT – most frequent (⩾10%) – on treatment – SAS – trial 4296

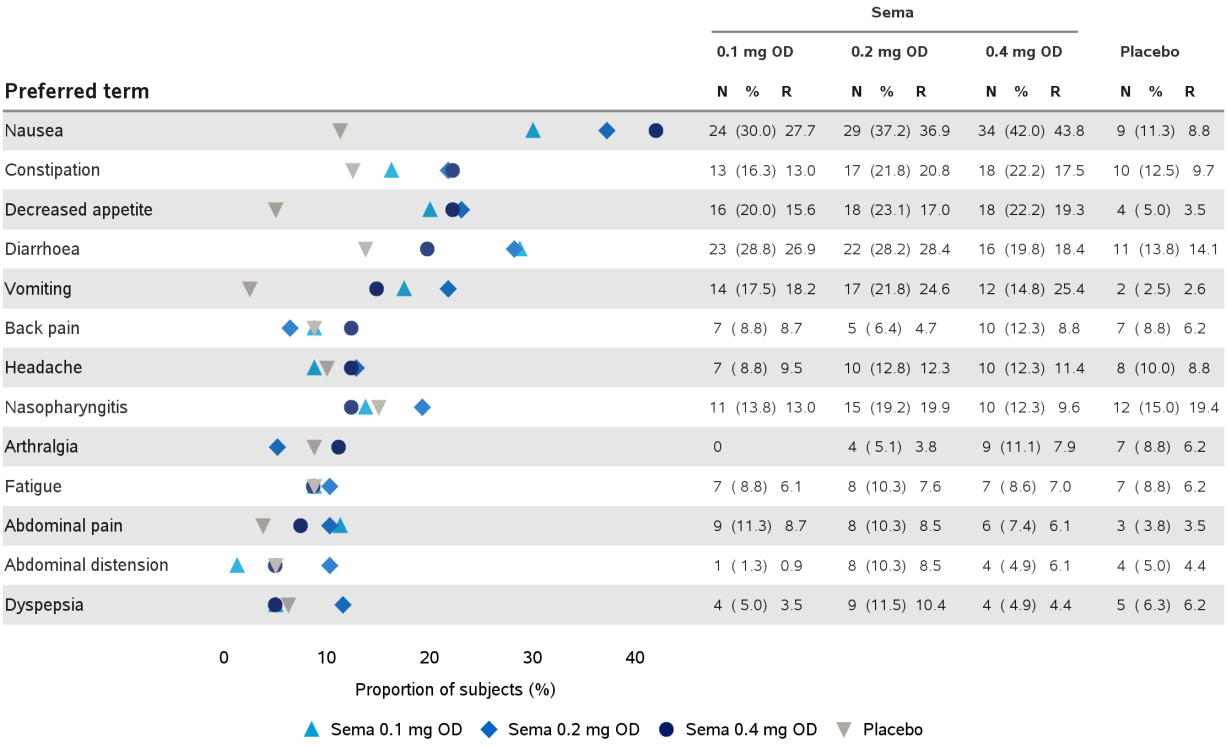

Figure is sorted in descending order on percentage within Semaglutide 0.4 mg OD
N: Number of subjects with at least one event, %:percentage of subjects with at least one event, R: events per 100 years of exposure
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In the supportive **trials 4492 and 4381**, including subjects with MASH F4c and subjects with NAFLD and increased liver stiffness, AEs reported by ≥10% of the subjects in any treatment group were all non-serious events, and the majority of events were mild to moderate in severity. The most frequent PTs were nausea, diarrhoea, vomiting and decreased appetite.

Semaglutide 2.4 mg for weight-management

The most frequently reported adverse reactions were gastrointestinal disorders including nausea, diarrhoea, constipation and vomiting. AEs and observed treatment differences between semaglutide 2.4 mg and placebo were similar to results in study 4553. In the semaglutide 2.4 mg group the PTs headache, dysgeusia and diabetic retinopathy were reported by a lower proportion of subjects with MASH compared to subjects with overweight or obesity (Wegovy), and the PTs increased lipase and delayed gastric emptying were reported by a higher proportion of subjects with MASH compared to subjects with overweight or obesity (Wegovy).

Adverse Events by severity

Study 4553

The majority of AEs were non-serious, in 85.5% of subjects on semaglutide vs 77.0 % of subjects on placebo. Most AEs were graded as mild or moderate (in 80.3% vs 72.7%, and 47.8% vs 42.8% of subjects on semaglutide vs placebo, respectively), and only a limited proportion of AEs was graded severe, with no imbalance for semaglutide vs placebo, 8.9% vs 8.4%.

Supportive studies

Study 4296 Across treatment groups, the majority of AEs were non-serious, mild in severity and with the outcome resolved. There were more SAEs in the semaglutide groups compared to placebo (ranging from 14.8% to 19.2% vs 10.0%). There was no apparent dose-relationship among the semaglutide groups with regards to the proportion of subjects with serious or severe AEs, or with AEs with outcome not resolved.
Study 4492 The majority of the AEs in the two treatment groups were of mild or moderate severity. Slightly more severe AEs were seen in the semaglutide group compared to placebo, though based on low numbers.
Study 4381 The majority of AEs, in both treatment groups, occurred primarily in the first 24 weeks of the trial, were non-serious, mild or moderate in severity, with outcomes of recovered or recovering.

Adverse events by relationship to study medication

Study 4553
Probably or possibly related treatment-emergent adverse events were reported with higher frequency on semaglutide, in 549 (68.6%) vs 161 (40.8%) subjects.

Most probably or possibly treatment-related adverse events reported more frequently on semaglutide 2.4 mg belonged to the SOC Gastrointestinal disorders, in 482 (60.3%) vs 122 (30.9) subjects, including nausea (34.1% vs 10.9%), diarrhoea (20.3% vs 10.4%), constipation (17.3% vs 5.3%), vomiting (15.9% vs 3.3%), dyspepsia (6.9% vs 2.3%), abdominal distention (6.5% vs 2.5%), and gastrooesophageal reflux disease (5.9% vs 0.5%). Also, decreased appetite (13.6% vs 2.3%), fatigue (6.4% vs 2.8%), headache (4.9% vs 3.0 %), and weight decreased (4.1% vs 0.5%) were reported (*CSR study 4553*).

Supportive studies

Study 4296 The proportion of subjects with AEs judged by the investigator as possibly or probably related to trial product was higher in the semaglutide groups (in 60.0%, 73.1% and 71.6% of the subjects in the semaglutide 0.1 mg, 0.2 mg and 0.4 mg groups, respectively) than in the placebo group (48.8%), mainly belonged to the SOC Gastrointestinal disorders (45.0%, 61.5%, and 54.3%, versus 28.8% in the placebo group). AEs assessed as being related to treatment were graded serious in 2.5%, 3.8% and 2.5% on semaglutide 0.1 mg, 0.2 mg and 0.4 mg, versus 1.3% on placebo. Severe treatment related AEs were reported in 6.3%, 5.1%, and 4.9% versus 1.3% of subjects. The semaglutide dose was reduced in 0, 1.3% and 3.7% of subjects on semaglutide versus 0 on placebo, and study drug was withdrawn in 2.5%, 10.3%, and 3.7% of subjects on semaglutide versus 5.0 of subjects on placebo.

Study 4492 The proportion of subjects with AEs judged by the investigator as possibly or probably related to trial product was higher in the semaglutide group (78.7%) than in the placebo group (45.8%), mainly due to events in the SOC Gastrointestinal disorders (70.2% in the semaglutide group versus 25.0% in the placebo group). All AEs assessed as being related to treatment were non-serious and none were severe, with outcomes of recovered/recovering in most events.

Study 4381 The proportion of subjects with AEs judged by the investigator as possibly or probably related to trial product was higher in the semaglutide s.c. 0.4 mg arm (84.8%) than in the placebo arm (54.5%). This was mainly due to the greater number of GI related AEs assessed as being related to trial product in the semaglutide arm (60.6%) than the placebo arm (30.3%). All AEs assessed as being related to treatment were non-serious, and most were mild (78.8% on semaglutide vs 51.5% on

placebo). The semaglutide dose was reduced in 2 cases. None of the AEs assessed as possibly/probably related to treatment resulted in withdrawals from the trial.

5.4.3.1. Adverse drug reactions

Table 33: Summary of ADRs proposed for inclusion by the applicant in the SmPC

Immune system disorders		Link to data
Very Common		
Common		
Uncommon		
Rare	Anaphylactic reaction	Summary 2.7.4 (Wegovy), Appendix 7.2.2
Metabolism and nutrition disorders		
Very Common		
Common	Hypoglycaemia (level 2+3) in patients with type 2 diabetes[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.124
Uncommon		
Nervous system disorder		
Very Common	Headache[b]	Summary 2.7.4 (Wegovy), Appendix 7.3.12
Common	Dysgeusia[b,c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.9
	Dizziness[b]	Summary 2.7.4 (Wegovy), Appendix 7.3.8
	Dysaesthesia[a,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.7
Eye disorders		
Very Common		
Common		
Uncommon	Diabetic retinopathy in patients with type 2 diabetes[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.58
Cardiac disorders		
Very Common		
Common	Hypotension	
Uncommon	Increased heart rate[a,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.6
	Orthostatic hypotension	
Gastrointestinal disorders		
Very Common	Vomiting[a,b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Diarrhoea[a,b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Abdominal pain[b,c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Constipation	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Nausea[a,b]	Summary 2.7.4 (Wegovy), Appendix 7.3.1
	Nausea[a,b]	
Common	Gastritis[b,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.2

	Gastroesophageal reflux disease[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Dyspepsia[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Eructation[b]	
	Delayed gastric emptying	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Gastroenteritis	
	Flatulence[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Increased lipase[c]	Summary 2.7.4 (Wegovy), Appendix 7.3.5
	Abdominal distension[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
		Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
Uncommon	Acute pancreatitis[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.61
	Increased amylase [c]	Summary 2.7.4 (Wegovy), Appendix 7.3.4
Not known	Intestinal obstruction[c,d,e]	Summary 2.7.4 (Wegovy), Appendix 7.3.10
Hepatobiliary disorders		
Very Common		
Common	Cholelithiasis[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.49
Uncommon		
Skin and subcutaneous disorders		
Very Common		
Common	Hair loss[a]	Summary 2.7.4 (Wegovy), Appendix 7.3.11
Uncommon		
General disorders and administration site conditions		
Very Common	Fatigue[b,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.3
Common	Injection site reactions[c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.67
Rare	Angioedema	

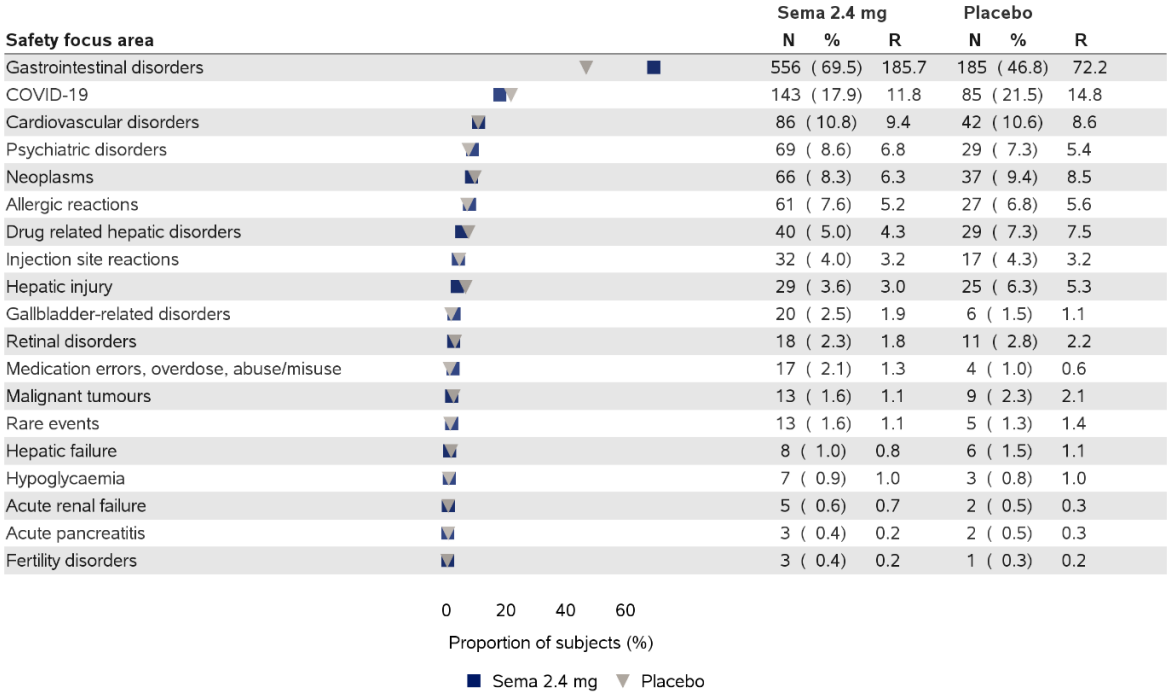
a) See description of selected adverse reactions below. b) Mainly seen in the dose-escalation period. c) Grouped preferred terms. d) From post-marketing reports with other marketed semaglutide products. e) Grouped term covering PTs Intestinal obstruction, ileus, small intestinal obstruction

During trial conduct, AEs were collected via investigator reporting and the investigator was to assess the AE with regards to relationship to trial product (probable, possible or unlikely). AEs for which a causal relation with semaglutide was judged by the investigator as at least a reasonable possibility, were proposed to be included in section 4.8 of the SmPC as Adverse Drug Reactions. In addition to AEs reported in pivotal study 4553 (ESSENCE) in the target population at the target dose of 2.4 mg once weekly that are judged as possibly or probably related to semaglutide, also ADRs reported in studies on Wegovy 2.4 mg once weekly in weight management are included in the listing of adverse events.

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Based on the therapeutic experience with GLP 1 RAs and regulatory feedback and requirements, safety focus areas were pre-defined as being of special interest in the evaluation of the safety of semaglutide 2.4 mg for MASH: Gastrointestinal disorders, Hepatic disorders, Gallbladder-related disorders, Acute pancreatitis, Cardiovascular disorders, Neoplasms, Acute renal failure, Hypoglycaemia, Retinal disorders, Immunogenicity, Psychiatric disorders, Rare events, Medication errors, drug abuse or misuse, and overdose, Suspected transmission of an infectious agent via trial product, COVID-19. Overall data from study 4553 on adverse events of interest based are presented in Figure 18.

Figure 18: Adverse events by safety focus areas - Incidence rate - summary plot - on-treatment - safety analysis set (interim)



%: Percentage of subjects with at least one event, N: Number of subjects with at least one event, R: Event rate (number of events per 100 PYE/PYO). Figure is sorted in descending order on percentage within Semaglutide 2.4 mg.

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5.4.4.1. Gastro-intestinal disorders

Gastrointestinal AEs are the most common adverse reactions reported with GLP-1 RAs, hence considered a class effect for all GLP-1 RAs. The precise mechanism remains unclear, but it involves an activation of the GLP-1 receptor. The frequency of gastrointestinal AEs is known to be dependent on the GLP-1 RA dose level, which may be mitigated by following the intended dose escalation scheme. MASH is closely associated with metabolic abnormalities, such as obesity, which appears to be associated with a higher frequency of certain gastrointestinal disorders e.g., upper abdominal pain, gastroesophageal reflux disease, diarrhoea, vomiting and haemorrhoids.

Gastrointestinal AEs are evaluated based on a pre-defined MedDRA search using the on-treatment observation period.

Study 4553

Gastrointestinal AEs were reported by a higher proportion of subjects and at higher event rates for semaglutide 2.4 mg (69.5%, 185.7 events per 100 PYE) compared to placebo (46.8%, 72.2 events per 100 PYE) (Table 34). The majority of gastrointestinal AEs were non-serious, and mild or moderate in severity. Overall, the majority of events were reported within the dose-escalation period. For events of nausea, most subjects reported their first event during the dose-escalation period; however, events of nausea were reported throughout the trial duration in the semaglutide 2.4 mg group. Nausea increased dose-dependently across the semaglutide groups, whereas no clear dose relationship was observed for diarrhoea, vomiting or constipation. Estimated median durations were comparable between semaglutide 2.4 mg and placebo for nausea, diarrhoea and vomiting, whereas for constipation, the median duration was longer with semaglutide 2.4 mg than with placebo. The majority of the AEs were reported as recovered or resolved and judged by the investigator to be either possibly or probably related to trial product. Gastrointestinal AEs were assessed as possibly or probably related to trial product for a larger proportion of subjects with semaglutide 2.4 mg compared to placebo (75.3% vs 36.5%).

Table 34: Gastrointestinal AEs – overview and most common PTs (⩾10%) – on treatment – SAS (interim) – trial 4553

	Semaglutide 2.4 mg			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	800			395		
Observation time (years)	1335.3			627.0		
All AEs	556 (69.5)	2479	185.7	185 (46.8)	453	72.2
SAEs	20 (2.5)	25	1.9	6 (1.5)	6	1.0
Severe AEs	16 (2.0)	24	1.8	3 (0.8)	3	0.5
Most common PTs						
Nausea	289 (36.1)	761	57.0	49 (12.4)	80	12.8
Diarrhoea	214 (26.8)	338	25.3	48 (12.2)	61	9.7
Constipation	177 (22.1)	213	16.0	31 (7.8)	37	5.9
Vomiting	148 (18.5)	218	16.3	22 (5.6)	25	4.0

N: number of subjects with at least one event; %: percentage of subjects with at least one event; E: number of events; R: events per 100 years of exposure; AE: adverse event; SAE: serious adverse event, PT: preferred term; SAS (interim): safety analysis set – all exposed subjects.

Most common PTs are defined as reported by ≥10% of subjects in one of the treatment groups.
Values for PYI (patient-years at risk of incident event) and I (incidence [number of incident events per 100 PYI]) are available in the TFL.

The most **common PTs** reported were nausea, diarrhoea, vomiting and constipation. AEs related to gastroparesis (PT: impaired gastric emptying) were reported by 8 subjects (1.0%, 9 events) with semaglutide 2.4 mg and 1 subject (0.3%, 1 event) with placebo. All but one of the events were non-serious, and all events were mild or moderate in severity. The outcomes for these events were reported as not resolved for 6 subjects with semaglutide 2.4 mg and for the one event with placebo. For pre-defined grouped PTs for abdominal pain, gastritis, and intestinal obstruction the proportions of subjects reporting events were comparable between semaglutide 2.4 mg and placebo. These grouped

PTs have previously been reported by a higher number of subjects with semaglutide 2.4 mg compared to placebo in the semaglutide 2.4 mg for weight management (Wegovy).

SAEs of gastrointestinal disorders were reported by 2.5% of subjects with semaglutide 2.4 mg and 1.5% of subjects with placebo, these were spread across multiple PTs.
The majority of AEs were reported during the dose escalation period; however, events of nausea were reported throughout the trial duration in the semaglutide 2.4 mg group.
The number of gastrointestinal AEs leading to **premature discontinuation** of trial product were low in both treatment groups, reported by 1.6% of subjects with semaglutide 2.4 mg and 0.5% of subjects with placebo.

Supportive studies

In study 4296, the proportion of subjects reporting gastrointestinal disorders ranged between 63.8%−76.9% in the semaglutide group versus 45.0% in the placebo group. The majority of gastrointestinal AEs were non-serious, and mild in severity. The most frequent PTs were nausea, diarrhoea, vomiting and constipation; all reported by greater proportions of subjects and at higher rates in the semaglutide groups than in the placebo group. The proportion of subjects who reported nausea increased dose-dependently across the semaglutide groups, whereas no clear dose relationship was observed for diarrhoea, vomiting or constipation.

5.4.4.2. Hepatic disorders

Hepatotoxicity and drug-induced liver injury (DILI) are important regulatory focus points for new drugs targeting MASH, hence hepatic disorders are assessed as a safety focus area. Marketed GLP-1 RAs are not known to be hepatotoxic and there have been no indications of treatment-related liver toxicity in the non-clinical toxicology studies with semaglutide. Semaglutide is metabolised by enzymes widely distributed throughout the body, with no single organ seen as responsible for the metabolism. The GLP-1 receptors have not been detected on liver cells.

AE evaluations are based on the in-trial period for trial 4553 and the on-treatment period for the clinical pharmacology and phase 2 trials. Event adjudication of selected AEs, including AEs related to hepatic decompensation, liver-induced MELD score ≥15 and potential DILI events is performed by an independent, blinded external event adjudication committee.

Definition of DILI. In general, liver injury is defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 x ULN and total bilirubin ≥2 x ULN where no alternative aetiology exists (Hy's law). In the clinical programme, for subjects with elevated AST and ALT levels at baseline potential DILI was defined by per protocol as AST/ALT>=2 or >=300 U/L).

Study 4553
In trial 4553 (interim evaluation), hepatic events were reported by comparable proportions of subjects and event rates for semaglutide 2.4 mg (5.0%, 4.3 events per 100 PYO) compared to placebo (7.8%, 7.6 events per 100 PYO) (Table 37). The majority of the events were non-serious and mild or moderate in severity. None of the events led to premature treatment discontinuation in the semaglutide 2.4 mg group. The most commonly reported PTs were related to elevated laboratory values, these were reported by a lower proportion of subjects with semaglutide 2.4 mg than with placebo, for ALT (0.4% and 2.0%, respectively) and AST (0.3% and 1.3%, respectively), and with comparable proportion of subjects across treatment groups for GGT (0.5% and 0.5%, respectively),

bilirubin (0.6% and 0.3%, respectively), INR (0.8% and 1.5%, respectively) and MELD score (0.3% and 0.5%,respectively).

Table 35: Hepatic events – overview and PTs ⩾1% – in trial – SAS (interim) – trial 4553

	Semaglutide 2.4 mg			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	800			395		
Observation time (years)	1373.3			667.5		
All AEs	40 (5.0)	59	4.3	31 (7.8)	51	7.6
SAEs	1 (0.1)	3	0.2	3 (0.8)	3	0.4
Severe AEs	2 (0.3)	4	0.3	2 (0.5)	2	0.3
PTs ≥1%						
INR increased [b]	6 (0.8)	6	0.4	6 (1.5)	8	1.2
ALT increased [b]	3 (0.4)	4	0.3	8 (2.0)	8	1.2
AST increased [b]	2 (0.3)	2	0.1	5 (1.3)	6	0.9

N: number of subjects with at least one event; %: percentage of subjects with at least one event; E: number of events; R: events per 100 years of observation; AE: adverse event; SAE: serious adverse event, PT: preferred term; INR: international normalised ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAS (interim): safety analysis set – all exposed subjects.

a: Based on MedDRA search: drug related hepatic disorders. Data from the overlapping MedDRA searches, hepatic injury and hepatic failure are available in the CSR.

b: Abbreviated PT names.

