Assessment report for pharmaceutical medicinal product

Ozempic® 0.25 mg, 0.5 mg and 1 mg

21 March 2019

Division of Innovative Health Products and Services

Thai Food and Drug Administration

Name of product	1) Ozempic® 0.25 mg 2) Ozempic® 0.5 mg 3) Ozempic® 1 mg
Active Substance(s) (ATC code)	Semaglutide ATC code: A10BJ06
Pharmaceutical form	Solution for injection
Strength	Semaglutide 1.34 mg/ml
Routes of administration	Subcutaneous injection (SC)
Therapeutic indication)s(	Indication as stated in SmPC: Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise. • as monotherapy when metformin is considered inappropriate due to intolerance or contraindications. • in addition to other medicinal products for the treatment of diabetes.
	Indications as stated in the patient information leaflet (PIL) ยานี้ใช้เพื่อรักษาโรคเบาหวานชนิดที่ 2 โดยใช้เป็นยาเดี่ยวหรือใช้ร่วมกับยาอื่น ยานี้ช่วยลดระดับน้ำตาลในเลือด
Submitted number and date of submission	**Submitted number:** 1.Ozempic® 0.25 mg – 1C15023/62 (NB) 2.Ozempic® 0.5 mg – 1C15024/62 (NB) 3.Ozempic® 1 mg – 1C15025/62 (NB) **Date of submission:** 21 Mar 2019
E-Identifier Number	e6200006

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Submitted number: Ozempic® 0.25 mg: 1C15023/62 (NB), Ozempic® 0.5 mg: 1C15024/62 (NB) and Ozempic® 1 mg: 1C15025/62 (NB)

E-identifier: E6200006 (sequence 0000-0003)

Manufacturing site: Novo Nordisk A/S, Novo Allé, DK-2880, Bagsværd, Denmark
Submitted date : 21 Mar 2019

Part 1 :Introduction and summary review

Type 2 Diabetes Mellitus (T2D) is a progressive chronic metabolic disease primarily characterised by abnormal glucose metabolism. Data support a heterogeneous pathogenesis that involves environmental, lifestyle, and genetic components leading to chronic hyperglycaemia caused by insulin resistance in the peripheral tissue, reduced insulin production in the pancreatic β-cells and increased hepatic glucose release.

The prevalence of diabetes is increasing rapidly worldwide especially in middle- and low-income countries. It can cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. Due to the progressive nature of T2D, most patients will require treatment intensification, which can be in the form of additional anti-glycaemic oral agents or an injectable therapy.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is the one of effective medication group for DM. The GLP-1 peptide hormone belongs to the superfamily of glucagon-related peptides. Physiologically, GLP-1 is secreted as a response to food intake from the pre-proglucagon gene in the endocrine L-cells of the intestine as well as in the hindbrain from neurons in *nucleus tractus solitarus*. This agonists effect in the pancreas glucose-dependent release of insulin as well as an up-regulation of the biosysthesis of insulin glucokinase and glucose transporters. GLP-1R agonist also induces glucose-dependent lowering glucagon secretion, which in turn lowers the hepatic glucose output. Therefore, GLP-1 stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in glucose-dependent manner.

Semaglutide is structurally similar to liraglutide but modified to have a longer half-life. The extended half-life of the semaglutide molecule is primarily obtained by increased albumin binding, which is facilitated by a large fatty acid-derived chemical moiety attached to the lysine in position 26. The increasing of albumin binding promotes slowly degradation of semaglutide in plasma and results in decreased renal clearance prolonging the half-life of semaglutide to approximately 1 week.

The clinical development of semaglutide includes sixteen completed Phase 1 studies, one Phase 2 study and eight completed Phase 3 studies and one ongoing trial. The studies were performed in line with the Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus.