PTs ≥1% includes PTs reported by ≥1% of subjects in any of the treatment groups.
Values for PYI (patient-years at risk of incident event) and I (incidence [number of incident events per 100 PYI]) are available in the TFL.

SAEs related to hepatic disorders were reported by 4 subjects, 1 subject was in the semaglutide 2.4 mg group (SAE of elevated GGT with liver-biopsy confirmed diagnosis of autoimmune hepatitis) and 3 subjects in the placebo group (and one case of elevated liver function test due to alcoholic liver disease).

Hepatic disorders based on liver-related laboratory parameters. At baseline, a large proportion of subjects had elevated levels of ALT (56% on semaglutide vs 56.4% on placebo) and/or AST (76.5% vs 77%). ALT and AST values decreased from baseline to week 72 in both treatment groups (Table 38). The reductions were greater with semaglutide 2.4 mg than with placebo and occurred within the first 36 weeks. The mean level of ALP decreased from baseline to week 72 in the semaglutide 2.4 mg group, with no change in the placebo group. Mean values of total bilirubin, albumin and INR, and MELD score remained stable over time in both treatment groups.

Table 36: Liver-related laboratory parameters – baseline and ratio to baseline values at week 72 – on treatment – SAS (interim) trial 4553

	Sema 2.4 mg OW	Placebo
Number of subjects[a]	Baseline: 798-800 Week 72: 472-486	Baseline: 395 Week 72: 221-223
Alanine aminotransferase (U/L)		
Baseline	55.2 (64.5)	55.3 (65.6)
Ratio to baseline at week 72	0.5 (67.8)	0.8 (61.0)
Albumin (g/dL)		
Baseline	4.4 (6.7)	4.4 (7.2)
Ratio to baseline at week 72	1.0 (5.5)	1.0 (5.9)
Alkaline phosphatase (U/L)		
Baseline	82.6 (33.0)	82.3 (33.6)
Ratio to baseline at week 72	0.9 (21.1)	1.0 (19.0)
Amylase (U/L)		
Baseline	54.5 (42.5)	53.8 (40.8)
Ratio to baseline at week 72	1.1 (26.7)	1.0 (18.8)
Aspartate aminotransferase (U/L)		
Baseline	45.8 (52.2)	45.3 (53.6)
Ratio to baseline at week 72	0.5 (55.2)	0.9 (54.5)
Creatinine (µmol/L)		
Baseline	65.3 (25.8)	65.1 (23.6)
Ratio to baseline at week 72	1.0 (12.7)	1.0 (12.3)
eGFR (mL/min/1.73m^2)[a]		
Baseline	93.11 (21.15)	95.27 (19.15)
Ratio to baseline at week 72	0.98 (11.05)	0.99 (9.60)
Ferritin serum (µg/L)		
Baseline	142.92 (148.76)	135.38 (144.82)
Ratio to baseline at week 72	0.67 (70.25)	0.78 (79.20)
INR (ratio)		
Baseline	1.1 (10.6)	1.1 (12.6)
Ratio to baseline at week 72	1.0 (13.1)	1.0 (15.7)
Lipase (U/L)		
Baseline	33.1 (63.6)	31.5 (60.2)
Ratio to baseline at week 72	1.4 (43.8)	1.0 (35.8)
Potassium (mmol/L)		
Baseline	4.2 (8.9)	4.2 (8.7)
Ratio to baseline at week 72	1.0 (8.8)	1.0 (10.2)
Sodium (mmol/L)		
Baseline	140.0 (1.8)	140.2 (1.5)
Ratio to baseline at week 72	1.0 (1.9)	1.0 (1.7)

Total Bilirubin (mg/dL)		
Baseline	0.61 (45.24)	0.60 (48.02)
Ratio to baseline at week 72	1.01 (36.79)	1.03 (37.53)
MELD score (no unit)[b]		
Baseline	7.2 (1.6)	7.2 (1.7)
Change from baseline at week 72	-0.1 (1.8)	0.0 (1.8)

Overall, the proportions of subjects who had abnormal liver values during the trial were comparable between the semaglutide 2.4 mg group and the placebo group.

Table 37: Abnormal values - categorical summary - on-treatment - safety analysis set (interim)

	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	800	395
Alanine Aminotransferase in Serum (U/L)		
>8x ULN	*	*
>3x ULN where TBL > (2 x ULN)	0 (0)	0 (0.0)
>5x baseline where baseline < (2 x ULN)	1 (0.1)	2 (0.5)
>3x baseline or >300 where baseline >= (2 x ULN) and baseline < (5 x ULN)	1 (0.1)	1 (0.3)
>3x ULN where signs and symptom(s) compatible with DILI*	2 (0.3)	1 (0.3)
>5x ULN	4 (0.5)	3 (0.8)
Aspartate Aminotransferase in Serum (U/L)		
>8x ULN	0 (0.0)	0 (0.0)
>3x ULN where TBL > (2 x ULN)	*	*
>5x baseline where baseline < (2 x ULN)	*	*
>3x baseline or >300 where baseline >= (2 x ULN) and baseline < (5 x ULN)	0 (0.0)	0 (0.0)
>3x ULN where signs and symptom(s) compatible with DILI*	3 (0.4)	2 (0.5)
>5x ULN	6 (0.8)	5 (1.3)
Total Bilirubin in Serum (mg/dL)		
>2.0	21 (2.6)	6 (1.5)
INR in Plasma (ratio)		
>1.5	23 (2.9)	12 (3.0)
MELD Score (no unit)		
>=15	19 (2.4)	12 (3.0)

%: Percentage of subjects, DILI: Drug induced liver injury, INR: International normalized ratio, MELD: Model For End-Stage Liver Disease, N:
Number of subjects, TBL: Total bilirubin, ULN: Upper limit of normal range. *: such as fatigue, nausea, vomiting, abdominal pain/tenderness,
fever, rash pruritus, jaundice/icterus, altered mental state. Data include post-baseline laboratory values from the central laboratory
(scheduled and unscheduled visits), including subjects with elevated levels at baseline. The thresholds presented in this table were used ascriteria for drug discontinuation based on elevated liver enzymes until updated in Protocol v. 7 (May 2021).
* information removed to avoid unblinding

Drug-Induced-Liver-Injury. Per protocol definition there were no cases of Hy's law. One (1) case of biochemical Hy's law (AST ≥3×ULN + TBL ≥2×ULN) was identified based on data from an unscheduled visit. However, this subject had elevated AST and ALT levels at baseline and therefore did not fulfil the per protocol defined cutoff for potential drug-induced liver injury for subjects with elevated levels at baseline (AST/ALT ≥2x baseline level or ≥300 U/L with concurrent total bilirubin ≥2xULN). Throughout the trial normal fluctuations in liver-related values were observed for the subject and values normalised under treatment without any changes to trial product.

Supportive studies

Study 4296 The proportion of subjects reporting hepatic events ranged between 7.7% and 11.3% in the semaglutide groups versus 13.8% in the placebo group. All reported hepatic events were non serious and mild or moderate in severity. For the majority of events the outcome was reported as resolved. Overall, the events were distributed across multiple PTs (mainly blood bilirubin increased, hepatic enzyme increased, and INR increased) with few events reported for each PT. Only increased blood bilirubin was reported by a slightly higher proportion of subjects in the semaglutide 0.1 mg (3.8%) and 0.4 mg (3.7%) groups (no events in 0.2 mg group) than in the placebo group (1.3%). One (1) subject (in the semaglutide 0.2 mg group) had 1 event of the PT hepatitis acute that led to premature treatment discontinuation. Two events led to treatment discontinuation in the placebo group. The proportions of subjects who had abnormal liver values during the trial were generally lower in the semaglutide groups than in the placebo group, and no cases fulfilling biochemical Hy's Law were identified.

Study 4492 In this study in subjects with biopsy-defined MASH and compensated cirrhosis (F4c), a total of 10 hepatic events in 6 subjects were reported: 9 events in 5 subjects in the semaglutide group (2 cased of ascites, in one case after study treatment discontinuation, and single cases of increased bilirubin, AST, ALT, GGT, MELD score increased to 12, portal hypertensive gastropathy and oesphageal varices) and 1 event in the placebo group (hepatic lesion following liver biopsy). All of the events were non serious, and mild or moderate in severity. None of the events led to premature treatment discontinuation. Mean values for the liver enzymes ALT and AST decreased from baseline to week 48 in the semaglutide 2.4 mg group and remained stable in the placebo group. No cases of biochemical Hy's Law were identified.

Study 4381 A total of 7 hepatic events were reported: 2 events in one subject in the semaglutide 0.4 mg group, and 5 events in 4 subjects in the placebo group. All events were non serious and mild in severity, and the outcome was reported as recovered/recovering for all subjects. All reported events were related to elevated liver parameters (ALT, AST or INR). Mean values for the liver parameters AST, ALT and GGT were assessed as efficacy parameters, these all decreased more with semaglutide 2.4 mg compared to placebo.

5.4.4.3. Gall-bladder related disorders

Gallbladder-related disorders such as gallstones (cholelithiasis) are associated with metabolic risk factors, including NAFLD, with a bidirectional relationship between the incidence of NAFLD and gallstones. Additional risk factors include obesity (especially central obesity, which is closely related to MASH), female gender, and rapid and large weight loss. Gallstones may lead to complications such as cholecystitis and acute pancreatitis. GLP-1 RA treatment has been associated with increased risks of gallbladder or biliary diseases. The risk was dose dependent and increased with longer duration of GLP-1 RA use. Acute gallstone disease (cholelithiasis) is considered a class risk for GLP-1 RA products.

Study 4553

In trial 4553 (interim evaluation), AEs of the known risk, gallbladder-related disorders, were reported by 2.5% of subjects with semaglutide 2.4 mg (1.9 events per 100 PYE) compared to 1.5% of subjects with placebo (1.1 events per 100 PYE). This was consistent with previous trials with semaglutide 2.4 mg (Wegovy). The majority of events were non-serious, mild in severity and unlikely related to trial product. Approximately 2/3 of the events in the semaglutide 2.4 mg group and half of the events in the placebo group were resolved or resolving. None of the events led to premature trial product discontinuation

The most frequently reported PT was cholelithiasis, which was reported by 1.4% of subjects with semaglutide 2.4 mg and 0.8% of subjects with placebo. Five (5) subjects in the semaglutide 2.4 mg group and 1 subject in the placebo group reported blood bilirubin increased. The remaining events were distributed across multiple PTs with single events reported for each.

Events of *symptomatic acute gallbladder disease* were reported in 5 subjects with a total of 6 events in the semaglutide 2.4 group and 2 subjects with a total of 3 events in the placebo group. A total of 3 SAEs (PTs cholangitis acute, cholecystitis and cholelithiasis) were reported by 2 subjects, 1 in each treatment group. All 3 events resolved.

Supportive studies

Study 4296 The proportion of subjects reporting gallbladder-related disorders ranged between 5.1%-7.4% in the semaglutide groups versus 2.5% in the placebo group. The majority of the events were non-serious and mild or moderate in severity. Approximately half of the events were judged by the investigator as unlikely related to trial product. The most frequently reported gallbladder-related AE was blood bilirubin increased. In total, 5 SAEs were reported by 3 subjects, all in the semaglutide groups; of these, 1 led to treatment discontinuation, the other 4 led to treatment interruption.

5.4.4.4. Acute pancreatitis

Acute pancreatitis is considered a class risk associated with the use of GLP-1 RA, and subjects with a history pancreatitis or with recent acute pancreatitis were excluded from participating in the trials. In addition, trial product was to be discontinued in case of suspicion of acute pancreatitis during trial conduct. Increases in amylase and lipase levels are well known from GLP-1 RAs including semaglutide. The exact mechanism behind this observation is at present unknown but may be attributed to the pharmacological effects of GLP-1 RAs on the pancreatic acini.

Study 4553

In trial 4553 (interim evaluation), there were few AEs related to acute pancreatitis. AEs of acute pancreatitis were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (0.4%, 0.2 events per 100 PYE) compared to placebo (0.5%, 0.3 events per 100 PYE). One event was moderate, the rest were mild in severity. All events resolved. Reported PTs were either pancreatitis acute or pancreatitis.

In total, 3 SAEs (all PT pancreatitis acute) were reported, 2 in the semaglutide 2.4 mg group and 1 in the placebo group. All 3 events were considered possibly related to trial product and led to either trial product discontinuation or interruption. All 3 events resolved.

Pancreatic enzymes. Amylase and lipase levels increased from baseline to week 72 with semaglutide 2.4 mg. The increase was most pronounced during the first 12 weeks. There was no change from baseline in the placebo group.

For amylase increased few events were reported and the proportion of subjects reporting events as well as event rates were comparable between semaglutide 2.4 mg (0.8%, 0.6 events per 100 PYE) and placebo (0.5%, 0.3 events per 100 PYE). All were non serious, and the majority were mild in severity. For increased lipase, the proportion of subjects reporting events and event rates were higher for semaglutide 2.4 mg (2.5%, 1.8 events per 100 PYE) compared to placebo (1.3%, 0.9 events per 100 PYE). One (1) SAE, moderate in severity, considered possibly related to trial product and leading to dose interruption was reported. No acute complications, pancreatitis or other pancreas issues were present. The event resolved, with no recurrence reported.

Supportive studies

In **study 4296**, no events related to pancreatitis were reported. Amylase and lipase levels increased from baseline to week 72 in all semaglutide groups. The increase was greater in the semaglutide groups compared to placebo.

5.4.4.5. Cardiovascular disorders

There is a strong association between NAFLD/MASH and increased CV risk with CVD being the overall most frequent complication. NAFLD/MASH and CVD share several cardiometabolic risk factors, including obesity, T2D, metabolic syndrome, hypertension, dyslipidaemia, and chronic kidney disease (CKD). The effect of semaglutide 2.4 mg on the risk of MACE was investigated in CVOT EX9536-4388, that included a prespecified analysis of the subpopulation at risk of MASH (see section 5.3.5 Supportive studies). Drugs of the GLP-1 RA class are known to increase pulse rate. In contrast, SBP is decreased by some GLP-1 RA including semaglutide, as observed for semaglutide s.c. for weight management and T2D oral semaglutide for T2D and in subjects with established CVD.

Study 4553

AEs of cardiovascular disorders were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (10.9%, 9.2 events per 100 PYO) compared to placebo (11.4%, 9.0 events per 100 PYO) (Table 40). The majority of the events were non-serious and mild or moderate in severity. Cardiovascular AEs leading to premature treatment discontinuation were reported by 2 subjects in each treatment group. The AEs were distributed across multiple SOCs and PTs, PTs reported by ≥1% of subjects are listed in Table 40. The majority of subjects reported the AEs as recovered or not recovered. In total, 3 subjects died of AEs related to cardiovascular disorders, these were all in the placebo group.

SAEs of cardiovascular disorders were reported by comparable proportions of subjects in both treatment groups (semaglutide 2.4 mg: 2.9%; placebo: 2.8%), these SAEs were spread across multiple PTs.

Table 38: Cardiovascular disorders – overview and PTs ⩾1% – in trial – SAS (interim) – trial 4553

	Semaglutide 2.4 mg			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	800			395		
Observation time (years)	1373.3			667.5		
All AEs	87 (10.9)	127	9.2	45 (11.4)	60	9.0
SAEs	23 (2.9)	26	1.9	11 (2.8)	13	1.9
Severe AEs	15 (1.9)	17	1.2	6 (1.5)	8	1.2
Fatal AEs	0 (0.0)	0	0	3 (0.8)	4	0.6
PTs ≥1%						
Chest pain	12 (1.5)	13	0.9	4 (1.0)	4	0.6
Palpitations	10 (1.3)	13	0.9	4 (1.0)	4	0.6
Dyspnoea	6 (0.8)	6	0.4	5 (1.3)	5	0.7
Angina pectoris	*	*	*	*	*	*

N: number of subjects with at least one event; %: percentage of subjects with at least one event; E: number of events; R: events per 100 years of observation; AE: adverse event; SAE: serious adverse event, PT: preferred term; SAS (interim): safety analysis set – all exposed subjects.

PTs ≥1% includes PTs reported by ≥1% of subjects in any of the treatment groups.
Values for PYI (patient-years at risk of incident event) and I (incidence [number of incident events per 100 PYI]) are available in the TFL.

* information removed to avoid unblinding

The proportion of subjects reporting events of pre-defined grouped PT *increased heart rate* were comparable between semaglutide 2.4 mg (0.8%) and placebo (1.3%). All of these events were non-serious, mild or moderate in severity. The majority of events were reported as resolved or not resolved, and none of the events led to a change in trial product.

Cardiovascular disorders based on event adjudication. Events of acute coronary syndrome, cerebrovascular events and heart failure requiring hospitalisation were assessed by an independent EAC. Three (3) deaths were reported as due to AEs of cardiovascular disorders.

Pulse rate. The mean pulse rate at baseline was 75 beats/min in the semaglutide 2.4 mg group and 74 beats/min in the placebo group. Mean (SD) change from baseline at week 72 was 2 (10) beats/min with semaglutide 2.4 mg and no change for placebo. The proportion of subjects with increase of pulse >= 10 beats/min on at least one occasion was comparable for both treatment arms (n=345; 43.1% vs n=198; 50.1%).

Blood pressure. Blood pressure assessments (SBP and DBP) are evaluated using the FAS (interim). Overall, baseline levels of mean SBP and DBP were within the normal ranges and comparable across treatment groups. Change from baseline to week 72 showed reduction of the (mean) SBP in both treatment groups, with a greater reduction in the semaglutide 2.4 mg group than in the placebo group (-5.39 mmHg vs 1.39 mmHg). No relevant changes were seen for DBP (-1.90 mmHg vs 0.24 mmHg).

Supportive studies

Study 4296 A total of 4 AEs in 3 subjects (2 subjects in the semaglutide 0.2 mg group and 1 subject in the 0.4 mg group) were classified as cardiovascular events based on event adjudication. Of these, there was 1 event of ischaemic stroke considered non-serious and mild, with the outcome resolved and judged as unlikely related to trial product. Further, 2 events of transient ischemic attack were seen in 1 subject. Of these, 1 was considered mild and 1 moderate and both considered resolved. Further, both events were judged as possibly related to trial product and drug was interrupted. Finally, there was 1 event of sudden cardiac death in the semaglutide 0.2 mg considered unlikely related to trial product. In trial 4296, there were no statistically significant or clinically meaningful changes in pulse rate versus placebo at week 72.

5.4.4.6. Neoplasms

Subjects with MASLD/MASH have a higher risk of developing cancer, especially hepatic cancer. The higher risk of cancer seems to be partially linked to the metabolic dysfunction and comorbidities often related to MASH, such as obesity and T2D. To mitigate the risk of carcinomas in the trials, subjects were not eligible for inclusion if they had presence or history within the past 5 years prior to screening of malignant neoplasms other than hepatocellular carcinoma, personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma (MTC), or presence or history of hepatocellular carcinoma at randomisation (only trials 4553 and 4492).

Study 4553

In trial 4553 (interim evaluation), AEs of neoplasms (benign and malignant) were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (8.5%, 6.3 events per 100 PYO) compared to placebo (9.9%, 8.4 events per 100 PYO). The majority of events were non-serious, mild in severity and unlikely related to trial product. Two (2) events in 2 subjects in the semaglutide 2.4 mg group and 3 events in 3 subjects in the placebo group led to premature trial product discontinuation.

The most frequently reported PTs were renal cyst, large intestine polyp and colorectal adenoma. Renal cysts were reported by more subjects in the semaglutide 2.4 mg group (1.6%) compared to placebo (0.5%). The majority of subjects reporting renal cysts in the semaglutide 2.4 mg group co-reported gastrointestinal AEs or other AEs (e.g. musculoskeletal disorders) that could lead to imaging and thereby incidental findings of renal cysts. The remaining AEs were distributed across multiple PTs with few events reported for each PT and with no notable pattern with respect to organ system of origin or distribution between the treatment groups.

The proportions of subjects with SAEs were comparable with semaglutide 2.4 mg (2.3%) and placebo (2.8%). The SAEs were distributed across multiple PTs with few events (1−3) reported for each PT. Of the subjects with SAEs, 3 subjects (1 in the semaglutide 2.4 mg group and 2 in the placebo group) had events with fatal outcome.

Malignant neoplasms based on AEs. AEs of malignant neoplasms were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (1.8%, 1.2 events per 100 PYO) compared to placebo (2.5%, 2.1 events per 100 PYO). The majority of events were severe and/or serious. In each group, 1 event was considered possibly related to trial product. The remaining events were unlikely related to trial product. Two (2) events in the semaglutide 2.4 mg group and 1 event in the placebo group led to premature trial product discontinuation. Overall, AEs were distributed across multiple PTs with few events (1−2) reported for each PT. Approximately 1/3 of the events reported were different PTs of skin neoplasms (4 events in the semaglutide 2.4 mg group versus 7 events in the

placebo group). The remaining events showed no clustering of specific PTs. One (1) subject in the semaglutide 2.4 mg group and 2 subjects in the placebo group had events with fatal outcomes.

Supportive studies
In trial 4296 (dosing: 0.1 mg/day, 0.2 mg/day or 0.4 mg/day in 80, 78 and 81 subjects, respectively) neoplasms formed in 12.5%; 14.1% and 17.5 % of subjects, respectively. In the placebo group (80 subjects) neoplasms formed in 7.5 % of subjects. Gastrointestinal (sema 0.1mg: 1 subject (1.3%), sema 0.2 mg: 4 subjects (5.1%), sema 0.4 mg: 5 subjects (6.2%) vs placebo: 0) and hepatobiliary neoplasms (sema 0.1mg: 0, sema 0.2 mg: 1 subjects (1.3%), sema 0.4 mg: 2 subjects (2.5%) vs placebo: 0) were reported at higher frequency at higher semaglutide dose. Renal cysts don't show dose-dependency (sema 0.1mg: 3 subject (3.8%), sema 0.2 mg: 1 subject (1.3%), sema 0.4 mg: 0, placebo: 1 (1.3%).

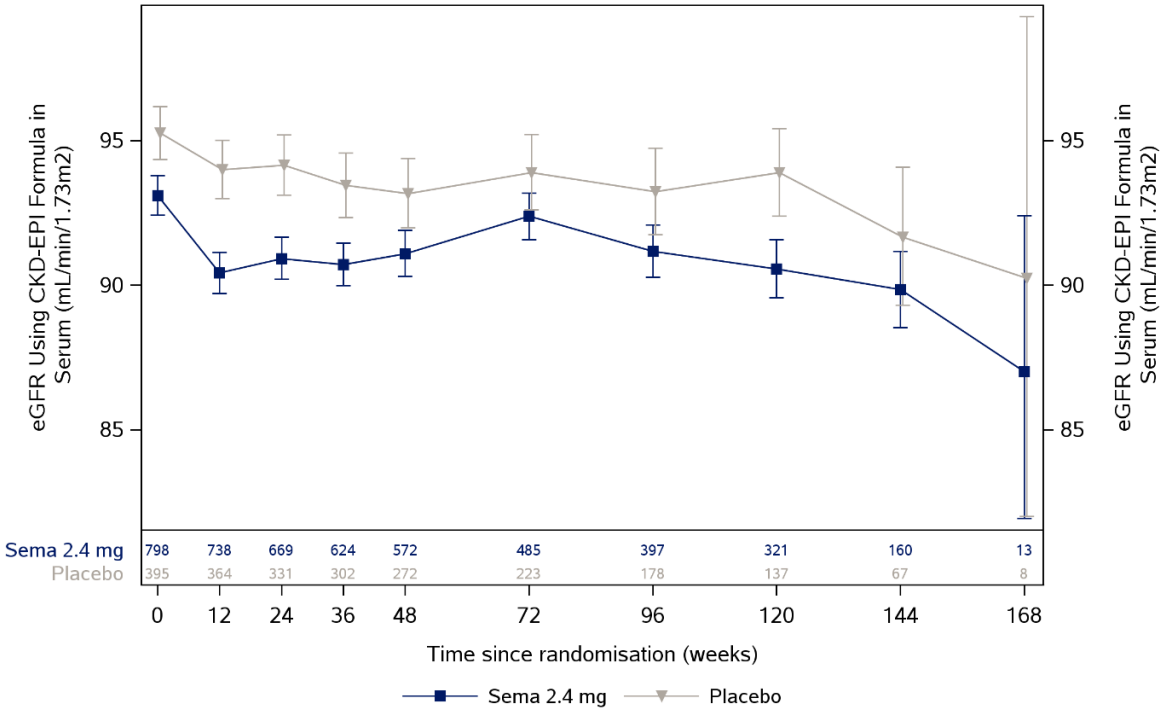
5.4.4.7. Acute renal failure

Gastrointestinal side effects associated with GLP-1 RA may cause dehydration, which in rare cases can lead to a deterioration of renal function. MASH and obesity are linked to an increased risk of developing chronic kidney disease (CKD), which could cause increased vulnerability in case of dehydration. To mitigate the risk of acute renal failure, subjects were not eligible for inclusion in any of the trials if they had eGFR < 30 ml/min/1.73 m^2.

Study 4553
AEs of acute renal failure were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (0.6%, 0.7 events per 100 PYE) compared to placebo (0.5%, 0.3 events per 100 PYE). The majority of AEs related to acute renal failure were non-serious, mild or moderate in severity and unlikely related to trial product. More than half of the events resolved. One (1) subject had 1 event leading to premature trial product discontinuation. AEs were distributed across the PTs acute kidney injury, renal failure, azotaemia, renal impairment. With 4 events reported by 3 subjects in the semaglutide 2.4 mg group and 1 event reported by 1 subject in the placebo group, acute kidney injury was the most frequently reported PT.
Two (2) subjects, reported a total of 3 SAEs (azotaemia, acute kidney injury and renal failure). One (1) event led to premature trial product discontinuation and 2 events to temporary discontinuation.

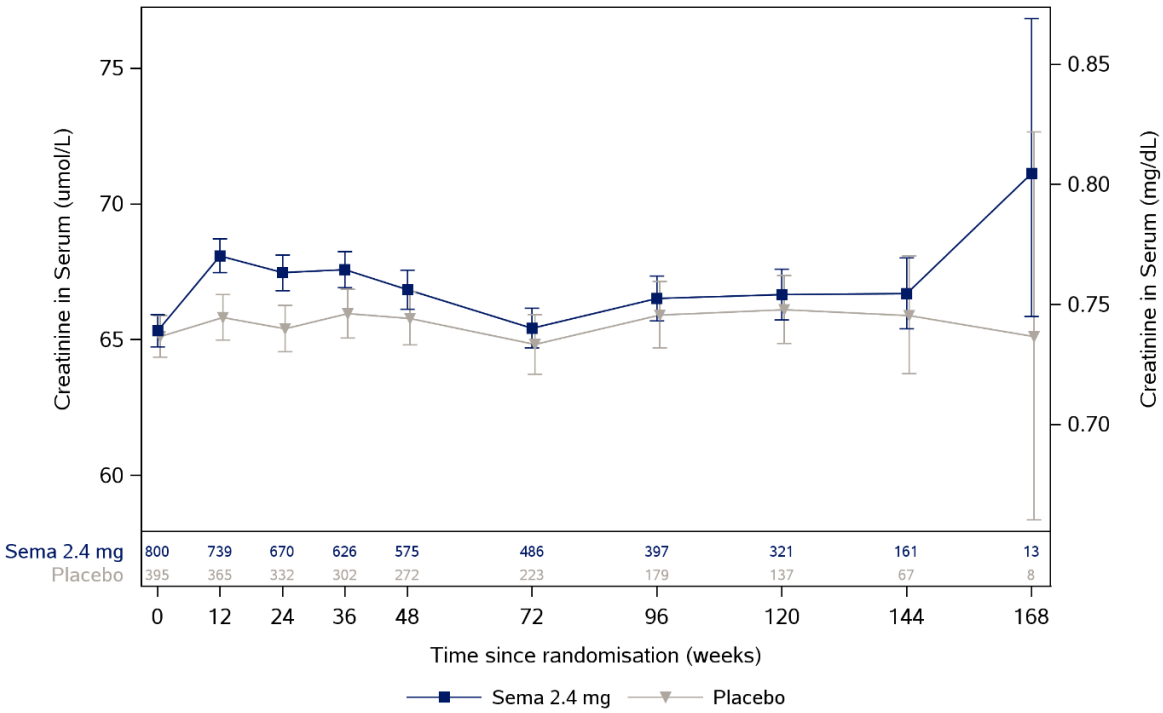
eGFR and creatinine. Mean eGFR values decreased slightly during the first 12 weeks. At week 72 (interim), there was no change compared to baseline. There was no difference in mean eGFR values for semaglutide 2.4 mg compared to placebo (Figure 19). Mean creatinine values increased slightly for semaglutide 2.4 mg during the first 12 weeks, after which values stabilised and then slowly decreased towards baseline values. At week 72 (interim), there was no change compared to baseline and no difference compared to placebo. No change in creatinine values was seen for placebo.

Figure 19: eGFR (per CKD-EPI formula) (left) and Creatinine (right) - by week - geometric mean plot - on-treatment - safety analysis set (interim)



Numbers shown in the lower panel represent number of subjects contributing to the summary. Observed mean +/- standard error of the mean calculated on log-scale and back-transformed to original scale. The normal range is >= 90 (mL/min/1.73m2).

nn9931/nn9931-submission-level1/20250115_4553_csr_er
29JAN2025:16:48:53 - fmean.sas/fmeanegfr.png



Numbers shown in the lower panel represent number of subjects contributing to the summary. Observed mean +/- standard error of the mean calculated on log-scale and back-transformed to original scale. The normal ranges are 49 to 90 (umol/L) for females and 64 to 104 (umol/L) for males.

nn9931/nn9931-submission-level1/20250115_4553_csr_er
29JAN2025:16:48:41 - fmean.sas/fmeancreat.png

Supportive studies

Study 4296 Within the SOC Renal and urinary disorders, a total of 6 events with PTs renal impairment, acute kidney injury or renal failure were identified, 4 (1.7%) events in subjects on semaglutide (n=1, n=2, and n=1 on semaglutide 0.1 mg, 0.2 mg and 0.4 mg OD) and 2 (2.5%) events on placebo. Two (2) events of acute kidney injury, both in the semaglutide 0.2 mg group, were considered SAEs and led to temporary discontinuation of trial product. In addition, one of these events were considered severe. All other events were mild or moderate in severity.

5.4.4.8. Hypoglycaemia

During conduct of trial 4553, non-serious events of hypoglycaemia occurring in subjects with T2D, were not to be recorded as AEs, but using the hypoglycaemic-episodes form only, whereas serious episodes were to be reported as SAEs. For subjects without T2D, blood glucose was not monitored, any events of hypoglycaemia were to be reported as AEs only. For trial 4553, hypoglycaemic episodes reported by subjects with T2D are categorised as level 1−3 according to the ADA 2023 classification (Table 41). For subjects without T2D, AEs of hypoglycaemia are evaluated based on a predefined MedDRA search.

Table 39: Classification of hypoglycaemia – subjects with T2D – trial 4553

Level	Glycaemic criteria	Description
Hypoglycaemia alert value (level 1)	<3.9 mmol/L (70 mg/dL) and ≥3.0 mmol/L (54 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycaemia (level 2)	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (level 3)	No specific glucose threshold	A severe event characterised by altered mental and/or physical functioning that requires assistance from another person for recovery.

T2D: type 2 diabetes.

In trial 4296, hypoglycaemic episodes reported by subjects with T2D are evaluated using the ADA 2013 classification and further evaluated as 'severe or blood glucose (BG) confirmed symptomatic hypoglycaemia' based on the Novo Nordisk classification (Table 40).

Table 40: NN classification of hypoglycaemia – subjects with T2D – trial 4296

Classification	Glycaemic criteria
Severe or BG confirmed symptomatic hypoglycaemia:	Severe according to the ADA classification [a] *or* BG confirmed by a plasma glucose value <3.1 mmol/L (56 mg/dL) with symptoms, consistent with hypoglycaemia

a: Severe hypoglycaemia according to the ADA 2013 classification: plasma glucose ≤3.9 mmol/L (70 mg/dL); or alleviation of symptoms; or seizure, coma or fatal.
ADA: American Diabetes Association; BG: blood glucose

Study 4553

The proportion of subjects with T2D at baseline reporting hypoglycaemic episodes was higher with semaglutide 2.4 mg (19.3%, 39.6 events per 100 PYE) compared to placebo (13.1%, 51.3 events per 100 PYE) whereas event rates were higher in the placebo group (Table 41). In both groups a few subjects reported multiple events, which impacted the event rates.

Table 41: Hypoglycaemic episodes – on treatment – subjects with T2D at baseline – SAS (interim) – trial 4553

	Semaglutide 2.4 mg			Placebo		
	N (%)	E	R	N (%)	E	R
Number of subjects	446			222		
Observation time (years)	749.3			355.1		
All episodes	86 (19.3)	297	39.6	29 (13.1)	182	51.3
Hypoglycaemia alert value (level 1)	62 (13.9)	157	21.0	20 (9.0)	120	33.8
Clinically significant hypoglycaemia (level 2)	27 (6.1)	51	6.8	11 (5.0)	42	11.8
Severe hypoglycaemia (level 3)	10 (2.2)	11	1.5	1 (0.5)	1	0.3
Level 2 or 3	33 (7.4)	62	8.3	12 (5.4)	43	12.1

N: number of subjects with at least one event; %: percentage of subjects with at least one event; E: number of events; R: events per 100 years of exposure; AE: adverse event; SAE: serious adverse event; PT: preferred term; SAS (interim): safety analysis set – all exposed subjects.

Values for PYI (patient-years at risk of incident event) and I (incidence [number of incident events per 100 PYI]) are available in the CSR.

Hypoglycaemic episodes are categorised according to the ADA 2023 classification.

Based on the ADA 2023 classification, the majority of episodes were level 1. Hypoglycaemic episodes of level 2 or 3 (combined) were reported by 7.4% of the subjects with semaglutide 2.4 mg and 5.4% with placebo. Of the subjects experiencing level 2 or 3 hypoglycaemic episodes, approximately half in the semaglutide 2.4 mg group and 2/3 in the placebo group were treated with sulfonylureas and/or insulin at the time of the episode. For most of the subjects potential contributing factors (e.g., treatment with insulin or sulfonylureas or changes in diet or missed meals) were present. Two (2) subjects needed IV glucose treatment. For half of the events, plasma-glucose values were >3.0 mmol/L (54 mg/dL).

Episodes of severe hypoglycaemia (level 3) were reported by 2.2% (corresponding to 10 subjects) in the semaglutide 2.4 mg group and 0.5% (corresponding to 1 subject) in the placebo group, requiring IV treatment in 2 out of 11 subjects . The frequency of severe hypoglycaemia on semaglutide 2.4 mg in study 4553 is higher than previously seen with for subjects with T2D in semaglutide 2.4 mg for weight management, with only 1 severe event of hypoglycaemia reported (0.2% of subjects, 0.002 events/patient year).

Hypoglycaemia based on AEs. Of subjects *without T2D*, 1 subject in each treatment group reported 1 event of hypoglycaemia. Both events were non-serious and mild in severity, resolved and did not lead to premature trial product discontinuation.

Onset of T2D during trial 4553. A total of 11 subjects in the semaglutide 2.4 mg group and 18 subjects in the placebo group had onset of T2D during trial 4553.

Supportive studies

Study 4296 The subpopulation of *subjects with T2D* comprised 62.2% of the total population. A higher proportion of subjects with T2D reported hypoglycaemic episodes in the semaglutide 0.1 mg and 0.4 mg groups than in the placebo group, with no dose-relationship across the semaglutide groups. In the semaglutide groups, 5.9% to 10.2% of the subjects reported severe or BG confirmed symptomatic episodes (Novo Nordisk classification) versus 4.0% in the placebo group.

Based on the ADA 2013 classification, documented symptomatic episodes accounted for the majority of the hypoglycaemic episodes, and occurred in the highest proportion of subjects and at the highest rates in the semaglutide 0.4 mg group. A total of 4 severe episodes (none in the semaglutide 0.4 mg group) and 15 probable symptomatic episodes were reported in the semaglutide groups.

5.4.4.9. Retinal disorders

Diabetic retinopathy is a common microvascular complication of diabetes. Rapid improvements in glycaemic control may be associated with an initial worsening of diabetic retinopathy. This risk has especially been seen in patients with long-standing diabetes, poor glycaemic control, rapid or large drop in HbA1c and pre-existing diabetic retinopathy. Complications of diabetic retinopathy is a known risk with treatment of semaglutide for patients with T2D, hence subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from all the trials. In trial 4553, the risk of retinal disorders is evaluated based on a pre-defined MedDRA search, data from event specific form, and eye-examinations that were performed during trial conduct for subjects with T2D. The evaluation is based on the in-trial observation period, due to the potential long latency between onset and diagnosis.

Study 4553

In trial 4553 (interim evaluation), for subjects with T2D at baseline AEs of retinal disorders were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (3.1%, 2.6 events per 100 PYO) compared to placebo (4.1%, 3.2 events per 100 PYO). One (1) event in each group was moderate in severity, the rest of the reported AEs were mild. The majority of events were not resolved. All AEs were considered unlikely related to trial product, and none led to treatment discontinuation. The most frequently reported PT was diabetic retinopathy with 5 subjects in the semaglutide 2.4 mg group reporting a total of 7 events and 3 subjects in the placebo group reporting a total of 3 events. The remaining AEs were distributed across multiple PTs with few events reported for each. One (1) SAE of age-related macular degeneration was reported. The event was moderate in severity and not resolved. It was considered unlikely related to trial product and did not lead to premature trial product discontinuation.

A total of 12 AEs reported by 10 subjects and deemed due to a new onset or worsening of diabetic retinopathy had additional data collection. All events were non-serious, mild and non-proliferative, with no worsening in visual acuity and did not require treatment.

Supportive studies

Study 4296 The number of subjects reporting events of retinal disorders was 1 (1.3%), 3 (3.8%) and 1 (1.2%) on semaglutide 0.1 mg, 0.2 mg, and 0.4 mg, respectively, and was 1.3% in the placebo group. No serious adverse events were reported. Two (2) subjects in the semaglutide 0.2 mg group had 1 event each of diabetic retinopathy, the rest of the events comprised retinal artery occlusion,

visual impairment and vitreous floaters. All of the events were non-serious, none led to treatment discontinuation, and all were mild in severity. All of the events were judged by the investigator as unlikely related to trial product.

5.4.4.10. Immunogenicity

The risk of immunogenicity is evaluated based on assessments of anti-semaglutide antibodies at selected site visits. Furthermore, immunogenicity is evaluated by two pre-defined MedDRA searches, allergic reactions and injection site reactions based on the on-treatment observation period.

Antibodies

An overview of the ADA incidences and impact on efficacy and safety for the marketed GLP-1 RA products based on human GLP-1 are presented in Table 42. All marketed analogues of human GLP-1 have similar and low incidences of ADA development (below 10%). The ADAs are of a low titre, few are cross-reactive to endogenous GLP-1 and even fewer are in vitro neutralising.

Table 42: Marketed GLP-1 receptor agonists – observed immunogenicity and impact on efficacy and safety

GLP-1 receptor agonist	Wegovy®	Ozempic®	Rybelsus®	Victoza®	Saxenda®	Trulicity®
Administration	s.c.	s.c.	Oral	s.c.	s.c.	s.c.
Active drug	Semaglutide	Semaglutide	Semaglutide	Liraglutide	Liraglutide	Dulaglutide
Indication	weight management	T2D	T2D	T2D	weight management	T2D
Homology to human GLP-1	94%	94%	94%	97%	97%	90%
Level of ADA in Phase 3	3% (low titres)	1–2% (low titres)	0.5% (low titres)	8.6% (low titres)	2.8% (low titres)	1.6% (low titres)
Level of cross-reactivity to GLP-1	2.0%	0.6%	0.2%	4.8–6.9%	-	0.9%
Level of *in vitro* neutralising ADA	0%	0%	0%	1.0–2.3%	1.2%	0.9%
Impact on efficacy	None	None	None	None	None	None
Impact on safety	None	None	None	None	Mild injection site reactions	-

ADA: anti-drug antibodies; GLP-1: glucagon-like peptide 1; %: Percentage of the treated patients with antibody measurements; - : information not available. Based on human-GLP-1

Study 4553

A total of 763 subjects were exposed to semaglutide 2.4 mg and of these, a total of 3 subjects (0.4%) were positive for anti-semaglutide antibodies. None of these subjects were positive for antibodies at

baseline. All 3 subjects with anti-semaglutide antibodies, had antibodies that cross-reacted with native GLP-1. The levels of the antibody response ranged between titre 15-120 with a median titre of 30. One of the three subjects was only positive at one timepoint. However, no further visits had been collected and analysed after this timepoint for this subject. The other two subjects were positive at multiple visits at least 16 weeks apart. Anti-semaglutide antibodies first occurred in week 24. The on-going status of trial 4553 means that neutralising effect of the antibodies was not assessed, as this assessment requires wash out of semaglutide.

AE reported by subjects with ADA was evaluated and compared to the total AE reporting. The events reported by the 3 subjects were mainly GI AEs and mostly PT Nausea. The majority of these AEs were non-serious; the events were mild to moderate in severity and mostly resolved and did not lead to change in dose. No SAEs were reported. One AE of allergic reaction (Eczema) was reported by 1 subject, and no AEs of injections site reactions were reported by 3 subjects positive for anti-semaglutide antibodies by the data cut-off date. Based on the reported AEs in subjects with anti-semaglutide antibodies at any time and compared to subjects without anti-semaglutide antibodies, there was no indication that formation of anti-semaglutide antibodies impacted the safety profile of semaglutide 2.4 mg.

Allergic reactions. AEs of allergic reactions were reported by comparable proportions of subjects and event rates for semaglutide 2.4 mg (7.6%, 5.2 events per 100 PYE) compared to placebo (6.8%, 5.6 events per 100 PYE) for the on-treatment period. All but one of the AEs were non-serious, and of these, all but one were mild or moderate in severity. The majority of the AEs were judged by the investigator to be unlikely related to trial product. None of the AEs led to premature trial product discontinuation. The most frequently reported PTs were rash (in 2.1% of subjects on semaglutide versus 1.3% of subjects on placebo), eczema (1.6% vs 1.5%), and urticaria (0.5% vs 1.0%). One (1) SAE related to allergic reactions was reported as the PT Allergy to vaccine, deemed unrelated to trial product by the investigator.

Injection site reactions. AEs of injection-site reactions were reported by comparable proportions of subjects and the same event rates for semaglutide 2.4 mg (4.0%, 3.2 events per 100 PYE) compared to placebo (4.3%, 3.2 events per 100 PYE) for the on-treatment period. All AEs were non-serious, and mild or moderate in severity. More than half of the events were assessed as probably or possibly related to trial product by the investigator. None of the AEs led to premature trial product discontinuation. The most frequently reported PTs were Injection site bruising (1.8% vs 2.0 %) and injection site pain (1.1% vs 1.0%).

Supportive studies

Study 4296. A total of 239 subjects were exposed to semaglutide OD, and 7 subjects distributed across the semaglutide treatment groups tested positive for anti-semaglutide antibodies, which were mostly of a transient nature; none of the subjects tested positive at baseline. The levels of anti-semaglutide antibodies in terms of % B/T were low (<7.0% bound antibodies in the radioimmunoassay).

A total of 6 subjects (corresponding to 86% of all ADA positive subjects in trial 4296) had antibodies that cross-reacted with native GLP-1. No subjects had anti-semaglutide antibodies with in vitro neutralising effect against semaglutide or endogenous GLP-1. None of the anti-semaglutide antibody positive subjects had any antibodies with clinically relevant effect.

The proportion of subjects reporting allergic reactions ranged between 6.2% and 9.0% in the semaglutide groups versus 7.5% in the placebo group, most frequently rash with only a few of moderate severity. The proportion of subjects reporting injection-site reactions ranged between 5.0%

7.7% in the semaglutide groups versus 6.3% in the placebo group, most frequently injection site bruising.

5.4.4.11. Psychiatric disorders

GLP-1 receptors are expressed in multiple tissues and organs in the body, including the brain. For centrally acting drugs, there is attention to the potential to affect mental health. No associations between semaglutide and mood-related disorders, or suicidal ideation or behaviour have been described in the clinical development programmes for semaglutide for T2D or weight management.

Study 4553

AEs of psychiatric disorders were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (8.6%, 6.8 events per 100 PYE) and placebo (7.3%, 5.4 events per 100 PYE). The majority of the events were mild. One (1) event in each treatment group were considered severe. In both treatment groups, approximately 2/3 of the events were not resolved. The remaining events were either considered resolved or resolving. In both treatment groups, the most frequently reported PTs were insomnia, depression and anxiety. The remaining AEs were distributed across multiple PTs with few events for each PT. The majority of AEs were considered unlikely related to trial product. One (1) event in each treatment group led to treatment discontinuation. A total of 2 SAEs were reported (PTs suicide attempt and depression).

PT insomnia was reported by a higher proportion of subjects and higher rates in the semaglutide 2.4 mg group compared to placebo (4.1% versus 1.8%). All events were non-serious, mild or moderate in severity and most were considered unlikely related to trial product. No pattern relating to the onset of events was observed. No imbalance was observed in the development programme with semaglutide 2.4 mg for weight management (Wegovy).

Supportive studies

Study 4296 The proportion of subjects reporting psychiatric disorders ranged between 6.3%-9.9% in the semaglutide groups and was 10.0% in the placebo group. The most frequently reported PT was insomnia. The remaining AEs were distributed across multiple PTs with few events for each PT. SAEs of psychiatric disorders were reported by 2 subjects in the semaglutide 0.1 mg group. One (1) subject had 1 severe event of worsening of bipolar disorder leading to discontinuation of trial product and 1 subject had 1 event of major depression and 2 events of suicidal ideation. The relationship to trial product was considered possible in one case of suicidal ideation and unlikely for the other 3 SAEs.