Semaglutide provides improvement of blood glucose with a low risk of hypoglycaemia together with the convenience of once-weekly dosing. In addition, semaglutide induces a robust, consistent weight loss by decreasing appetite and food intake. So, it can improve patient compliance because it is once-weekly dosing.

Semaglutide is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.

- in addition to other medicinal products for the treatment of diabetes.

Part 2 :Summary of the dossier

2.1 Type of marketing authorization application

- **Product type:** New Biological medicinal products
- **Application type** : Stand-alone application

- **Review method:** Abbreviated review (internal reviewer using un-redacted assessment reports from EMA together with expert panel meeting for overall assessment)

2.2 Administrative data

2.2.1 Product information

Name of Product :Invented name	Ozempic® 0.25 mg, Ozempic® 0.5 mg, Ozempic® 1 mg
Active Substance (s)	INN: Semaglutide
Strength	1.34 mg/ml
Therapeutic class (ATC Code)	Glucagon-like peptide-1 (GLP-1) analogues (A10BJ06)
Pharmaceutical form	solution for injection
Route of administration	subcutaneous use
Drug Characteristics	Clear and colourless solution
Packaging	cartridge (glass) in pre-filled pen
Package size(s)	1 pre-filled pen + 4 needles

2.2.2 Source

- **Name and address of the applicant for importation**

  Novo Nordisk Pharma (Thailand) Ltd. 98 Sathorn Square Office Tower, Unit 2101-2105, 21th Floor, North Sathorn Road, Silom, Bangrak, Bangkok, 10500, Thailand

- **Name and address of the manufacturer(s) of the dosage form**

  Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

- **Name and address of the packaging and the secondary packaging**

  Primary Packaging: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

  Secondary Packaging: Novo Nordisk A/S, Brennum Park, DK-3400 Hillerød, Denmark

- **Name and address of the manufacture(s) which take responsibility on inspection before release**

  Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark

Evaluation results

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark was licensed as manufacturer for Semaglutide, solution for injection. The manufacturer has been certified GMP compliance of a manufacturer by Danish Medicines Agency on 28 September 2017.

Marketing authorization holder, Novo Nordisk Pharma (Thailand) Ltd., also attached GMP clearance certificate approved by Bureau of drug control, Thai FDA.

Part 3 :Analytical Physico-Chemical, Biological and Microbiological Documentation

3.1 Drug substance

3.1.1 General Information

Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

3.1.2 Manufacture

3.1.2.1 Manufacturer(s)

Semaglutide was manufactured by Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark.

3.1.2.2 Description of Manufacturing Process and Process Controls

Manufacturing process

For manufacturing process data, All steps have been described and explained in dossier.

3.1.2.3 Control of Materials

The construction of the expression plasmid and the source and history of strain producing semaglutide precursor are described in detail. The cell bank system (master cell bank (MCB), working cell bank (WCB)) is explained and characterisation of MCB, WCB are reported. Stability results of MCB and WCB are available and the results comply with the specification acceptance criteria for the MCB and WCB.

No animal-derived substances are used in the production of semaglutide.

3.1.2.4 Control of critical steps and intermediates

Critical operational parameters and critical in-process tests are defined for process steps. A small set of critical operational parameters have been defined for the multistep process as has been supported by the evaluation studies in manufacturing process development. This limited selection and the fact that only these parameters have been fixed in the process description did raise questions on the criticality assignment. The issue was adequately addressed.

3.1.2.5 Process Validation

The manufacturing process design consists of process characterisation and process justification. This is followed by process performance qualification (PPQ) on consecutive batches, confirming that the semaglutide manufacturing process is capable of consistently producing semaglutide active substance of the required quality in manufacturing scale.

To ensure that the semaglutide active substance manufacturing process remains in a state of control during commercial manufacture and that the validated state following PPQ is maintained, ongoing process verification (referred to as continued process verification) has been initiated.

Based on the totality of the experiments performed during process justification, ranges of both critical and non-critical operational parameters and the acceptance criteria for the critical in-process tests have been supported. Steps having one or more critical operational parameters have been defined as critical steps.