5.4.4.12. Medication errors, drug abuse or misuse, and overdose

In study 4553, AEs of *medication errors* (classified as wrong dose or wrong frequency) were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (1.6%, 1.0 events per 100 PYE) compared to placebo (0.8%, 0.5 events per 100 PYE). Four (4) of the events were related to technical complaints. In study 4296, medication errors were reported by similar proportions of subjects with semaglutide and placebo (1.3%-3.7% versus 2.5%). In total, 6 events occurred on trial day 1, where the subjects were administered a higher dose of trial product than intended according to the dose escalation schedule.

In study 4553, events of *overdose* were reported in 0.8% of subjects on semaglutide compared to 0.5% of subjects on placebo. All events were non-serious, mild, resolved and did not lead to trial product discontinuation. 1 suicide attempt was reported as an SAE. The event was serious and severe

and trial product was discontinued. The event resolved and was considered unrelated to the trial product.

5.4.4.13. COVID-19

In trial 4553 (interim evaluation), AEs of COVID-19 were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (17.9%, 11.8 events per 100 PYE) compared to placebo (21.5%, 14.8 events per 100 PYE). The majority of events were non-serious, mild, resolved and considered unlikely related to trial product. SAEs were reported by 3 subjects in the semaglutide 2.4 mg group and 2 subjects in the placebo group. Trial 4296 was minimally impacted by COVID-19, since the pandemic emerged as the last subjects were to attend their last visit.

5.4.4.14. Deaths

The evaluation of deaths is based on investigator-reported AEs with fatal outcome in pivotal study 4553 as well as in all 3 supportive trials. For trials 4553 and 4296, the evaluations are also based on event adjudication by the external adjudication committee (EAC).

Study 4553

In total, 9 deaths occurred among subjects exposed to trial products. Of these, 3 subjects (3 events) were in the semaglutide 2.4 mg group, and 6 subjects (9 events) were in the placebo group (semaglutide 2.4 mg: 0.4% of subjects, 0.2 events per 100 PYO; placebo: 1.5% of subjects, 1.3 events per 100 PYO).

No clustering of causes was seen, and all fatal events were assessed as unlikely related to trial product by the investigator and by Novo Nordisk.

Supportive studies

In study 4296 one (1) death occurred in a subject exposed to semaglutide 0.2 mg once daily. This event was assessed as unlikely related to trial product. No deaths were reported in the supportive trials 4492 and 4381.

5.4.4.15. Other serious adverse events

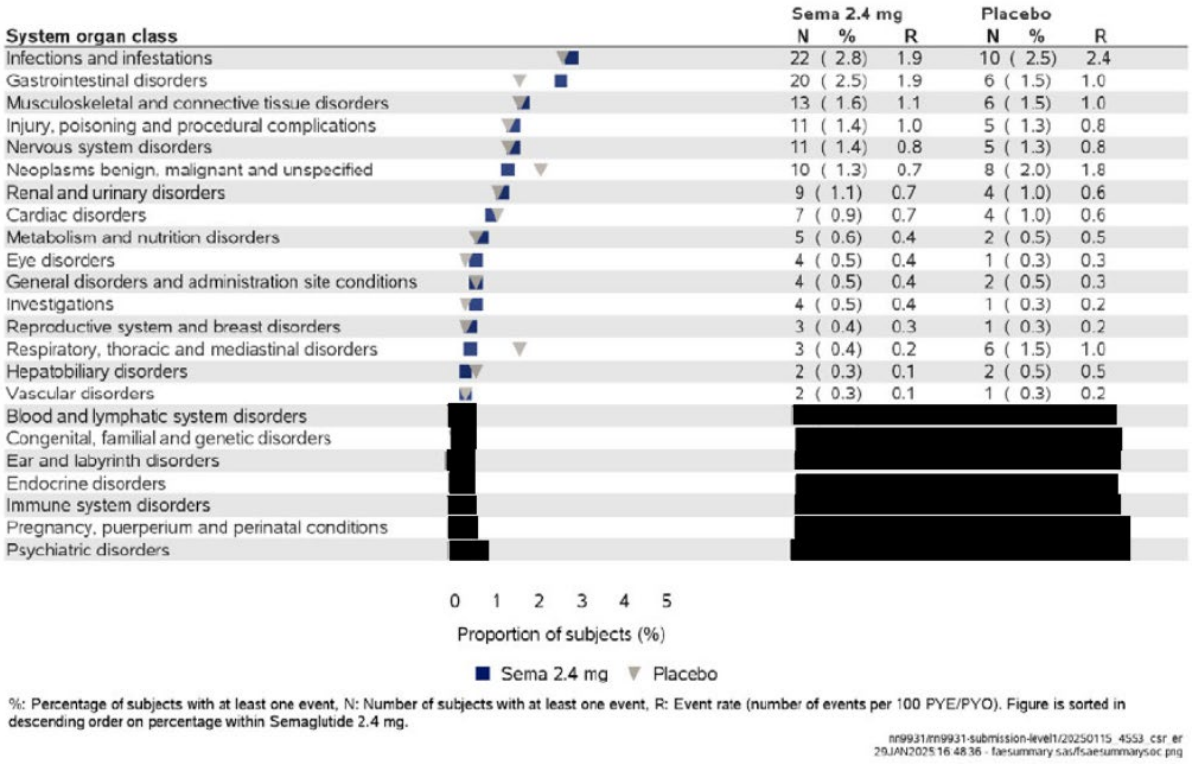
Study 4553

SAEs were reported by comparable proportions of subjects and event rates with semaglutide 2.4 mg (13.0%, 11.9 events per 100 PYE) compared to placebo (12.9%, 12.3 events per 100 PYE) (Table 35). Less than half of the events were severe with both semaglutide 2.4 mg and placebo. In both groups, the majority of the subjects were reported to have recovered from their SAEs. Fatal outcomes were reported for a total of 9 subjects; 3 subjects in the semaglutide 2.4 mg group and 6 subjects in the placebo group (*see section Deaths*). The majority of events were assessed as unlikely related to trial product and did not lead to premature trial product discontinuation.

The most frequently reported SAEs were within the SOCs Infections and infestations and Gastrointestinal disorders. SAEs related to gastrointestinal disorders were reported for a higher proportion of subjects with semaglutide 2.4 mg compared to placebo (in 20 subjects (2.5%) vs. 6 subjects (1.5%)). Infections/inflammation seen in more than one case were appendicitis (n= 3), diverticulitis (n= 3), and Covid-19 (n= 6). Gastro-intestinal disorders seen more than once were intestinal polyps (n= 5), ischaemic colitis (n= 2), gastritis (n= 2), nausea (n= 2), and pancreatitis (n=

3). Overall, SAE were distributed across multiple PTs with each PT reported by no more than 0.5% of subjects.

Figure 20: SAEs by SOC – summary plot – on treatment – SAS (interim) – trial 455



* information removed to avoid unblinding

Supportive studies

Study 4296 SAEs were reported by 14.8%-19.2% in the semaglutide groups and 10% in the placebo group. There was no apparent dose-relationship among the semaglutide groups with regards to the proportion of subjects with serious or severe AEs, or with AEs with outcome not resolved.

Across treatment groups, the SAEs were distributed across multiple SOCs. The most frequently reported SAEs across all treatment groups belonged to the SOCs Infections and infestations (10 events in 7 subjects) and Gastrointestinal disorders (8 events in 8 subjects; all in the semaglutide groups), single events of constipation, ischaemic colitis, intestinal diverticulum, megacolon, abdominal adhesion, colitis, gastro-intestinal polyps, and haemorrhage. The majority of the SAEs reported in the trial were reported as single events and judged by the investigator as unlikely related to trial product. In all treatment groups, SAEs were reported throughout the trial. Five (5) SAEs lead to premature trial product discontinuation; all were single PTs from different SOCs with nothing in common.

Study 4492 SAEs were reported by 12.8% of the subjects in the semaglutide group compared to 8.3% in the placebo group. The SAEs were distributed across multiple SOCs. The most frequently reported SAEs in both treatment groups belonged to the SOC Gastrointestinal disorders. Apart from this no clustering of events was observed and the majority of the SAEs were reported as single events. The majority of the events were considered moderate (6 out of 18) or severe (11 out of 18), but none of the SAEs were judged by the investigator to be possibly or probably related to trial product. All except one (a SAE of PT Osteoarthritis) were reported as resolved.

Study 4381 SAEs were reported by 12.1% of the subjects in the semaglutide group compared to 9.1% in the placebo group. The SAEs were distributed across multiple SOCs. All were assessed by the investigators as being unlikely related to treatment and all except one subject were reported as recovered or recovering. The event that was not recovered was a malignant neoplasm (diffuse large b-cell lymphoma) in the semaglutide s.c. 0.4 mg arm, which was deemed unlikely related to trial product.

5.4.5. Discontinuation due to adverse events

Study 4553

Premature discontinuation. In trial 4553 at interim, AEs leading to premature discontinuation of trial product were reported by a low proportion of subjects in both treatment groups (semaglutide 2.4 mg: 2.6%, 2.4 events per 100 PYE; placebo: 3.3%, 2.6 events per 100 PYE). The majority of the events were non-serious, and mild or moderate in severity.

AEs leading to premature discontinuation of trial product were distributed across multiple SOCs. Premature discontinuation of trial product due to gastrointestinal AEs was reported by a low number of subjects, with slightly higher proportion of subjects with semaglutide 2.4 mg (1.6%) compared to placebo (0.5%). The majority of the events in the semaglutide 2.4 mg group occurred during the dose-escalation period.

SAEs leading to premature discontinuation of trial product were reported for 0.8% of subjects with semaglutide 2.4 mg and 1.5% of subjects with placebo, with event types spread across multiple SOCs and PTs.

Temporary interruption. AEs leading to temporary interruption of trial product were reported by a higher proportion of subjects and at higher event rates with semaglutide 2.4 mg (12.0%, 13.2 events per 100 PYE) compared to placebo (6.8%, 7.5 events per 100 PYE). The majority of the events were non-serious, and mild or moderate in severity. The imbalance was mainly driven by gastrointestinal AEs, which accounted for around half of the events leading to temporary interruption of trial product in the semaglutide 2.4 mg group. The remaining events were distributed across multiple SOCs.

SAEs leading to temporary interruption of trial product were reported by comparable proportions of subjects treated with semaglutide 2.4 mg (3.3%) compared to placebo (2.3%).

Dose reduction. AEs leading to dose reduction were reported by a higher proportion of subjects and at higher event rates for semaglutide 2.4 mg (10.0%, 11.8 events per 100 PYE) compared to placebo (2.0%, 1.8 events per 100 PYE). These events were spread across multiple SOCs and PTs, with the most common PTs being nausea, vomiting, diarrhoea, decreased appetite and weight decreased.

Supportive studies

Study 4296 The proportion of subjects with AEs leading to *premature discontinuation* of trial product was higher in the semaglutide 0.2 mg once daily group (12.8%) than in the other treatment groups (semaglutide 0.1 mg: 3.8%; semaglutide 0.4 mg: 4.9%; placebo: 5.0%). The majority of events were non-serious, and mild or moderate in severity. Gastrointestinal AEs accounted for approximately half of the AEs leading to premature discontinuation of trial product in the semaglutide groups. The remaining AEs were single events reported by single subjects, distributed across multiple SOCs with no apparent pattern.

AEs leading to *temporary interruption* of trial product were reported in ~ 15% of subjects on semaglutide vs 6.3% of subjects on placebo, with Aes mainly belonging to the SOCs Gastrointestinal disorders, Infections and infestations, and Investigations. AEs leading to *dose reduction* were reported

for 1 subject with semaglutide 0.2 mg (1 AE) and 3 subjects with semaglutide 0.4 mg once daily (4 AEs).

Study 4492 AEs leading to premature discontinuation of trial product were reported by 3 subjects (6.4%) with semaglutide 2.4 mg and no subjects with placebo, mainly due to the PT nausea. Temporary interruption of trial product was reported by 2 subjects, 1(2.1%) subject in the semaglutide 2.4 mg group (4 AEs) and 1(2.1%) subject in the placebo group (1 AE), and dose reduction was reported in 4 subjects in the semaglutide 2.4 mg group (6 AEs) and 1 subject in the placebo group (2 AEs). The most common SOC was Gastrointestinal disorders.

Study 4381 One (1) AE leading to *premature discontinuation* of trial product was reported by 1 (3.0%) subject with semaglutide 0.4 mg once daily, no events were reported with placebo. The AE reported in the semaglutide 0.4 mg group was diffuse large B-cell lymphoma, reported on day 92 and assessed as unlikely related to trial product. A total of 4 subjects (3 (9.0%) on semaglutide 0.4 mg OD vs 1 (3.0%) on placebo) reported AEs leading to *temporary interruption* of trial product, and a dose reduction was reported for 2 subjects with semaglutide. All events in the semaglutide group were reported within the SOC Gastrointestinal disorders.

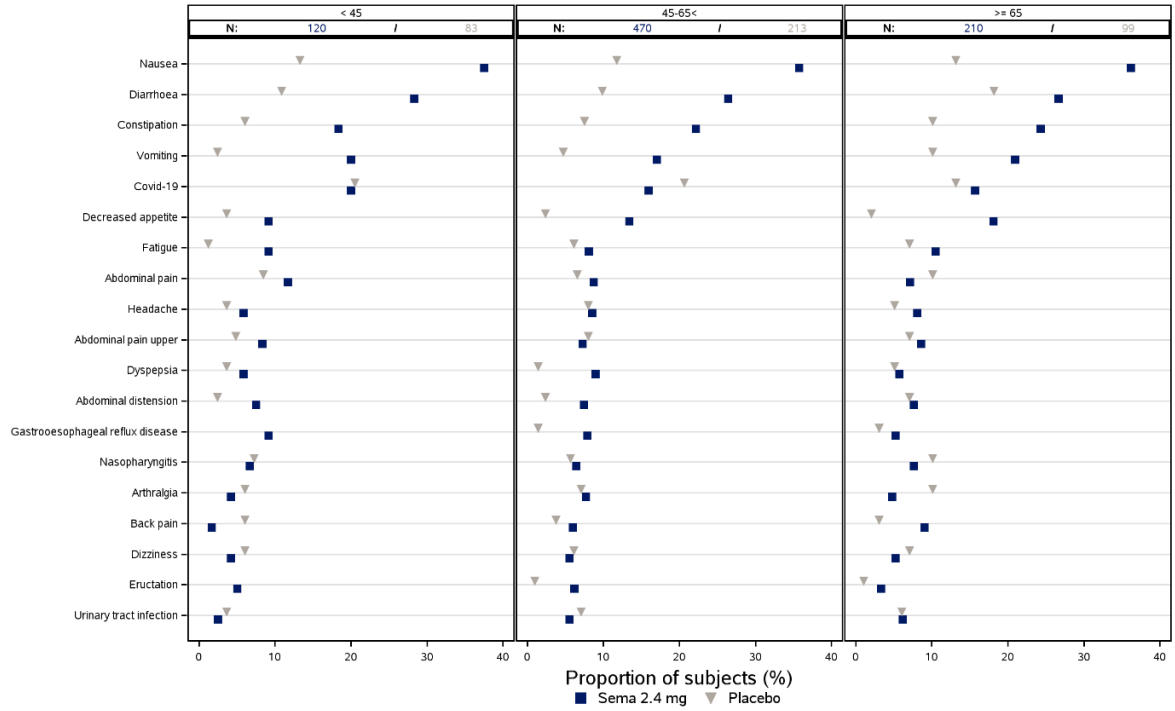
5.4.6. Safety in special populations

AEs across age-groups

In study 4553, a total of 210 (26.3%) out of 800 subjects randomised to semaglutide 2.4 mg were aged >= 65 years. AEs were reported at similar frequency across age-groups <45, 45-64, and >=65 years of age, in ~85% of subjects, leading to dose reduction in a higher proportion of patients >=65 years (13.8% vs ~8.5%) and discontinuation of semaglutide in 3.3% vs 0.8% at age <45 years. A higher proportion of subjects >= 65 years of age on semaglutide reported SAEs, in 14.8% at age >=65 years vs 10.8% < 45 years, as well as severe AEs (11.9% vs 5.0%).

Across age, the PT decreased appetite was reported by a higher proportion of subjects in the subgroups with high age (⩾65 years) in the semaglutide 2.4 mg group compared to the lower ages. The proportion of subjects reporting decreased appetite increased with increased age. This was not reflected in the matched placebo groups which had comparable proportions across the age groups.

Figure 21: Adverse events by age at baseline and preferred term – most frequent (>=5%) – dot plot – on-treatment – safety analysis set (interim) - trial 4553



N: Number of subjects. Adverse events with onset date during on-treatment period. MedDRA version 27.0. The figure is sorted in descending order by preferred term based on the percentage of subjects with at least one event in the Semaglutide 2.4 mg arm.

nn9931/nn9931-submission-level1/safety_l1_20250130_er
30JAN2025:09:42:02 - faesummarypt5grp.sas/faesumpt5ageot.png

Additionally, AEs by age subgroups in older patients (<65; ⩾65−<75; and ⩾75−<85) have shown no remarkable differences by SOCs or PTs. While more AEs occurred in older patients, the increase occurred similarly in both groups.

Intrinsic factors

The potential impact of various intrinsic factors on the safety profile of semaglutide 2.4 mg versus placebo was evaluated based on data from the on-treatment period for trial 4553 (SAS [interim]), by comparing the AE-reporting pattern across subgroups within the semaglutide 2.4 mg group, as well as any subgroup differences in the SOC/PT reporting. The results across subgroups should be interpreted with caution; the total trial population was randomised per treatment group and stratified by T2D status and fibrosis stage at baseline only. The trial population was not stratified by the remaining intrinsic factors, hence uneven distributions within subgroups are observed. Furthermore, the number of subjects in some of the subgroups are low, increasing the likelihood of chance findings.

AEs by fibrosis stage at baseline

MASH F2 vs NASH F3. In study 4553, AEs (in 90.2% of subjects with MASH F2 vs 85.1% of subjects with MASH F3), SAEs (20.1% vs 11.0%) and severe AEs (13.2% vs 7.7%) were reported at a slightly increased frequency in subjects with F2 as compared to F3. The same tendency was seen in the matching placebo subgroups for overall AEs, whereas comparable proportion of subjects with placebo reported SAEs and severe AEs across the F2 and F3 subgroups.

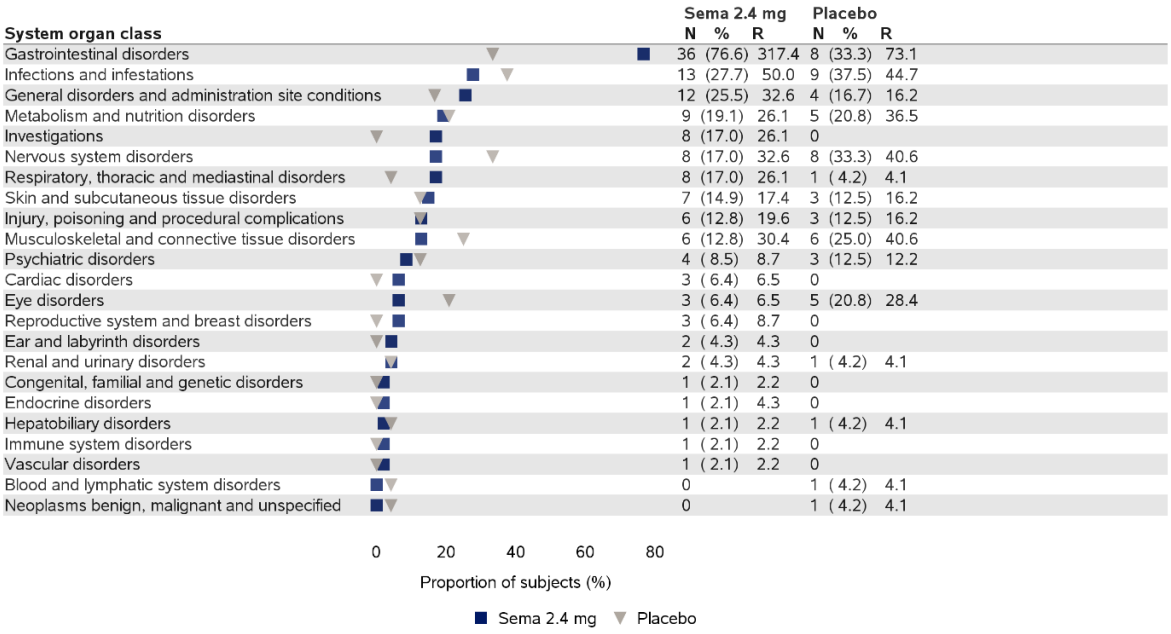
Slight variations between the F2 and F3 subgroups were seen for reporting of common PTs in the semaglutide 2.4 mg group. The overall higher reporting in the F2 subgroup was mainly driven by events within the SOCs Gastrointestinal disorders, and Infections and infestations, driven by the PTs

vomiting, nasopharyngitis and COVID 19. For the remaining events, no noteworthy differences between subgroups were seen when assessing AEs on SOC and PT levels.

MASH F1-F3 vs MASH F2-F3. When looking at the subjects in trial 4296 with F2 or F3 compared to the full trial population that also included subjects with MASH F1, similar results were seen for both AEs and SAEs, as well as AEs leading to premature discontinuation. For subjects with F2/F3, the proportions of AEs ranged between 87.7% and 96.6% in the semaglutide groups versus 84.5% in the placebo group, similar to the results seen for the full trial population (see section 5.4.3). The proportion of subjects with AEs leading to premature treatment discontinuation was higher in the semaglutide 0.2 mg group than in the other treatment groups, again matching the results for the overall trial population. Across treatment groups, the pattern of AEs and SAEs for subjects with F2/F3 was similar to that in the overall population.

MASH F4c (trial 4492). Overall, the proportions of AEs were comparable between the two treatment groups, with a higher event rate observed in the semaglutide group (proportion: 89.4%, rate: 630.5 per 100 PYE) compared to the placebo group (proportion: 79.2%, rate: 345.1 per 100 PYE). The higher event rates in the semaglutide group were primarily driven by gastrointestinal AEs. Three subjects in the semaglutide group vs none in the placebo group discontinued treatment due to AEs.

Figure 22: Adverse events by system organ class – summary plot – on-treatment – SAS



The proportion of subjects with SAEs was overall comparable but based on few subjects; 12.8% corresponding to 6 subjects in the semaglutide group and 8.3% corresponding to 2 subjects in the placebo group. A similar pattern was seen for severe AEs. The SAEs in the semaglutide group included SAEs within the Gastrointestinal disorders SOC, and otherwise by single PTs reported across multiple SOCs, with no observed clustering. All the reported SAEs were assessed as unlikely related to trial product by the investigators. No decompensation events took place in the trial and stable disease scores were reported (e.g., MELD score and Child-Pugh score).

Hypoglycaemia in MASH F4c (trial 4492) patients were reported by 12 (34.3%) of the subjects with T2D in the semaglutide group compared to 5 (27.8%) of the subjects with T2D in the placebo group. Five (5) subjects (14.3%) in the semaglutide group reported severe or blood glucose (BG) confirmed symptomatic episodes (Novo Nordisk classification) versus 3 subjects (16.7%) in the placebo group.

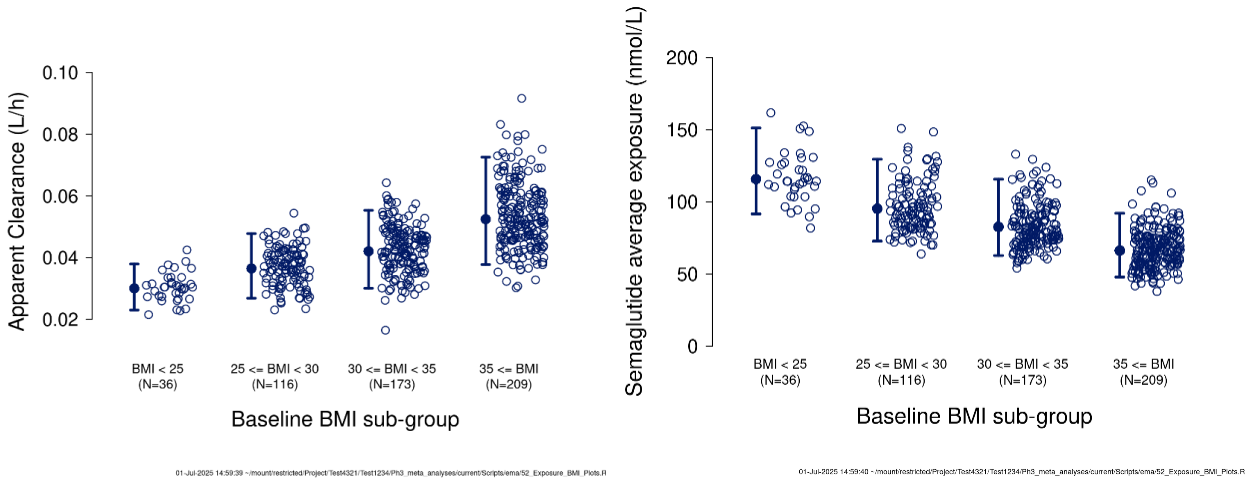
AEs by BMI at baseline

In study 4553, a total of 113, 115, 249 and 323 subjects with BMI <27, 27-<30, 30-<35, and >=35 kg/m2 were treated with semaglutide. AEs, SAEs and severe AEs were reported at comparable frequency across BMI ranges, in 84.1% to 88.7%, 12.0%t to 14.2%, and 7.0% to 9.6% of subjects on semaglutide, respectively. Interruption or reduction of semaglutide dose was reported more frequently in subjects with BMI < 27 kg/m^2, in 21.2% vs 8.0%-13.7% and 21.2% vs 5.9%-12.2%, respectively. This pattern was not fully reflected in the matching placebo subgroups, where overall AEs were reported by a higher proportion of subjects in the low-BMI subgroup; however, based on a low number of subjects.

In the semaglutide 2.4 mg group, the SOC Gastrointestinal disorders (and the most common PTs: nausea, diarrhoea, and constipation) were all reported by a lower proportion of subjects in the low BMI subgroup compared to the high-BMI subgroup, with varying reporting patterns in the matching placebo groups. The same was seen for the SOC Infections and infestations (driven by the PT COVID-19), which was reported by a lower proportion of subjects in the low-BMI subgroup with semaglutide 2.4 mg compared to the high BMI subgroup. In contrast, the PT decreased appetite was reported by a higher proportion of subjects in the low-BMI subgroup (17.7%) compared to the high-BMI subgroup (13.4%). This difference was not reflected in the matching placebo subgroups.

An increase in some AEs, dose reductions, and interruptions with lower BMI may be driven by higher drug exposure and greater susceptibility to gastrointestinal related AEs.

Figure 23: Semaglutide apparent Clearance (L/h) and average exposure (nmol/L) by baseline BMI subgroups – trial 4553 (interim)



Filled circles with error bars are geometric mean with 5th and 95th percentiles.

AEs across T2D at baseline

In study 4553, a total of 446 (55.8%) vs 222 (56.2%) subjects with T2D at baseline were randomised to semaglutide or placebo. When analysed across baseline T2D, AEs, SAEs and AEs leading to early

discontinuation of semaglutide 2.4 mg was reported in 87.0% vs 85.3%, 13.0% vs 13.0%, and 2.5% vs 2.8% of subjects with vs without baseline T2D, and for subjects on placebo in 76.6% vs 81.5%, 14.4% vs 11.0%, and 1.7% vs 2.0% of subjects with vs without baseline T2D.

AEs across sex

Female subjects treated with semaglutide 2.4 mg reported AEs at comparable frequency as male subjects, by 400 (88.7%) vs 290 (83.1%) subjects. However, adverse event lead to dose-reduction in a slightly higher proportion of women, 11.1% vs 8.6% of subjects and discontinuation of semaglutide in 3.3% vs 1.7% of subjects. SAEs were reported by 15.5% vs 9.7% of subjects.

Main differences were seen for GI AEs (72.9% vs 65.0%), and Infections and Infestations (50.6% vs 37.0%). GI events reported more frequently in females were nausea (41.2% vs 29.5%) and vomiting (20.8% vs 15.5%). However, no imbalance was seen for GI events of diarrhoea, constipation, or dyspepsia. Covid-19 (19.7% vs 12.3%) and UTI (8.4% vs 1.1%) were reported more frequently by female subjects.

AEs across race

When comparing across race in the semaglutide 2.4 mg group, a higher proportion of subjects of Asian race reported SAEs compared to Whites, in 17.2% vs 11.3% subjects, respectively. That was not reflected in the matched placebo subgroups which had comparable proportions for the two races. The remaining subgroups for race were too small for comparisons.

Extrinsic factors

The potential impact of extrinsic factors (region and trial-product pen-injector) on the safety profile of semaglutide 2.4 mg was evaluated by comparing the AE-reporting pattern across subgroups within the semaglutide 2.4 mg group, as well as any subgroup differences in the SOC/PT reporting. Overall, AEs by region showed comparable AE-reporting patterns across subgroups. No noteworthy differences between subgroups were seen when assessing AEs on SOC and PT levels.

AEs by trial-product pen-injector generally showed a higher proportion of subjects reporting AEs in the DV3396 subgroup compared to the PDS290 subgroup; however, this difference was as expected because subjects using PDS290 were enrolled later in the trial, hence there is a higher total exposure for DV3396 (1641 PYE) compared to PDS290 (321.6 PYE). For general AE reporting including SAEs and severe AEs, similar reporting patterns was seen for both semaglutide 2.4 mg and the placebo group.

5.4.7. Immunological events

See section on *Adverse events of special Interest, Immunogenicity*.

5.4.8. Safety related to drug-drug interactions and other interactions

Interactions with other medicinal products have been assessed for the use of semaglutide in the T2D and weight management programme (Ozempic, Wegovy). *In vitro* studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, or to inhibit drug transporters.

As with other GLP-1 receptor agonists, semaglutide may delay gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying has been observed with semaglutide 2.4 mg. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1.0 mg steady-state exposure (NN9535) as part of the T2D clinical development programme. No clinically relevant drug-drug interactions with semaglutide were observed based on the

evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.

5.4.9. Vital signs and laboratory findings

In this summary, the evaluations of laboratory data from the central laboratory are based on the on-treatment period for trials 4296 and 4553 (interim evaluation). Further, abnormal laboratory values deemed clinically relevant by the investigator (i.e., reported as AEs) are included in the evaluation.

Summary of clinical laboratory evaluations

Haematology. In trial 4553 (interim evaluation) and 4296, haematology parameters assessed included haemoglobin, leucocytes, erythrocytes, thrombocytes and differential cell counts (basophils, eosinophils, lymphocytes, monocytes and neutrophils). No clinically relevant mean changes in haematology parameters were observed from baseline to week 72 in any of the treatment groups.

Biochemistry. In study 4553 for the majority of the laboratory parameters assessed, the mean values remained stable from baseline to week 72 with both semaglutide and placebo. Mean levels of ALT and AST decreased more with semaglutide than with placebo, and amylase and lipase levels increased. Ferritin decreased in both semaglutide and placebo groups.

Across parameters, no relevant outlier patterns were observed, and no safety concerns were identified based on the central laboratory assessments nor on data obtained from local laboratory assessments.

Liver-related parameters (AST, ALT, ALP, INR, MELD, bilirubin and albumin), parameters related to renal failure (eGFR and creatinine), and pancreatic enzymes (lipase and amylase) are described in subsections *Hepatic disorders including potential DILI events*, *Acute renal failure* and *Acute pancreatitis* in section Adverse Events of Special Interest.

Ferritin. In trial 4553, the geometric mean values of ferritin decreased from baseline to week 72 for both semaglutide 2.4 mg and placebo. At baseline, geometric mean value of ferritin was 142,92 in the semaglutide group and 135,38 in the placebo group. At week 72, the ratio to baseline was 0,67 in the semaglutide group and 0,79 in the placebo group.

In trial 4296, dose-dependent ferritin decrease can be seen in ratio to baseline: sema 0.1mg: 0.660, sema 0.2 mg: 0.617, sema 0.4 mg: 0.603 vs placebo: 0.713.

Vital signs, physical findings, and other observations related to safety

In trial 4553, assessment of vital signs included pulse rate and blood pressure (SBP and DBP), which are evaluated as part of the safety focus area for cardiovascular disorders. Change in SBP and DBP from baseline to week 72 were also included as part of the efficacy assessment. Eye examinations are evaluated in subsection Retinal disorders.

In trial 4296, assessment of vital signs included pulse rate, blood pressure (SBP and DBP) and ECGs, which are evaluated as part of the safety focus area for cardiovascular disorders.

5.4.10. Post-marketing experience

Semaglutide s.c. 2.4 mg once weekly for weight management is marketed as Wegovy, with the first marketing authorisation granted on 04 June 2021.

Semaglutide s.c. for T2D has been marketed as Ozempic, with the first marketing authorisation received on 05 December 2017. Oral semaglutide for T2D has been marketed as Rybelsus, with the first marketing authorisation received on 20 September 2019.

The post marketing safety data for semaglutide received by the applicant are made available in the Periodic Safety Update Report/Periodic Benefit Risk Evaluation Report (PSUR/PBRER) according to the regulatory requirements. The latest submitted PSUR/PBRER for semaglutide provides a critical analysis of the safety and benefit-risk balance for Wegovy, Ozempic and Rybelsus (reporting interval: 01 Jun 2023 to 31 May 2024). Based on cumulative data from more than 40,000 subjects exposed to semaglutide in completed clinical trials and post-marketing data from ~20 million patients treated the applicant evaluated that no additional pharmacovigilance and risk minimisation activities were required.

5.4.11. In vitro biomarker test for patient selection for safety

Not Applicable

5.4.12. Overall discussion and conclusions on clinical safety

5.4.12.1. Discussion

5.4.12.1.1. Overall assessment of available safety data

Main **safety data** on semaglutide for the treatment of MASH are derived from pivotal study 4553 (ESSENCE) in patients with MASH F2-F3, with semaglutide dosed at 2.4 mg s.c. once weekly, similar to the proposed dose in the SmPC. Supportive data are obtained from study 4296, in patients with MASH F1-F3 with semaglutide dosed at either 0.1 mg, 0.2 mg or 0.4 mg OD, study 4492 in patients with biopsy-confirmed MASH and compensated cirrhosis (F4c) with semaglutide dosed at 2.4 mg once weekly, and study 4381 in patients with NAFLD and increased liver stiffness with semaglutide dosed at 0.4 mg OD. In line with EMA *reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH)*, the investigated population in the clinical program therefore covers non-cirrhotic MASH (fibrosis stages 2-3), and compensated cirrhotic MASH (fibrosis stage 4), which reflects grades of MASH that are associated with risk of progression to ESLD, liver transplantation and death and may also be related to differential risks of adverse events. Since the study population as well as the semaglutide dosing regimen differed between studies, data were presented separated per study and no pooled data were included. Results from study 4553 concern a predefined interim analysis, as per data cut-off date of 05 September 2024.

All studies were randomised double-blind placebo-controlled studies, enabling estimation of the frequency of adverse events. The lack of an active control is acceptable since there wasn't any approved medicinal treatment for MASH at the beginning of the clinical trials. Despite blinding, patients and investigators may still have been aware of the allocated treatment, due to the weight loss associated with semaglutide, however, potential bias introduced was mitigated by additional blinded adjudication of selected events in study 4553. Two separate analysis data sets were defined, based on the observation period. The definition of the in-trial observation period, reflecting time followed in the trial, and the on-treatment observation period, reflecting time on trial medication, is acceptable. The follow-up period after discontinuation of trial treatment, of 7 days after last dose for laboratory assessments and physical examination, and of 7 weeks for adverse events and hypoglycaemic episodes, is based on expected levels of systemic exposure of semaglutide for approximately 7 weeks after the last dose based on the elimination half-life of 1 week and is acceptable.

In addition, extensive safety data are available from prior clinical development programmes of

semaglutide in T2D and in weight management, as well as post-marketing data covering ~20 million patients. However, when translating these results to the proposed indication in patients with MASH, differences in dosing regimens (with maximum semaglutide dose of 2.0 mg once weekly in T2D, and oral administration of Rybelsus of 4 to 50 mg once daily) and in study populations must be taken into consideration, and most relevant safety data on semaglutide at a dose of 2.4 mg once weekly come from semaglutide for weight management (Wegovy). Though PK-modelling data demonstrated a comparable PK exposure on 0.4 mg once daily and 2.4 mg once weekly, still the safety profile may differ, as daily administration of semaglutide has been associated with increased frequency of (gastro-intestinal) AEs.

Exposure. At data-cut-off date of 05 September 2024, a total of 1585 subjects were exposed to the trial product in phase 3a trials 4553 [interim]), and phase 2 trials 4296 and 4492, 1086 subjects to semaglutide and 499 subjects to placebo. Total exposure to semaglutide in the on-treatment observation period was 1716.6 PYE. In addition, in study 4381, 66 subjects were exposed to the trial product, with 33 subjects exposed to semaglutide.

In the pivotal study 4553 in the target population with MASH F2-F3 and at the proposed dosing regimen of 2.4 mg once weekly, a total of 800 subjects was treated with semaglutide, with 643 subjects treated for at least 6 months, and a total of 542 subjects treated for at least 12 months, thereby fulfilling requirements of ICH-E1. The mean (SD) exposure time for subjects in SAS (interim) was 85.7 (50.4) weeks for the on-treatment observation period, 87.1 (50.7) weeks on semaglutide, and 82.8 (49.9) weeks on placebo. This may cause a slight overestimation of frequency of adverse events on semaglutide. However this effect is attenuated by the timing of most adverse events, that are reported mainly during the initial treatment phase.

Adverse events. In the pivotal study 4553, AEs were reported at higher frequency in subjects on semaglutide as compared with placebo (86.3% vs 78.7%), predominantly **gastrointestinal AEs** (69.5% versus 46.8%), mainly nausea (36.1% vs 12.4%), diarrhoea (26.8% vs 12.2%), constipation (22.1% vs 7.8%) and vomiting (18.5% vs 5.6%). Most AEs reported were graded as mild or moderate (in 80.3% vs 72.7%, and 47.8% vs 42.8%) and only a limited proportion of AEs was graded severe, with no imbalance for semaglutide vs placebo, 8.9% vs 8.4%.

Adverse drug reactions i.e. adverse events deemed probably or possibly related were reported in 68.6% of subjects on semaglutide vs 40.8% subjects on placebo. ADRs were graded as mild, moderate or severe, in 62.5% vs 35.9%, 26.9% vs 10.9% and 2.8% vs 1.0%, respectively. Most ADRs occurring at increased frequency on semaglutide concerned gastrointestinal disorders, in 60.3% vs 30.9% of subjects, including nausea (34.1% vs 10.9%), diarrhoea (20.3% vs 10.4%), constipation (17.3% vs 5.3%), vomiting (15.9% vs 3.3%), dyspepsia (6.9% vs 2.3%), abdominal distention (6.5% vs 2.5%), and gastro-oesophageal reflux disease (5.9% vs 0.5%). Also, decreased appetite (13.6% vs 2.3%), fatigue (6.4% vs 2.8%), headache (4.9% vs 3.0 %), and weight decreased (4.1% vs 0.5%) were reported at increased frequency on semaglutide. The frequency of nausea-events increased dose-dependently on semaglutide, whereas no clear dose relationship was observed for diarrhoea, vomiting or constipation or other adverse events. ADRs graded as severe and reported in > 2 subjects mainly concerned gastro-intestinal AEs (nausea, diarrhoea, and vomiting). Semaglutide and associated weight loss have been associated with reduction of bone density. However, the mechanisms for this risk are not fully elucidated yet. Given the limited number of back pain events and that all three subjects had pre-existing risk factors for back pain (i.e., history of spinal stenosis and degenerative disc disease, history of osteopenia, and myalgia) the current data does not allow to establish a decisive connection between semaglutide and back pain nor reduced bone density.

In study 4553, according to protocol semaglutide was started at a dose of 0.25 mg once weekly, to be escalated based on tolerability, at intervals of 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg, and reaching

the final dose of 2.4 mg once weekly at week 16. The target dose of 2.4 mg was reached by 508 (81.7%) subjects treated with semaglutide at week 24, and remained stable thereafter, with 479 (84.0%) at target dose at week 72. The majority of adverse events was reported within the dose-escalation period, though events of nausea were reported throughout the trial duration. Temporary discontinuation or dose reduction of semaglutide were reported at increased frequency compared with placebo, in 12% vs 6.8% and 10.0% vs 2.0%, respectively. However premature discontinuation of study treatment was only required in a small proportion of subjects without imbalance between study-arms (3.3% vs 2.6 %).

A total of 9 deaths were reported in study 4553 (interim), 3 subjects in the semaglutide group and 6 subjects on placebo. All fatal events were assessed as unlikely related to trial product, which is agreed with.

Serious AEs were reported at comparable frequency in semaglutide (13.0%) vs placebo (12.9%), with comparable grading of severity for both treatment arms, and deemed possibly or potentially related in 2.4% vs 1.3% of subjects. A dose reduction was required in a limited number of subjects (n=1) and study drug withdrawal in 0.8% vs 1.5% of subjects. Fatal SAE was reported in 0.4% vs 1.3% of subjects. The SAEs mainly concerned infections and gastro-intestinal disorders. Serious infections/inflammation seen in more than one case on semaglutide were appendicitis (n= 3), diverticulitis (n= 3), and Covid-19 (n= 6). Gastro-intestinal disorders seen more than once were intestinal polyps (n= 5), ischaemic colitis (n= 2), gastritis (n= 2), nausea (n= 2), and pancreatitis (n= 3). The number of events is low, without clear imbalance between treatment arms. Of note, in a recent pharmacovigilance study based on the FDA adverse event reporting system (FAERS) 10 cases of serious (0.56%) and 2 cases of nonserious appendicitis (0.05%) associated with semaglutide over the span of 2018 to 2022 were reported (*Shu et al, Frontiers in Public Health, 2022*). However, the signal of appendicitis has already been discussed in semaglutide PSUSAs (PSUSA/00010671/202405), resulting in no updates to the label of the product. The imbalance in the number of appendicitis events is in line with previous studies, and it is not considered sufficient to raise a safety issue at this stage.

Supportive studies. In supportive study 4296 in MASH F1-F3, a comparable frequency of adverse events was reported on semaglutide 0.1 mg, 0.2 mg and 0.4 mg OD. SAEs were reported at increased rate on semaglutide 0.2 mg OD, in 19.2% of subjects, vs 3.8% and 4.9% subjects at 0.1 mg and 0.4 mg OD. However, SAEs were distributed over multiple SOCs, and increased frequency at semaglutide 0.2 mg was mainly seen for neoplasms (benign or malignant) and nervous system disorders without clustering of events, which is likely due to chance finding. Safety data of study 4381 in NAFLD with increased liver stiffness with semaglutide dosed at 0.4 mg OD, in general were consistent with findings in the pivotal study 4553. In supportive study 4492 in MASH F4c with semaglutide dosed 2.4 mg once weekly AEs and SAEs in the semaglutide group were reported at a comparable frequency as in study 4553 in MASH F2/F3, in 89.4% vs 86.3% and 12.8% vs 13.0%, respectively. Severe AEs were reported at higher frequency in subjects with MASH F4 in study 4492, by 17% of subjects as compared with 8.9% of MASH F2-F3 subjects in study 4553. This mainly concerned gastro-intestinal AEs, however without clustering of specific events and a causal relation with semaglutide is deemed unlikely.

No new AEs/safety concerns were identified for the MASH population as compared to the other semaglutide indications, despite the small differences in AE frequencies.

Hepatotoxicity and drug-induced liver injury (DILI) are important aspects for drugs intended for treatment of MASH. Based on prior results in T2D and weight management, semaglutide was not known to be hepatotoxic. In the pivotal study 4553, subjects with ALT / AST > 5xULN or ALP> 2xULN were excluded. Though signs of hepatic dysfunction were seen in most subjects, as reflected by

elevated baseline AST or ALT up to 3x ULN in 68.2% and 49.8% of subjects, only a limited number of patients with more severe elevated AST, ALT or ALP > 3x ULN were enrolled (90, 42, and 45 subjects, respectively). During the treatment phase, mean values for ALT and AST decreased from baseline to week 72 in both treatment groups, whereas mean ALP decreased only in the semaglutide group, as also reported in the clinical efficacy section. Total bilirubin, albumin, and INR remained stable over time in both groups. Also, the MELD score remained unchanged up to 72 weeks in both groups.

Numerically, the frequency of hepatic events was lower on semaglutide as compared with placebo (5.0% vs 7.8%). Most hepatic events were mild or moderately severe, and serious hepatic event was reported in 1 (0.1%) vs 3 (0.8%) subjects. No patient qualified for either Hy's law or potential DILI. Based on these results, no signal of hepatic toxicity is seen in study 4553.

Results from supportive studies 4296 in MASH F1-F3 and study 4381 in subjects with NAFLD with increased liver stiffness are consistent.

Gall-bladder-related disorders such as cholelithiasis are associated with NAFLD, obesity, and rapid and large weight loss. In subjects treated with GLP-1 RA this risk was increased in a dose-dependent way and acute cholelithiasis is considered a class risk for GLP-1 RA. In study 4553, gallbladder related disorders were reported at slightly increased frequency on semaglutide (2.5% vs 1.5% of subjects), most frequently concerning cholelithiasis (1.4% vs 0.8%). Also, symptomatic acute gallbladder disease was seen at increased frequency on semaglutide, in 5 vs 2 subjects, reported as serious in 1 subject on semaglutide and placebo, each. The frequency of cholelithiasis on semaglutide was comparable with the frequency on semaglutide for weight management, in 1.6% of subjects, and no increase in severity nor in the required invasive treatments was seen in the MASH studies. However, in patients with hepatic cirrhosis symptomatic cholelithiasis and cholecystectomy have been associated with increased risks (*Malick et al, 2021; Perkins et al. 2004*), and therefore events related to cholelithiasis may have a more unfavourable course in MASH patients. Also, the risk of developing cholelithiasis may increase during prolonged semaglutide treatment. Though the cholelithiasis-related events reported in the MASH studies so far do not raise additional concern as compared with semaglutide for other indications, the number of investigated subjects and the duration of follow-up are too limited to allow for robust conclusions. Data on cholelithiasis and treatments from the T2D and weight management programs as well as from post-marketing experience was provided, showing that the rates of cholelithiasis identified in study 4553 are in line with the known profile of semaglutide and the risk is adequately reflected in the SmPC. Additional data on prolonged semaglutide treatment will become available following completion of study 4553, which will relevantly contribute to further estimation of the risks of cholelithiasis in MASH subjects.

Acute pancreatitis is considered a class risk associated with the use of GLP-1 RA, and MASH has been associated with increased severity of acute pancreatitis (*Yoon et al,. 2017; Váncsa et al. 2020*). In study 4553, amylase and lipase levels slightly rose during semaglutide treatment. A total of 3 events were categorised as SAE, 2 (0.3%) vs 1 (0.3%). Though numbers are small and so far do not signal a considerable safety risk, the high proportion of adverse events of acute pancreatitis graded as serious do reflect the potential severity of this condition, and also, the wide range of ratio to baseline values for lipase as well as amylase up to 44 in study 4553, and up to 88 in study 4296 does signal relevant effects on pancreatic functioning. Similar to gall-bladder related adverse events, acute pancreatitis may also be expected to occur throughout long term treatment as opposed to other GI AEs that were mainly seen during the initial treatment phase. The number of subjects investigated in the MASH studies and duration of follow-up are still limited to fully explore this safety risk in MASH patients. At this point acute pancreatitis is not seen at increased frequency on semaglutide as compared with placebo in MASH subjects, and the reported event rates are in line with the rates of other semaglutide studies for weight management and T2D. Nevertheless, additional data during prolonged semaglutide treatment that will come available following completion of study 4553 will

relevantly contribute to further estimation of this potential safety issue.

Cardiovascular events. Though increased pulse rate is known as a class effect of GLP-1 Ras, the mean increase of pulse rate on semaglutide of 2 beats/min, and similar frequency of events related to palpitations on semaglutide as compared with placebo is reassuring. No safety signals were seen due to cardiovascular events, and the reduction of SBP of 5.39 mmHg on semaglutide may be of additional clinical benefit.

Neoplasms. In a review by EMA to evaluate the risk of pancreatic adverse events associated with use of GLP1-based therapies no evidence for an increased risk of pancreatic malignancy was found. However, uncertainties remained to exist since long-term consequences of stimulation of beta-cells and suppression of alpha cells as well as possible effects on exocrine pancreas were considered largely unknown. Therefore, pancreatic cancer was classified as potential class risk. Currently, based on data in T2D, weight management, and post-marketing no evidence of increased risk of pancreatic cancer has been seen. In study 4553, malignant neoplasms were reported in 14 (1.8%) subjects on semaglutide vs 10 (2.5%) subjects on placebo, without clustering of specific types of malignancies or evident imbalance between treatment groups. One case of ductal adenocarcinoma of the pancreas in study 4553 was reported as considered unlikely related to study drug. Though no signal of increased risk of malignancy on semaglutide is seen, pancreatic cancer remains in the RMP as important potential risk, in line with the *EC regulation 726/2004 Article 5(3) referral procedure from 2013 (EMEA/H/A-5(3)/1369)*.

Renal cysts were reported at increased frequency on semaglutide, in 13 (1.6%) vs 2 (0.5%) of subjects. Information is to some extent limited since additional information for renal cysts was not systematically collected. From the information available it has been established that there were 11 cases of single cysts and 5 cases of multiple cysts. Simple cysts are classified as level I-II in the Bosniak classification, which have a negligible risk of malignancy. One of the events was classified as a SAE, and all 16 were mild and considered unlikely related to trial product. None of the events did lead to treatment discontinuation or changes in dose, except for 1 subject. The majority of subjects reporting renal cysts co-reported gastrointestinal AEs or other AEs (e.g. musculoskeletal disorders or nephrolithiasis), which are AEs that could lead to imaging and thereby incidental findings of renal cysts. This hypothesis cannot be confirmed with the data available, although it is considered plausible. No safety signal on renal cysts has ever been raised for semaglutide in other populations/indications, which supports an unlikely relation between semaglutide and renal cysts.

In trial 4296 neoplasms (benign or malignant) formed in 12.5%, 14.1% and 17.5 % of subjects on semaglutide 0.1 mg, 0.2 mg and 0.4 mg OD, respectively. In the placebo group neoplasms formed in 7.5 % of subjects. Though numbers of subjects are small, overall neoplasm formations seems to be dose-dependent, including gastrointestinal neoplasms in 1.3%, 5.1% and 6.2% of subjects on semaglutide vs 0 subjects on placebo, and hepatobiliary neoplasms (in 0, 1.3%, and 2.5% of subjects on semaglutide vs 0 on placebo). Renal cysts don’t show dose-dependency (in 3.8%, 1.3% and 0% of subjects on semaglutide vs 1.3% of subjects on placebo). The Applicant was asked to discuss the differences in neoplasm formation between the 2 trials) and also discuss the possible dosage-dependence in trial 4296.

In trial 4296, neoplasm formation AEs were reported by a higher proportion of subjects in the semaglutide groups than in the placebo group. However, this evaluation was based on relatively small treatment groups and numerically few events. The applicant considered that the number of neoplasms reported are too low to conclude on dose dependence and this was accepted.

According to the interim safety evaluation of trial 4553 based on 1195 subjects, AEs of neoplasms were reported by comparable proportions of subjects and event rates in the semaglutide 2.4 mg group (8.5%, 6.3 events per 100 PYO) and in the placebo group (9.9%, 8.4 events per 100 PYO).

This is in line with the development programme of Wegovy and data from the large, long-term CVOT EX9536-4388.

Renal function and AKI. Adverse events of acute renal failure were reported infrequently, at comparable rate on semaglutide and placebo, in 0.6% vs 0.5% respectively, which is reassuring. However, a numerically slightly higher number of serious cases of AKI were reported on semaglutide versus none on placebo. These cases concerned AKI stage 3, likely due to prerenal causes since cases improved following measures to correct BP and hydration. These were most probably caused by the known GI AEs leading to dehydration. This risk was already reflected in the SmPC.

Adverse events of urolithiasis seem to have been reported frequently, though it is difficult to get a complete overview due to a variety of PT's that can be used, including nephrolithiasis, urolithiasis, and hydronephrosis, and also cases of AKI/CKD may be related. The events of urolithiasis occurred slightly more frequently in study 4553 (semaglutide vs placebo: 1.8 vs 1.3 events per 100 PYE) compared to other clinical studies performed with semaglutide (in weight management and T2D programs, semaglutide vs placebo, range: 1.5 - 0.17 vs 1.4 - 0.09 events per 100 PYE). The increase, however, is considered small, and it may be explained by the different populations. In study 4553, MASH population with fibrosis stages 2 and 3 were included, and non-alcoholic liver disease has been associated with an increased risk of urolithiasis (*Miao, Int. J. Med. Sci. 2025*). A slight difference is noted in study 4553 between semaglutide and placebo, although the difference is also small, and it is not possible to conclude an effect of semaglutide. Regarding hydronephrosis and acute renal failure, the event rates in study 4553 are also in line with other semaglutide studies.

Hypoglycaemia. In study 4553, ~55% of patients enrolled had a concomitant diagnosis of T2D in both treatment arms, and mean baseline HbA1c of 7.2% (55 mmol/mol) vs 6.9% (52 mmol/mol) was close to clinical practice target level of 54-58 mmol/mol for subjects with T2D for <10 years treated with antidiabetic medication (ADA criteria). Diabetes treatment consisted of metformin in most cases (41.4% vs 39.7%) and included insulin in 6.4% vs 8.7% of subjects and sulfonylureas in 9.5% vs 8.4% of subjects. In study 4553, a substantial proportion of subjects was concomitantly treated with DPP-4 inhibitors (baseline use in 9.9% vs 8.4% of subjects) and semaglutide, despite it is not advised to use GLP1-RA and DPP4-inhibitors concomitantly (*Davies et al. Management of Hyperglycemia in Type 2 Diabetes, 2018.A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD*)).

The proportion of subjects with T2D at baseline reporting hypoglycaemic events was higher in the semaglutide group, 19.3% vs 13.1% on placebo. Also, serious, clinically important hypoglycaemia (level 2, <3.0 mmol/l) and severe hypoglycaemia (requiring assistance from another person) were reported more frequently on semaglutide, in 6.1% vs 5.0% and 2.2% vs 0.5% of subjects, respectively. Given the definitions of level 2 or 3 hypoglycaemia, a number of events could be considered as level 2 instead of level 3. As such, the events are assessed as pooled data. The events reported with the use of semaglutide are in line with other semaglutide trials, although higher than in other studies. For instance, similar rates were reported in STEP 2 trial, where hypoglycaemic events level 2/level 3 occurred in 6.5% (10.9 events per 100 PYE) with semaglutide and 2.5% (3.2 events per 100 PYE) with placebo. In the study protocol of study 4553, no instructions seem to be included on management of antidiabetic medication at initiation of semaglutide, though in clinical practice reduction or discontinuation of insulin and /or sulfonylurea is advised, based on HbA1c levels. In study 4553, in MASH subjects without T2D hypoglycaemia was only rarely reported without imbalance between treatment groups (in 0.3% vs 0.6% of subjects). However, AEs of hypoglycaemia were evaluated based on a predefined MedDRA search only, as opposed to recording using a specific hypoglycaemic-episode form in patients with T2D, and therefore may be at risk of underreporting. In order to further estimate the risk of hypoglycaemia in patients without T2D, the applicant was asked to provide all the adverse events of the non-diabetic subjects in 4553 trial which could be related to

hypoglycaemia in the semaglutide and in the placebo group. Slightly higher frequencies and event rates were observed for the non-T2DM (NT2DM) population in the semaglutide 2.4 mg arm compared to the NT2DM population in the placebo arm with regards to frequencies, event rates, frequency of probably/possibly related events and discontinuation. Upon request, the Applicant clarified that there were 1 and 2 patients in the semaglutide and placebo groups respectively, who were NT2DM at baseline, but were diagnosed with T2DM later on during the study. Based on the above results, the Applicant was asked to include a general warning in SmPC 4.4 for the potential risk of hypoglycaemia concerning the whole patient population (instead of the present warning which concerns the patient population with comorbid T2D). Applicant was also asked to amend the ADR table in the SmPC 4.8 with the finding on Hypoglycaemia AE in NT2DM subpopulation. Based on the Applicant's answer there is no clear additional risk for hypoglycaemia in NT2DM subjects thus no update of SmPC is needed. Additionally, the possible relation between hypoglycaemic events and age, diabetes duration, and HbA1c at baseline, has been explored, showing no clear differences. The effect of concomitant medication was also explored, and a considerably larger proportion of subjects in the semaglutide 2.4 mg group reporting level 2 or 3 hypoglycaemic episodes were treated with insulin and SU at baseline compared to those not reporting episodes (insulin: semaglutide vs placebo, 15.2% vs 8.5%; SU: semaglutide vs placebo, 42.4% vs 15.0%). Additionally, subjects who initiated insulin or SU during the study reported hypoglycaemic events more often. This increase in hypoglycaemia is known and already stated in the SmPC of semaglutide. The effect of the combination of semaglutide and DDP-4 in relation to hypoglycaemia has also been explored, which showed no clear effect on hypoglycaemia and no need to further update the SmPC. The relation between MASH status and hypoglycaemic events among T2D patients has also been also explored, with no relevant relation between MASH status and hypoglycaemia.

Diabetic retinopathy. Worsening of diabetic retinopathy is a known risk of semaglutide in patients with T2D, and patient with uncontrolled diabetic retinopathy or maculopathy were excluded from all trials. In study 4553, events of retinal disorders were reported at a comparable frequency on semaglutide vs placebo (3.1% vs 4.1%), most frequently concerning diabetic retinopathy, all non-proliferative, with no worsening of visual acuity, and age-related macular degeneration in one case on semaglutide, not likely related. Similar results were seen in supportive study 4296. These results are reassuring, though patients who may be at increased risk were excluded. The lack of data in MASH-patients with uncontrolled diabetic retinopathy is appropriately reported in section 4.4 of the SmPC.

Non-arteritic anterior ischaemic optic neuropathy (NAION). The PRAC has recently reviewed a signal suggesting a potential association between semaglutide and NAION, which it classified as a very rare adverse reaction. The SmPC has been updated accordingly. As for Eye disorders SOC, one Blurred vision AE and one Double vision AE were considered as related Eye disorder AEs in the semaglutide arm of ESSENCE study. Since blurred vision, visual impairment and decreased visual acuity might be the symptoms of NAION the applicant has clarified that subjects with T2D at baseline or who developed T2D during the trial were to undergo regular eye examinations according to the trial protocol. If a subject (with or without T2D) experienced visual impairment AEs during the trial, it was at the discretion of the investigator to follow up on the clinical sign or symptom as part of normal safety follow-up at each visit. As for eye examinations performed outside the clinical trial, the applicant would not have access to the findings, until it was reported as an adverse event. The Applicant also provided the numbers and frequencies of visual impairment-like AEs as requested. The intensity and time-course of these AEs were not indicative for NAION and their occurrence was balanced between the two treatment groups.

Immunogenicity. A low rate of ADAs without subjects with in vitro neutralising antibodies and no impact on safety was seen across studies in MASH subjects, in line with data on semaglutide for T2D and weight management.

Ferritin. In trial 4553, the geometric mean values of ferritin decreased from baseline to week 72 for both semaglutide 2.4 mg and placebo, with ratio to baseline of 0,67 in the semaglutide group and 0,79 in the placebo group. As ferritin correlates to the iron-content of the body, the long-term risk of iron deficient anaemia cannot be excluded. Taking into account that semaglutide has gastrointestinal side effects which can cause malabsorption of nutrients including iron, the applicant was asked to show how haemoglobin varies depending on ferritin levels and give an explanation of the change of ferritin and if it can be related to hepatic functions. Haemoglobin levels seem to decrease until the 120th week, which might cause anaemia in the long term. The Applicant therefore was requested to provide graphical analyses of ferritin and haemoglobin over time. In addition, the Applicant was asked to formally assess the correlation between changes in ferritin and haemoglobin, including the possibility of a lag effect (i.e. that haemoglobin levels may follow ferritin changes with some delay). Based on these analyses, the Applicant was also asked to discuss the potential clinical implications for the risk of anaemia during long-term treatment. Ferritin levels remained in the normal ranges. Note that statistically significant conclusion cannot be made from the longer-term results due to the rather limited patient number beyond Week 120, and the decreasing ferritin levels still can be the sign of reduced inflammation and not the risk of slowly developing anaemia.

Changes in the mean Hb concentration is rather slight in both placebo and semaglutide groups, however a seemingly opposite trend can be observed in the semaglutide and in the placebo group from Week 72. This might suggest a delay in the decrease of the mean Hb concentration in the semaglutide group compared to the drop of the ferritin level which raises the possibility of the correlation between the ferritin and Hb decrease in the semaglutide group.

However, it was not considered as an important safety issue, so it is was not pursued further.

Safety in special populations

MASH subgroups. In addition to safety data from pivotal study 4553 in 800 subjects with MASH F2 (n=174) and F3 (n=628) treated with semaglutide 2.4 mg, supportive data across stages of MASH come from study 4296 in 239 subjects with MASH F1 (n=68), F2 (n=50) and F3 (n=122) treated with semaglutide 0.1 mg, 0.2 mg or 0.4 mg, study 4492 in 47 subjects with MASH F4c treated semaglutide 2.4 mg, and study 4381 in 33 subjects with NAFLD with increased liver stiffness treated with semaglutide 0.4 mg OD. In general, a comparable safety profile was seen across subjects with MASH F1, F2, F3 and NAFLD with increased liver stiffness.

Specifically, though MASH compensated cirrhosis (fibrosis stage F4c) is not the intended target population for semaglutide 2.4 mg, patients with MASH and significant liver fibrosis may over time progress to compensated cirrhosis. While limited data is available (Study 4492) an no firm conclusions can be drawn, severe AEs were reported more frequently in MASH F4c patients (17%) compared to MASH F2 F3 patients (8.7%). However, the main events were related to GI AEs, which is a known risk, and no cluster of events was observed.

Baseline BMI. In study 4553, a total of 113, 115, 249 and 323 subjects with BMI <27, 27-<30, 30-<35, and >=35 kg/m^2 were treated with semaglutide. AEs, SAEs and severe AEs were reported at comparable frequency across BMI ranges, but interruption or reduction of semaglutide dose was reported more frequently in subjects with BMI < 27 kg/m^2, in 21.2% vs 8.0%-13.7% and 21.2% vs 5.9%-12.2%. Most of the events triggering dose adjustments were related to GI AEs, which is expected given differences in exposure by BMI and the known safety profile of semaglutide. Differences in exposure due to low and high BMI are acknowledged and already reflected in section 5.2 of the SmPC in an adequate manner. Further, dose recommendations in section 4.2 of the SmPC already mention the need of dose escalation, including the likelihood of significant gastrointestinal symptoms and the possibility of delaying the dose escalation or lowering the dose according to these symptoms, which is considered sufficient to guide a personalised approach for each patient.

In study 4553, a comparable safety profile was seen when analysed separately in subjects with or without T2D, or across race. When analysed across sex, AEs were reported at comparable frequency by female and male subjects, and most events are considered unlikely related to study drug treatment. No additional warnings by sex are considered necessary.

The **thyroid function** is commonly affected in metabolic syndrome, and hepatic hypothyroidism is known as an important underlying pathophysiology in NASH/MASH. TSH level wasn't tested neither in the screening period nor during visits, however, in total 115 subjects (14,4%) had hypothyroidism at baseline and further 44 subjects had other thyroid-related illnesses. 120 (15%) subjects were already on levothyroxine medication. The Applicant was therefore asked to provide a subgroup analysis of safety parameters (overall safety, AEs by SOC and PTs, SAEs, AESIs) comparing subjects with hypothytroidism to non-hypothyroid subjects. According to the Applicant's response, slight but clear differences can be seen for hypothyroid patients compared to the non-hypothyroid ones. However, these differences are not consistent over the whole AE spectrum, and they do not seem to be clinically meaningful.

Age. In study 4553, a substantial proportion of subjects randomised to semaglutide 2.4 mg were aged >= 65 years (26.3%). AEs were reported at similar frequency across age-groups <45, 45-64, and >=65 years of age, in ~85% of subjects, leading to dose reduction in a higher proportion of patients >=65 years (13.8% vs ~8.5%) and discontinuation of semaglutide in 3.3% vs 0.8% at age <45 years. A higher proportion of subjects >= 65 years of age on semaglutide reported SAEs, in 14.8% at age >=65 years vs 10.8% < 45 years, and severe AEs (11.9% vs 5.0%). Decreased appetite was reported more frequently in subjects >= 65 years of age as compared with younger age groups, and as compared with placebo, which may result in (unwanted) weight loss and loss of muscle mass. At higher age, patients may benefit less from long-term beneficial effects with regard to progression of MASH due to a more limited life expectancy and may be more at risk due to unwanted adverse effects like loss of weight or muscle mass. However, this is part of the mechanism of action of semaglutide and well-known in clinical practice. Updates in the SmPC were not considered necessary. In the current application, data from the pivotal study 4553 on treatment for 72 weeks are provided. Final results of study 4553 will be submitted after completion of the planned 240 weeks of treatment, providing relevant additional safety data, including data on several safety risks that are expected to persist (like hypoglycaemia) or increase (like cholelithiasis and acute pancreatitis) during long-term treatment.

5.4.12.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 above.

Table 43: Summary of ADRs proposed for inclusion by the applicant in the SmPC

Immune system disorders		Link to data
Very Common Common Uncommon Rare	Anaphylactic reaction	Summary 2.7.4 (Wegovy), Appendix 7.2.2
Metabolism and nutrition disorders		
Very Common Common Uncommon	Hypoglycaemia (level 2+3) in patients with type 2 diabetes[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.124
Nervous system disorder		

Very Common	Headache[b]	Summary 2.7.4 (Wegovy), Appendix 7.3.12
Common	Dysgeusia[b,c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.9
	Dizziness[b]	Summary 2.7.4 (Wegovy), Appendix 7.3.8
	Dysaesthesia[a,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.7
Eye disorders		
Very Common		
Common		
Uncommon	Diabetic retinopathy in patients with type 2 diabetes[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.58
Cardiac disorders		
Very Common		
Common	Hypotension	
Uncommon	Increased heart rate[a,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.6
	Orthostatic hypotension	
Gastrointestinal disorders		
Very Common	Vomiting[a,b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Diarrhoea[a,b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Abdominal pain[b,c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Constipation	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Nausea[a,b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Nausea[a,b]	Summary 2.7.4 (Wegovy), Appendix 7.3.1
Common	Gastritis[b,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.2
	Gastroesophageal reflux disease[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Dyspepsia[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Eructation[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Delayed gastric emptying	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Gastroenteritis	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Flatulence[b]	Summary 2.7.4 (Wegovy), Appendix 7.3.5
	Increased lipase[c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
	Abdominal distension[b]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.47
Uncommon	Acute pancreatitis[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.61
	Increased amylase [c]	Summary 2.7.4 (Wegovy), Appendix 7.3.4

Not known	Intestinal obstruction[c,d,e]	Summary 2.7.4 (Wegovy), Appendix 7.3.10
Hepatobiliary disorders		
Very Common Common Uncommon	Cholelithiasis[a]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.49
Skin and subcutaneous disorders		
Very Common Common Uncommon	Hair loss[a]	Summary 2.7.4 (Wegovy), Appendix 7.3.11
General disorders and administration site conditions		
Very Common	Fatigue[b,c]	Summary 2.7.4 (Wegovy), Appendix 7.3.3
Common	Injection site reactions[c]	Trial 4553 (M 5.3.5.1), TFL Table 8.3.1.67
Rare	Angioedema	

AEs for which a causal relation with semaglutide was judged by the investigator as at least a reasonable possibility, are proposed to be included in section 4.8 of the SmPC as Adverse Drug Reactions. The majority of ADRs included in the SmPC 4.8 ADR table are in accordance with the information on related AEs as presented in the CSR of ESSENCE study. For the events of myalgia and muscle spasms, depression and depressed mood, and diverticulitis minor increases are observed in the semaglutide group, although the differences are small and most cases were considered unlikely to be related to the drug. No updates of the SmPC were considered necessary.

In addition to AEs reported in pivotal study 4553 (ESSENCE) in the target population at the target dose of 2.4 mg once weekly that are causally related to semaglutide, also ADRs reported in studies on Wegovy in weight management are included in the listing of adverse events.

5.4.12.2. Conclusions on clinical safety

Based on the currently available safety data in patients with MASH F2/F3 treated for at least 72 weeks, semaglutide appears to be acceptably tolerated, with 82% of subjects uptitrated to the target dose of 2.4 mg once weekly, and only 3.3% discontinuing treatment due to AEs. Gastrointestinal AEs were the most common AEs reported, predominantly nausea, diarrhoea, vomiting and constipation, mainly occurring during dose escalation phase, though nausea was reported throughout treatment. SAEs were reported in a limited number of cases, without clustering of specific events, leading only to discontinuation of semaglutide in 0.3% of subjects. No differences in safety profile were seen across stages of MASH, or presence of concomitant T2D, and in general the safety profile was consistent with semaglutide in T2D and for weight management.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP:

Table 44: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	• Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy • Breastfeeding • Patients with severe hepatic impairment • Patients with lean MASH*

*BMI<25 in non-Asians or BMI<23 in Asians. Abbreviations: MASH = metabolic dysfunction-associated steatohepatitis; T2D = type 2 diabetes mellitus

6.1.2. Discussion on proposed safety specification

Extensive data from clinical development programs as well as post-marketing data are available on semaglutide in T2D and in weight management. The RMP for Kayshild is overall in line with the RMP of previous semaglutide products.
Nevertheless, for Kayshild "patients with lean MASH" is proposed as missing information in the RMP. The number of subjects included in study 4553 with lean MASH (MASH and BMI < 25 kg/m2 (or BMI < 23 kg/m2 for Asian population) is very limited (N=76; n=52 in semaglutide and n=24 in placebo) and the current indication is the first indication for semaglutide that includes patients with BMI<27. Further, interruption or reduction of semaglutide dose was reported more frequently in subjects with BMI < 27 kg/m2 vs BMI>27kg/m2, in 21.2% vs 8.0%-13.7% and 21.2% vs 5.9%-12.2%, respectively, pointing to potential tolerance issues of semaglutide in this population. Therefore, inclusion in the listing of Missing information was accepted, and the limited information in lean MASH patients was appropriately reflected in section 4.4 of the SmPC.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan

Routine Pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting/ PSURs and signal detection are deemed necessary to monitor the risks related to semaglutide.

Additional Pharmacovigilance activities

In addition, the applicant has proposed the following additional pharmacovigilance activities (on-going

and planned), see Table 45.

Table 45: Planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk) – semaglutide s.c. for T2D, oral semaglutide for T2D, semaglutide s.c. 2.4 mg for WM and semaglutide s.c. 2.4 mg for MASH.				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk) – semaglutide s.c. for T2D, oral semaglutide for T2D, semaglutide s.c. 2.4 mg for WM and semaglutide s.c. 2.4 mg for MASH.				
None				
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) – semaglutide s.c. for T2D, oral semaglutide for T2D, semaglutide s.c. 2.4 mg for WM and semaglutide s.c. 2.4 mg for MASH.				
MTC-22341 Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry On-going	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace.	Medullary thyroid cancer	**Semaglutide s.c. for T2D**	
			Submitted protocol	February 2019
			Final report	December 2033
			Oral semaglutide for T2D	
			Submitted protocol	November 2020
			Final report	February 2037
			Semaglutide s.c. 2.4 mg for WM and semaglutide s.c. 2.4 mg for MASH	
			Submitted protocol	August 2022
			Final report	February 2039
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide in patients with type 2 diabetes On-going[a]		Pancreatic cancer	**Semaglutide s.c. for T2D**	
			Adopted protocol	20 Sep 2018
			Final report	March 2026
			Oral semaglutide for T2D	

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	The study will evaluate whether exposure to semaglutide increases the risk of pancreatic cancer in patients with T2D. (Results from the study will also be relevant for the ongoing evaluation of the risk for semaglutide s.c. 2.4 mg for WM and semaglutide s.c. 2.4 mg for MASH)		Adopted protocol	12 Nov 2020
			Final report	March 2026
NN9535-4352 Long-term effects of semaglutide on diabetic retinopathy in participants with type 2 diabetes (FOCUS). Ongoing	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy (Results from the study will also be relevant for the ongoing evaluation of the risk for oral semaglutide for T2D, ~~and~~ semaglutide s.c. 2.4 mg for WM in patients with T2D and semaglutide s.c. 2.4 mg for MASH in patients with T2D)	Diabetic retinopathy complications (only for patients with T2D)	**Semaglutide s.c. for T2D**	
			Adopted protocol	19 Nov 2018
			Final report	February 2028

[a]Patient-level data on exposure to Ozempic® and Rybelsus® and follow-up for pancreatic cancer in the period 2018-2023 will be included in the study. The first extraction of data was done in 2020 and the last data extraction is planned in 2024 with final reporting of the study in 2025.

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; MASH = metabolic dysfunction-associated steatohepatitis; MTC = medullary thyroid cancer; NCA = national competent authority; PRAC = Pharmacovigilance Risk Assessment Committee; T2D = type 2 diabetes mellitus; TBD = to be determined.

6.2.2. Discussion on the pharmacovigilance plan

The routine pharmacovigilance activities proposed by the applicant are considered acceptable.

Additional pharmacovigilance activities include on-going post-authorisation safety studies (PASSs) regarding the important identified risk of diabetic retinopathy complications, the important potential risks of medullary thyroid cancer (MTC) and pancreatic cancer. The MASH patients were suggested to be included in the PASS for MTC, which was agreed. Information was added for the PASSs of diabetic retinopathy complications and pancreatic cancer that the results of these PASSs would also be relevant for the on-going evaluation of the risk for semaglutide s.c. 2.4 mg for MASH. The additional pharmacovigilance activities proposed above are acceptable.

6.3. Plans for post-authorisation efficacy studies

Table 46: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due date
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NN9931-4553 (ESSENCE) The effect of semaglutide in participants with non-cirrhotic MASH Part 1 (week 72) completed Part 2 (week 240) ongoing	Part 1: To demonstrate that treatment with semaglutide s.c. 2.4 mg improves liver histology compared to placebo in participants with MASH and fibrosis stage 2 or 3. Part 2: To demonstrate that treatment with semaglutide s.c. 2.4 mg lowers the risk of liver-related clinical events compared to placebo in participants with MASH and fibrosis stage 2 or 3.	Part 1: the effect of semaglutide on liver histology in participants with MASH Part 2: the effect of semaglutide on clinical outcomes in participants with MASH	Interim study report Study completion Final report	February 2025 (data cut off 05 Sep 2024) June 2029 December 2029

Abbreviations: MASH = metabolic dysfunction-associated steatohepatitis; s.c. = subcutaneous.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 47: Description of routine risk minimisation measures by safety concern – semaglutide s.c. 2.4 mg for MASH

Safety concern	Routine risk minimisation measures
Diabetic retinopathy complications (only for patients with T2D)	**Routine risk communication:** SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** A recommendation to monitor patients with a history of diabetic retinopathy is included in the SmPC. Instructions to inform the HCP about a history of diabetic eye disease are included in the PL. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pancreatic cancer	**Routine risk communication:** None. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Medullary thyroid cancer	**Routine risk communication:** Nonclinical findings are presented in the SmPC Section 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Pregnancy	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during pregnancy and should be discontinued at least 2 months in advance if a patient wishes to become pregnant. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Breastfeeding	**Routine risk communication:** SmPC Section 4.6 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC and PL that semaglutide should not be used during breastfeeding. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

Safety concern	Routine risk minimisation measures
Patients with severe hepatic impairment	**Routine risk communication:** SmPC Sections 4.2, 4.4, and 5.2 and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that semaglutide is not recommended to be initiated for use in patients with moderate and severe hepatic impairment. **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.
Patients with lean MASH[a]	**Routine risk communication:** SmPC Section 4.4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** It is stated in the SmPC that there is limited experience in patients with MASH and BMI<25 kg/m^2 (or BMI<23 kg/m^2 for Asian population). **Other risk minimisation measures beyond the Product Information:** By the legal status of the product; prescription only.

[a]BMI<25 in non-Asians or BMI<23 in Asians.

Abbreviations: HCP = healthcare professional; MASH = metabolic dysfunction-associated steatohepatitis; PL = package leaflet; SmPC = Summary of Product Characteristics.

The applicant did not propose any additional risk minimisation measures. This was acceptable.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The routine risk minimisation measures (RMMs) proposed for the new indication MASH are acceptable.

6.4.2.2. Additional risk minimisation measures

The applicant did not propose any additional risk minimisation measures, which was considered acceptable.

6.5. RMP summary and RMP annexes overall conclusion

The RMP part VI and the RMP Annexes are acceptable.

6.6. Overall conclusion on the Risk Management Plan

The PRAC considers that the risk management plan version 10.2 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

Since this is an application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of Regulation (EC) No 726/2004, the PRAC rapporteur is of the opinion that a separate entry in the list of Union reference dates (EURD list) for Kayshild is needed, as it cannot follow the already existing entry for semaglutide. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The PSUR cycle for Kayshild should follow a half-yearly cycle. The data lock point (DLP) of the new EURD list entry for Kayshild should be aligned with the DLP of the existing semaglutide entry, facilitating for a fusion of the two if desired in the future.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The proposed indication is aligned with the population studied in the pivotal study.

8.1.2. SmPC section 5.1 justification

Information on the pivotal study supporting the indication is included in the SmPC section 5.1.

Besides key findings under alpha spending control, some additional secondary endpoints have been included which are considered of clinical relevance to the prescriber comparable to other approved medicinal products for MASH.

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Rybelsus and Wegovy. The bridging report submitted by the applicant has been found acceptable.

8.2.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group. In the 113th QRD meeting (June 2025) it was accepted to use mg per dose, instead of the QRD reference for the expression of strength for parenteral in multidose containers (mg/mL).

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kayshild ([semaglutide]) is included in the additional monitoring list since it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Metabolic dysfunction associated steatohepatitis (MASH) is a progressive liver disease, part of the spectrum of metabolic associated fatty liver diseases (MAFLD). It is estimated that the global prevalence of NAFLD is approximately 30% and increasing, and the global prevalence of MASH in the general population is estimated to be between 4% and 14%.

In approximately 20% of people with NAFLD, fatty liver disease progresses to MASH. As MASH progresses, fibrosis can lead to cirrhosis, associated with further complications such as hepatic decompensation events, liver failure and hepatocellular carcinoma (HCC), and increased risk for cardiovascular disease and (CV) mortality. NAFLD/MASH and cardiovascular disease share several cardiometabolic risk factors, including obesity, T2D, metabolic syndrome, hypertension, dyslipidaemia, and chronic kidney disease (CKD). Further, the presence of obesity and T2D increases the risk of fibrosis progression in MASH. Around 34% of people with obesity are believed to have MASH. Amongst people with T2D, global data indicate that around 66% have MASH, with 41% having significant liver fibrosis.

NAFLD and MASH are multifactorial diseases. Contributing factors include dysregulation of the lipogenic pathway, oxidative stress, genetic predisposition, altered immune responses, and gut microbiome dysbiosis. There is a growing body of evidence linking NAFLD and MASH pathogenesis with mechanisms of metabolic dysfunction, through liver lipid accumulation, insulin resistance, inflammation, apoptosis, and liver fibrosis.

The applicant proposed the following indication:

Kayshild is indicated in conjunction with diet and exercise for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1 of this document.

Liver fibrosis may be reversible, the evolution of MASH can be bidirectional, and the progression of MASH could potentially be stabilised or even reversed. The *Reflection paper on regulatory requirements for the development of medicinal products for non-alcoholic steatohepatitis (NASH)* (EMA/CHMP/111529/2024) acknowledge the unmet medical need.

Lifestyle changes, including diet and exercise have been considered standard of care. Treatments used off-label for the treatment MASH include Vitamin E, pioglitazone and GLP-1 Ras, which have been recommended by learned societies.

Recently, a medicinal product for MASH (Rezdiffra, INN: resmetirom) was granted a conditional marketing authorisation (Commission Decision issued on 18 August 2025).

Obesity and diabetes are risk factors for MASH, and a considerable proportion of the MASH population are obese patients and/or T2DM patients. Semaglutide is indicated to treat overweight patients (a BMI of 30 kg/m² or greater (obesity) or a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) who have weight-related health problems (such as diabetes, high blood pressure, dyslipidemia), or for the treatment of T2DM.

Bariatric surgery may be optional, however, is an invasive procedure that remains associated with several major risks, including surgical complications.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2 of this document.

The pivotal phase 3 study was a randomised, multicentre, double-blind, parallel-group phase 3 design to compare semaglutide s.c. 2.4 mg once weekly versus placebo s.c. once weekly (on top of standard of care) in 800 subjects (2:1) with MASH and F2 or F3 (recruitment cap of approximately 20% for subjects with F2), with a 16-week dose escalation phase, to demonstrate at the interim analyses that treatment with semaglutide s.c. 2.4 mg improves liver histology as based on the co-primary endpoints of *Resolution of steatohepatitis and no worsening of liver fibrosis*, and *Improvement in liver fibrosis and no worsening of steatohepatitis,* at Week 72. The (alpha controlled) key secondary endpoints included Resolution of steatohepatitis and improvement in liver fibrosis, Reduction in body weight, and Change in SF-36 Bodily Pain. The study included patients with confirmed stage F2 or F3 (with biopsy within 180 days), and a NAS ≥ 4 with a score of 1 or more in steatosis, lobular inflammation and hepatocyte ballooning, as based on a central pathologist evaluation. Both existing marketed single and multiple injectors (and placebo paired injectors) were used. A data monitoring committee independently and adjudicated events in a blinded manner.

The objective of Part 2 of the study is to demonstrate that treatment with semaglutide s.c. 2.4 mg lowers the risk of liver-related clinical events compared to placebo in subjects with MASH and fibrosis stage 2 or 3 at latest of 240 weeks.

9.3. Favourable effects

Primary endpoints Semaglutide was superior to placebo on intermediate histological endpoints at the pre-planned Week 72 interim of resolution of steatohepatitis and no worsening of liver fibrosis (62.9% vs 34.4%; 28.65 %-points [21.09; 36.21]95% CI; p-value <0.0001), and improvement in liver fibrosis

and no worsening of steatohepatitis (36.8% vs 22.4%; 14.39 %-points [7.51; 21.27]95% CI; p-value <0.0001). Sensitivity analyses were in agreement with these main findings.

Subgroup analyses The results were consistent across important subgroups of both endpoints. Especially, consistent findings were observed for the F2 and F3 subgroups, and for all subgroup categories of BMI also including <25 kg/m2 and 25-30 kg/m2 patients. Weight lowering in relation to MASH for patients at the lower weight/BMI spectrum was also achieved, and some limited data suggest that the greatest reduction was achieved on fat mass instead of lean body mass (STEP 12 in China/Asia).

Key secondary endpoints (under alpha control) Hierarchical testing demonstrated statistical significant effect of semaglutide on secondary endpoints of change in body weight (-10.51 kg for semaglutide vs -2.04 kg for placebo; -8.46 %-points [-9.55; -7.38]95%CI; p-value < 0.0001), and resolution of steatohepatitis and improvement in liver fibrosis (32.7% vs 16.1%; 16.54% [10.24; 22.83]95%CI; p-value <0.0001).

Other secondary (and exploratory) liver related endpoints Numerical statistical improvements could be observed for other (exploratory) secondary endpoints of histological MASH/liver related endpoints, liver-related imaging-based endpoints (FibroScan), and numerical statistical improvements in liver enzymes including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and other blood fibrosis biomarkers (Pro-C3 score and Enhanced Liver Fibrosis score).

Other secondary (and exploratory) cardiometabolic endpoints Numerical improvements were generally observed in other cardiometabolic markers (diabetes markers (HbA1c, HOMA-IR (exploratory)) (both diabetic and non-diabetic), lipid markers, and inflammation markers (hsCRP (secondary), TNF-alpha and IL-1R antagonist (exploratory)).

9.3.1. Uncertainties and limitations about favourable effects

Patient reported outcomes A clear effect on patient reported outcomes could not be demonstrated. The fourth hierarchical tested endpoint of patient reported outcome of SF-36 Bodily pain was not significant (0.86 vs -0.47; 1.34 [0.01; 2.67]95% CI; p-value =0.0488). Numerical improvement could be observed for the SF-36 Physical Component, SF-36 Mental Component, but not for MASH-CHECK abdominal pain. The general nature of the instrument of Change in SF-36 Bodily Pain does not entirely discriminate whether the changes in score from baseline to 72 weeks may be due to an effect of MASH or due to other related factors, such as reduction in BMI.

Mechanism of action The mechanism of action remains not entirely elucidated. Numerical improvements in cardiometabolic markers of weight reduction, diabetes markers (HbA1c, HOMA-IR (exploratory)) (both diabetic and non-diabetic), lipid markers, and inflammation markers (hsCRP, TNF-alpha and IL-1R antagonist) across the studies, may only constitute an indirect benefit. Non-clinical models could identify 72 proteins could be associated with the resolution of MASH, of which 26 may not be associated to weight loss, rather potentially to fibrosis and inflammation or other mechanism that have not been elucidated. These could also be associated with a proteomic phenotype in the phase 2 study and could possibly also be verified once the phase 3 study has been completed. Nevertheless, based on *post hoc* analyses, a relevant proportion of the treatment effects appears independent of HbA_{1c} control and body weight reduction.

Clinical endpoints and long-term efficacy As per the current interim results, no treatment effect has been demonstrated on clinical endpoints. Such evidence is expected at the end of the on-going phase 3 study. Nevertheless, once a positive opinion would be disseminated, this could raise a risk to the study integrity, e.g. causing additional drop-outs. The measures proposed by the Applicant in this

respect, as described further in the discussion on CMA below, were considered sufficient.

Age A consistent effect for patients over 65 years of age has been demonstrated for the primary endpoints, however, data on older age categories are limited. Only 20 patients were included in the study for the 75-85 age subgroup and none above 85 years of age. However, there appears to be comparable PK, and efficacy across subgroups of more or less than 70 years of age.

9.4. Unfavourable effects

Exposure In the pivotal study 4553, a total of 800 subjects with the indication of MASH F2-F3 were exposed to semaglutide targeted at a dose of 2.4 mg once weekly, with a total of 542 subjects treated for at least 12 months. The target dose of 2.4 mg was reached by 81.7% subjects treated with semaglutide at week 24.

Adverse events were reported at higher frequency in subjects on semaglutide as compared with placebo (86.3% vs 78.7%), predominantly gastrointestinal AEs (69.5% versus 46.8%), and were deemed probably or possibly related to the study drug in 68.6% vs 40.8%. Serious AEs were reported at comparable frequency on semaglutide (13.0%) vs placebo (12.9%).

Gastro-intestinal adverse events. Main adverse events reported concern gastro-intestinal adverse events, in 69.5% of subjects on semaglutide as compared with 46.8% of subjects on placebo, mainly nausea (36.1% vs 12.4%), diarrhoea (26.8% vs 12.2%), constipation (22.1% vs 7.8%) and vomiting (18.5% vs 5.6%). Decreased appetite was reported by 14.0% vs 2.5% of subjects.

Gallbladder related disorders were reported at slightly increased frequency on semaglutide (2.5% vs 1.5% of subjects), most frequently concerning cholelithiasis (1.4% vs 0.8%). Symptomatic acute gallbladder disease was seen at slightly increased frequency on semaglutide, in 5 vs 2 subjects.

Acute pancreatitis. A total of 5 events of acute pancreatitis were reported, 3 (0.4%) on semaglutide and 2 (0.5%) on placebo. Out of these, 3 events were categorised as SAE, 2 (0.3%) vs 1 (0.3%).

Hypoglycaemic events. In subjects with T2D at baseline, hypoglycaemic events were reported more frequently in the semaglutide group, 19.3% vs 13.1% on placebo. Also, serious, clinically important hypoglycaemia (level 2, <3.0 mmol/l) and severe hypoglycaemia (requiring assistance from another person) were reported more frequently on semaglutide, in 6.1% vs 5.0% and 2.2% vs 0.5% of subjects, respectively.

Safety profile across subgroups.

- Across MASH stage F1-F4c no difference in safety profile was seen.
- In subjects with baseline BMI< 27 kg/m2, interruption or reduction of semaglutide dose was reported more frequently than in higher BMI categories, in 21.2% vs 8.0%-13.7% and 21.2% vs 5.9%-12.2% of subjects, respectively.
- A higher proportion of subjects >= 65 years of age on semaglutide reported SAEs, in 14.8% at age >=65 years vs 10.8% < 45 years, and severe AEs (11.9% vs 5.0%).
- In female subjects in the semaglutide group, SAEs were reported more frequently than in male subjects, in 15.5% vs 9.7%.

9.4.1. Uncertainties and limitations about unfavourable effects

The **duration of exposure** to semaglutide 2.4 mg in the target population with MASH F2-F3, of 87.1 (50.7) weeks on semaglutide, and 82.8 (49.9) weeks on placebo is still limited, especially for assessing less frequently occurring adverse events that may occur at increasing frequency during

prolonged treatment, like cholelithiasis, acute pancreatitis, or neoplasms. This is accepted in the context of a CMA.

Temporary **discontinuation** or dose reduction of semaglutide were reported at increased frequency as compared with placebo, in 12% vs 6.8% and 10.0% vs 2.0%, respectively. Premature discontinuation of study treatment was only required in a small proportion of subjects without imbalance between study-arms (3.3% vs 2.6%).

There was a not-negligible **chance of unblinding** due to the characteristic and very common gastrointestinal AEs of semaglutide, and this effect in principle might hamper the assessment of clinical safety. Still, the safety profile of semaglutide in the general population is well established.

Higher rates of severe **hypoglycaemic events** were reported during the trial compared to previous studies with semaglutide. No new factors with a correlation to hypoglycaemic events have been identified. Additionally, the classification for severe hypoglycaemia in study 4553 did not include a specific glucose level threshold, but a description including an event with altered mental state and need of support from another person. Out of the 12 severe events, for half of the events plasma-glucose values were >3.0 mmol/L (54 mg/dL), and 10 were treated and resolved with water and food. This indicates that these events could have been classified as clinically relevant, rather than severe. In such case, the rates of severe events are considered less remarkable, and overall in line with other trials with semaglutide (e.g., STEP2).In study 4553, in subjects without T2DM at baseline AEs of **hypoglycaemia** were evaluated based on a predefined MedDRA search only, as opposed to recording using a specific hypoglycaemic-episode form in patients with T2D, and therefore may be at risk of underreporting. Additionally, a higher proportion of subjects without T2D reported potentially hypoglycaemia-related AEs in the semaglutide group (7.1 %) compared to placebo (5.8 %), however there is no clear additional risk for hypoglycaemia in NT2DM.

Safety data in patients >=75 years are very limited or not available. There is uncertainty about the **safety risks in elderly subjects**. The limited information available was reflected in the SmPC.

There is uncertainty about a potentially increased frequency of renal cysts (in 1.6% of subjects on semaglutide vs 0.5% on placebo), although none of the cysts showed malignancy and it is plausible that the higher number of events are due to chance finding when evaluating other AEs (primarily GI AEs).

In trial 4296 dose dependence of **AE frequencies in Neoplasm SOC** was observed with the highest AE frequency of 17.5% in the 0.4 mg/day dose group (vs 7.5% in placebo group). In Study 4553, however, the frequency of neoplasm AEs was roughly half compared to the previous study and in similar proportion compared to placebo (8.5% in semaglutide 2.4 mg/week vs 9.9% in placebo group).

9.5. Effects table

Table 48: Effects Table for Kayshild in the treatment of MASH with fibrosis stages F2 to F3 (data cut-off: 05 September 2024) based on study 4553

Effect (short description)	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*
Favourable effects			
Resolution of steatohepatitis and no worsening of liver fibrosis	62.9%	34.3%	**SoE:** Difference is significant (28.65 %-points [21.09; 36.21]95% CI; p-value <0.0001)); consistent across subgroups; improvement in key secondary endpoints of weight reduction and resolution of steatohepatitis and improvement in liver fibrosis **Unc:** Uncertain whether this intermediate histological endpoints translates in long-term clinical benefit; no clear benefit on patient reported outcomes
Improvement in liver fibrosis and no worsening of steatohepatitis	36.8%	22.4%	**SoE:** Difference is significant (14.39 %-points [7.51; 21.27]95% CI; p-value <0.0001)); consistent across subgroups; improvement in key secondary endpoints of weight reduction and resolution of steatohepatitis and improvement in liver fibrosis **Unc:** Uncertain whether this intermediate histological endpoint translates in long-term clinical benefit; no clear benefit on patient reported outcomes
Unfavourable effects			
Nausea	289/800 (36.1%)	49/395 (12.4%)	**SoE:** Similar findings in supportive MASH studies 4296, 4492, 4381, and on Wegovy for weight management **Unc:** N/A
Vomiting	148/800 (18.5%)	22/ 395 (5.6%)	
Diarrhoea	214/800 (26.8%)	48/ 395 (12.2%)	
Constipation	177/800 (22.1%)	31/395 (7.8%)	
Cholelithiasis	11/800 (1.4%)	3/395 (0.8%)	**SoE:** Similar findings on Wegovy for weight management **Unc:** Uncertain how risk will evolve beyond 72 weeks of treatment
Hypoglycaemia in subjects with T2D			**SoE:** Increased frequency on semaglutide consistent across levels of severity **Unc:** N/A
• Level 1	62/800 (13.9%)	20/395 (9.0%)	
• Level 2	27/800 (6.1%)	11/395 (5.0%)	
• Level 3	10/800 (2.2%)	1/395 (0.5%)	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; <sBA: serum bile acids>; <PELD: paediatric end-stage liver disease>; <MELD: model for end-stage liver disease score>; <SBD: surgical biliary diversion>; <OLT: orthotopic liver transplantation>; <PE: primary endpoint>; <SE: secondary endpoint>; <OR: odds ratio>.
Hypoglycaemia level 1: glucose <3.9 mmol/l and >=3.0 mmol/l; level 2: glucose < 3.0 mmol/l; level 3: a severe event characterised by altered mental state and/or physical functioing that requires assistance from another person for recovery (ADA 2023).

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

Semaglutide has demonstrated a significant treatment effect on both the histological endpoints of resolution of steatohepatitis and no worsening of liver fibrosis with a 29% difference (62.9% vs 34.4%) and 14% improvement in liver fibrosis and no worsening of steatohepatitis (36.8% vs 22.4%) in a reasonable time period of 72 weeks to expect a treatment effect. Histological evaluation of liver biopsies is currently considered the golden standard in the clinical trials for diagnosis and for follow-up of the disease, despite sampling error and possible evaluation variability. Still, histological endpoints have not been validated as true surrogates in absence of sufficient predictive data to quantitatively relate a treatment response to clinical improvement in the long-term. Nevertheless, histological intermediate endpoints are chosen as they reasonably predict the long-term outcome, and with independent statistical significance on both endpoints this is thought to account for uncertainties as much as possible in relation to possible clinical outcomes, as mentioned in the EMA MASH guideline. However, longer term data is needed to demonstrate that these intermediate benefits will also translate into clinical improvement.

Support has been provided by a significant improvement on the key secondary endpoint of resolution of steatohepatitis and improvement in liver fibrosis. However, this endpoint may highly overlap with the resolution of steatohepatitis and no worsening of liver fibrosis endpoint, and thus may have limited independent value, nevertheless increasing robustness of the combined data.

The demonstrated reduction in weight of -8.5% (10.5-2), comparable to what is seen in other indications, may indirectly support to some extent the benefits in MASH, as there appears an association between both. The exact mechanism has not been entirely elucidated, and other effects likely contribute to the treatment effect. Also, in the small subgroup of patients with BMI between 25 to 30 beneficial effects on the primary evaluation were demonstrated, which also could to some part be associated with weight reduction.

Results on patient reported outcomes were not that clear, with no clear beneficial treatment effects across the different questionnaire instruments. Also, it is questioned whether the key instrument of SF-36 Bodily Pain is able to specifically discriminate effects on MASH associated symptoms, especially in a non-cirrhotic population. The relevance of such findings is further complicated by symptoms possibly resulting from (other) co-morbidities in such a population. And although patients' well-being is important, given these uncertainties, such evaluation may thus be of limited value.

In general, the safety profile of semaglutide 2.4 mg once weekly in MASH F2-F3 is in line with findings from semaglutide in T2D and in weight management. Gastro-intestinal AEs of nausea, vomiting, diarrhoea and constipation occur frequently, mainly in the initial uptitration phase, and in general can be managed by (temporal) dose adaptation. Permanent discontinuation is only required in a small proportion of subjects. However, adverse events of cholelithiasis and acute pancreatitis, though occurring at low frequency, may have an unfavourable course in MASH patients, although current data do not show clear causality. Also, frequency of hypoglycaemia is higher than reported on other semaglutide trials, although comparable to trials such as STEP2. Long-term safety data in the MASH population are lacking, which may impact estimation of potential persistent or long-term safety risks, beyond what is known from experience with existing semaglutide indications.

9.6.2. Balance of benefits and risks

In general, semaglutide has demonstrated a beneficial effect by a significant improvement in both

intermediate relevant histological endpoints of resolution of steatohepatitis and no worsening of liver fibrosis and improvement in liver fibrosis and no worsening of steatohepatitis during an intermediate time frame of 72 weeks, which are thought to be reasonably likely to predict clinical outcome in the long term. Some supportive evidence on a beneficial effect come from an already known effect on body weight lowering, and a supportive histological endpoint of resolution of steatohepatitis and improvement in liver fibrosis. A series of other less relevant secondary endpoints of liver-related markers and cardiometabolic markers show numerical improvements, which may provide some further confidence on the observed treatment effect.

Nevertheless, whether these observed treatment effects will translate into long-term benefit remains to be seen and should be demonstrated by the on-going pivotal study.

The safety profile of semaglutide has already been largely characterised by evidence and experience in other approved indications. Semaglutide demonstrates a comparable safety profile in the current MASH population. Long-term safety data in the MASH population are lacking, which may impact estimation of potential persistent or long-term safety. Apart from these uncertainties, the safety profile could be considered acceptable.

Overall, semaglutide demonstrates a positive benefit risk based on interim results in a population of F2 or F3 fibrosis MASH.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Conditional marketing authorisation

9.6.3.1.1. Applicant's request for Conditional marketing authorisation

The applicant requested in the initial submission consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive in the following indication *Kayshild is indicated in conjunction with diet and exercise for the treatment of non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)*

The applicant has stated that the balance between the benefits and the risks identified for semaglutide 2.4 mg for the treatment of non-cirrhotic MASH with moderate to advanced liver fibrosis is considered favourable with the benefits outweighing the risks. In their view, the clinical development programme confirmed that semaglutide 2.4 mg led to clinically meaningful improvements in liver histology and other liver-related parameters, as well as to body weight loss and other cardiometabolic benefits. In addition, results confirmed that semaglutide 2.4 mg reduces the risk of MACE in people at risk of MASH. The safety and tolerability profiles were in line with those of semaglutide 2.4 mg for weight management (Wegovy) and of the GLP-1 RA drug class in general. The applicant has added that it is likely they will be able to provide comprehensive data.

The CMA application of semaglutide 2.4 mg for MASH is based primarily on an interim evaluation of trial 4553 (part 1) and the completed trial 4296. The primary endpoints of part 1 of trial 4553 as well as trial 4296 are intermediate liver histology endpoints, which according to the available regulatory guidelines and as supported by retrospective and prospective data are likely to predict a clinical benefit. The trial design is compliant with the EMA's reflection paper and has been discussed with EMA

in a scientific advice procedure.

To confirm that the documented improvements in liver histology with semaglutide 2.4 mg lead to meaningful benefits in clinically relevant liver-related outcomes, such as hepatic decompensation or progression to cirrhosis, the applicant has confirmed that part 2 of trial 4553 will continue in a blinded manner and be conducted with due diligence. Part 2 of trial 4553 also serves to assess long-term safety in patients with MASH. The primary endpoint for part 2 is a composite endpoint, which is pre-specified as cirrhosis-free survival at week 240 (cirrhosis-free survival corresponds to not having experienced one of the following types of liver-related clinical events: histological progression to cirrhosis, all-cause mortality, liver-induced model for end-stage liver disease (MELD) score ≥15, liver transplant or hepatic decompensation events.). Results from part 2 are anticipated to be available in 2029.

In order to ensure that Novo Nordisk will be able to provide comprehensive data, trial 4553 must remain double-blind after the interim evaluation (i.e., through mid-2029) and retention of the trial participants is crucial to ensure sufficient trial power.

Trial 4553 has completed global recruitment and a total of 1197 participants were randomised to trial products. The last patient, last visit (LPLV) is planned for April 2029. Novo Nordisk added that the company understands the importance of retaining participants in trial 4553 and has focused efforts to maximise retention.

Accordingly, Novo Nordisk has pre-emptively worked to ensure that initiatives to ensure adequate retention have been implemented during part 1 of the trial and that additional initiatives have been developed for part 2 of the trial. For example, trends in general retention, withdrawal and lost-to-follow-up, including patterns in the specific reasons, are closely monitored by trial management on an ongoing basis. Other important aspects of mitigatory actions include proactive identification and follow-up with participants at risk of withdrawing, close contact with the trial investigators and site staff as well as regular meetings with national lead principal investigators from all countries. Targeted participant and site material is available, including guidance on putting the part 1 results of trial 4553 in context. The current annual withdrawal rate in trial 4553 is 2.7%, which is in line with expectations. If needed, increased focus will be implemented, such as additional advising, education or retraining of site staff, development of new tools or revision of current tools and materials for retention.

The applicant motivated the choice of placebo as comparator, due to lack of pharmacological treatment options for patients with MASH. Furthermore, investigators were encouraged to provide standard of care in MASH. The company has added that, should a pharmacological treatment for MASH be approved during the conduct of this trial, the participants will also be able to initiate this treatment during part 2 after completing visit 13 (week 72) while continuing in the trial. This is in accordance with a pragmatic approach to compare two treatment regimens: one where semaglutide is available and another where it is not.

Additionally, protection of sensitive data by limiting public dissemination of such data until after the end of part 2 of trial 4553 is an important aspect to maintain trial integrity and minimise the impact on trial conduct and retention. Novo Nordisk has taken pre-emptive action to ensure that trial integrity-preserving procedures are pre-specified in an "Interim Evaluation Charter" (Interim evaluation charter for trial NN9931-4553 (M5.3.5.1)). It is acknowledged that it is crucial for the generation of comprehensive data that the integrity of the post-interim part of trial 4553 is not compromised by the interim evaluation, for example as a result of introduction of biases due to the disclosure of specific informationor unintentional unblinding of the trial until the end of part 2.

Based on experience from other large, long-term Novo Nordisk outcomes trials (e.g. the ongoing post-

authorisation safety trial FOCUS [NN9535-4352] and the completed CVOT SELECT), Novo Nordisk remains confident that comprehensive data can be provided at end of part 2 of trial 4553 to confirm the meaningful benefits on clinically relevant liver-related outcomes in patients with MASH.

- *Unmet medical needs will be addressed, as*

MASH is a serious progressive liver disease, which is part of the spectrum of metabolic dysfunction-associated steatotic liver disease (MASLD). The incidence of MASH is rising globally and may be underestimated due to a lack of awareness of MASH and missed diagnosis. It is estimated that the global prevalence of MASLD is approximately 30% and increasing. The global prevalence of MASH in the general population is estimated to be between 4% and 7%, based on data from 20194.

In approximately 20% of people with MASLD, steatotic liver disease progresses to MASH5, which is characterised by the presence of hepatic steatosis in at least 5% of hepatic cells with inflammation and hepatocyte injury (also known as hepatocyte ballooning), with or without evidence of liver fibrosis. As MASH progresses, fibrosis can lead to cirrhosis, which is associated with further complications such as hepatic decompensation events, liver failure and hepatocellular carcinoma. Consequently, MASH is one of the main indications for liver transplantation in many countries. The risk of mortality in MASLD/MASH increases with disease severity, with cardiovascular disease being the most common cause of death in people with MASLD. MASH progression is associated with increased risk of complications. In people with MASH and advanced fibrosis, liver-related events are the most frequent complication. A strong association between MASLD/MASH and increased cardiovascular risk is recognised with cardiovascular disease being the overall most frequent complication. MASLD/MASH and cardiovascular disease share several cardiometabolic risk factors, including obesity, T2D, metabolic syndrome, hypertension, dyslipidaemia, and chronic kidney disease.

MASLD and MASH are closely associated with metabolic abnormalities, such as visceral obesity, dyslipidaemia and insulin resistance, and may precede the development of obesity and T2D. Further, the presence of obesity and T2D increases the risk of fibrosis progression in MASH. Liver disease and mortality related to MASLD are predicted to continue to rise with the increase in the prevalence of obesity and diabetes, and an ageing population.

As discussed above, MASH is a serious progressive disease with substantial clinical, humanistic, and economic burdens. Still, with liver fibrosis being reversible, the evolution of MASH can be bidirectional, and the progression of MASH could potentially be stabilised or even reversed.

Hitherto, lifestyle changes, including diet and exercise have been considered standard of care. Excess body weight is an important risk factor for the development of MASH and progression of liver fibrosis. Although patients may achieve weight loss through lifestyle intervention, many are unable to maintain their weight loss.

When meeting the criteria for metabolic surgery and in the absence of decompensated cirrhosis, bariatric surgery is an option for people with MASH and has been shown to resolve MASH in around 80% of patients 1 year after surgery. Bariatric surgery, however, is an invasive procedure that remains associated with several major risks, including surgical complications.

Treatments used off-label for the treatment MASH include Vitamin E, pioglitazone and glucagon-like peptide 1 (GLP-1) receptor agonists (RAs).

In summary, MASH is considered a condition with high unmet need, which is also in accordance with EMA’s reflection paper stating that a CMA for MASH can be considered. Novo Nordisk considers that semaglutide 2.4 mg for MASH can address this unmet medical need, and the efficacy and safety of semaglutide 2.4 mg are described in the following sections.

- *The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.*

The Applicant has explained that, whilst semaglutide or any other GLP-1 RA are currently not approved for the treatment of MASH, the recent AASLD19 and AACE clinical practice guideline recommend considering semaglutide or other GLP-1 RAs for pharmacotherapy of MASH for patients who already have an indication for GLP-1 RAs. The AASLD guideline references semaglutide for the approved indications in T2D and obesity, its cardiometabolic benefits and the ability to improve MASH as shown in phase 1 and 2 clinical trials. In addition, the current EASL guidance recommend maximising the use of GLP-1 RAs for treatment of comorbidities in people with MASH.

In the Applicant's view, the clinical evidence provided from the on-going phase 3 and completed phase 2 trials demonstrated clinically relevant improvements in liver histology and other liver-related parameters as well as benefits on cardiovascular risk and cardiometabolic risk factors, including those related to key MASH-related comorbidities such as obesity and T2D.

In trial 4553 (part 1), the efficacy for the two intermediate endpoints (resolution of steatohepatitis and no worsening of liver fibrosis and improvement in liver fibrosis and no worsening of steatohepatitis) was demonstrated in a co-primary fashion. As supported by retrospective and prospective data and in accordance with available regulatory guidelines, the primary endpoints of the interim evaluation of the phase 3 trial 4553 are likely to predict clinical benefit.

Given the significant unmet need, Novo Nordisk considers that the immediate availability of semaglutide 2.4 mg for treatment of MASH clearly outweighs the risk inherent in the fact that fully comprehensive data, i.e. the validation of the meaningful benefits on clinically relevant liver-related outcomes, are still required.

9.6.3.1.2. Discussion on the request for a Conditional marketing authorisation

In regard to the request for conditional Marketing authorisation the rapporteur/CHMP consider the following:

Positive benefit risk balance

The benefit risk balance is currently considered positive, and the proposed defined target population has been appropriately defined. As per the interim clinical data provided within the procedure, semaglutide has demonstrated a beneficial effect on the intermediate relevant histological endpoints of resolution of steatohepatitis and no worsening of liver fibrosis and improvement in liver fibrosis and no worsening of steatohepatitis during current interim. These are thought to reasonably predict clinical outcome in the long-term.

It is likely that the applicant will be able to provide comprehensive data

Currently, data have been presented at the pre-defined interim stage up to week 72 out of the intended 240 weeks of follow-up for evaluation of clinical endpoints for MASH. Some supportive evidence from other endpoints strengthens these findings. Nevertheless, whether these observed treatment effects will translate in long-term benefit remains to be seen and should be demonstrated by the on-going pivotal study evaluating cirrhosis-free survival at week 240. Despite the known safety profile of semaglutide from existing indications, safety data from the pivotal study 4553 are based on treatment for 72 weeks which is rather limited, and final results of study 4553 after completion of the planned 240 weeks of treatment is expected to provide relevant additional safety data, including data on several safety risks that may persist (like hypoglycaemia) or may increase (like cholelithiasis and acute pancreatitis) during long-term treatment.

Once a marketing authorisation is granted, this could raise a risk to the study integrity, e.g. causing additional drop-out. Also, in the meantime available therapies could alter standard of care and jeopardize primary study estimation. However, the applicant has discussed measures to avoid publication of specific details and data that would pose a risk to the study design and integrity. These have been taken and will continue, to ensure that all recruited patients will remain in the study and include: close monitoring of potential drop-outs, close contact with study stakeholders, and advice and education and training on this aspect. Also, consideration is being given, including in the EPAR, to limiting public dissemination until the end of study. These measures are considered reassuring. The study is therefore overall considered feasible, and the provision of final study results will provide data post-authorisation for the comprehensiveness of the dossier and is therefore imposed as a specific obligation (SOB) to the CMA.

Additional safety studies are on-going, and it is expected that they will provide relevant information also in relation to the MASH indication: study MTC-22341 is an on-going medullary thyroid carcinoma surveillance study and study NN9535-4447 is an epidemiological assessment of the risk for pancreatic cancer associated with the use of semaglutide. They are both included in the RMP as non-imposed category 3 studies.

Unmet medical need

According to the EMA reflection paper, MASH is considered a progressive disease with a necro-inflammatory phenotype of non-alcoholic fatty liver disease, with the potential of development of cirrhosis and end-stage liver disease (ESLD) with increased risk of hepatocellular carcinoma (HCC). To that end, semaglutide would in principle fulfil an unmet medical need. In addition, a new medicine (resmetirom) has been granted a conditional marketing authorisation by the European Commission for the same indication as the one claimed for Kayshild. While the specific obligations are not yet fully completed, it is not possible to confirm the full benefit of a conditionally authorised product. Nevertheless, semaglutide is a medicinal product with a different mode of action (compared to resmetirom) extending the possibility of different treatment options in the treatment of MASH. Also, the demonstrated extra-hepatic benefits of semaglutide in addressing improvement (in other) cardiometabolic risk factors can be part of these considerations. Therefore, it is still considered that semaglutide would fulfil an unmet medical need to at least the same extent as for the already conditionally authorised product.

Benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

Very recently, another medicinal product for MASH with a comparable target population has been approved. Nevertheless, there is still an unmet medical need for this population as described above and for a part of the intended population, treatment with semaglutide is not yet indicated based on the already approved indications for semaglutide.

In addition, without treatment for MASH, F2/F3 patients are at high risk of disease progression to MASH cirrhosis, which increases the risk for liver-related morbidity and mortality. Semaglutide was superior to placebo on intermediate histological endpoints of resolution of steatohepatitis and no worsening of liver fibrosis, and improvement in liver fibrosis and no worsening of steatohepatitis, thus demonstrating a beneficial effect on MASH disease progression. Finally, the safety profile of semaglutide has been well established, although partly in a different population, which may provide a reasonable prediction of its risks in the current intended population. The benefits to public health of immediate availability of semaglutide to patients with MASH is considered to outweigh the risks although additional data regarding clinically relevant outcomes are still required to render the dataset to be comprehensive.

9.6.3.1.3. Conclusions and recommendation on conditional marketing authorisation

As comprehensive data on the product are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

The product is considered to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive in the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), in conjunction with diet and exercise, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.
- Unmet medical need will be addressed to at least the same extent as for the already conditionally authorised product, as semaglutide is a medicinal product with a different mode of action (compared to the already authorised medicinal product for this indication) extending the possibility of different treatment options in the treatment of MASH, which allows for a relevant contribution to a more individualised treatment approach. In addition, extra-hepatic benefits of semaglutide in addressing improvement (in other) cardiometabolic risk factors have been demonstrated.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. For a part of the intended population, treatment with semaglutide is not covered by the existing indications for semaglutide. Further, the safety profile of semaglutide has been well established, although partly in a different population, which may provide a reasonable prediction of its risks in the current intended population.

The CHMP considers the following measures necessary to address the missing data in the context of conditional marketing authorisation:

Table 49: Specific obligations in relation to the CMA

Description	*Due date*
In order to confirm the efficacy and safety of resmetirom in adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), the MAH shall submit the final results of NN9931-4553 (ESSENCE), a phase III, double-blind, randomized, placebo-controlled study.	31 December 2029

9.7. Benefit-risk conclusions

9.7.1. Final CHMP conclusions

The CHMP considered that the overall benefit /risk balance of Kayshild in the indication *treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3), in conjunction with diet and exercise*, is positive.