The purity of the peptide before further chemical modification is specified. The results from the PPQ of the critical operational parameters, critical in-process tests, and the results of the semaglutide active substance specification tests were all consistent and all acceptance criteria were fulfilled.

Based on these results it is concluded that the semaglutide manufacturing process consistently produces semaglutide active substance of reproducible quality in accordance with the predetermined specifications, the process is considered validated and ready for commercial production.

The evaluation of impurity reduction was carried out at manufacturing scale covering representative production batches from the PPQ.

3.1.2.6 Manufacturing Process Development

Description and explanation of every change during product and process development is presented, batch analysis data and the use of the batch is indicated.

Comparability and stability data demonstrates that the process has been improved during development with respect to impurity levels and robustness of the manufacturing process. The changes made during development have not adversely affected the product with respect to quality, safety, or efficacy.

Evaluation result

Semaglutide was manufactured by Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. The manufacturer has valid GMP certified by Lægemiddelstyrelsen Danish Medicines Agency, Denmark; membered in PIC/s country. Manufacturing process and quality control is suitable by identification of critical steps in process and control including process validation, so all of documents confirm that drug substance manufacturing processes are reliable suitable and acceptable.

3.1.3 Characterisation

3.1.3.1 Elucidation of structure and other characteristics

Structural characterisation and elucidation of the physico-chemical properties of semaglutide have been performed using active substance batches representative of the manufacturing process used for phase 3 clinical trials and intended for the commercial product. The results of the structural characterisation of semaglutide have confirmed the expected and theoretical structure.

3.1.3.2 Impurities

The product-related impurities and process-related impurities have been well clarified and managed.

3.1.4 Control of drug substance

3.1.4.1 Specification

The drug substance specification including control of identity, purity, bioactivity and other general test has been provided.

3.1.4.2 Analytical procedures

The analytical procedures which comply with Ph. Eur., USP and JP are described.

3.1.4.3 Validation of Analytical procedure

All the analytical procedures for testing of semaglutide drug substance according to the specification have been established. The non-pharmacopoeia methods have been validated according to the ICH Q2 (R1) guideline. The pharmacopoeia analytical procedures have been verified under the actual conditions of use.

3.1.4.4 Batch analyses

All batch release data shown comply with the drug substance specification for semaglutide.

3.1.4.5 Justification of specification

The semaglutide drug substance batches included in the establishment of the proposed specification acceptance criteria for semaglutide drug substance have been manufactured for clinical phase 3 trials and onwards, including PPQ batches.

The semaglutide drug substance specification acceptance criteria have been established based one or more of the considerations. Relation to the drug product specification has been ensured. Justification of individual specification parameters and acceptance criteria is provided.

Evaluation result

Specification, analytical method and validation method of drug substance were followed by European Pharmacopeia and in-house methods were also evaluated by method validation on suitable parameters. In addition, manufacturer tested consistency on commercial batches the results shows all batches were consistency. Then all can summarized that manufacturing process, analytical method and process validation of drug substance was reliable, suitable and acceptable.

Evaluation result

Drug substance contained in standard container is suitable, reliable and acceptable.

3.1.5 Stability

All data for each test parameter from both primary and PPQ stability studies, when stored at long-term condition are within the acceptance criteria and shows no change over time. Furthermore, the batches have comparable trends.

In addition, all data for each test parameter from both primary and PPQ stability studies, when stored at accelerated condition, shows no change over time. The batches have comparable trends.

Based on data, a shelf life for semaglutide drug substance when stored at long term conditions has been established.

Evaluation results

Number of batches, condition, duration and parameters followed by ICH guideline are suitable. The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container.

3.2 Drug product

3.2.1 Description and Composition of the Drug Product

Component	Reference to Standard
Active substance	
Semaglutide	Novo Nordisk A/S
Excipients	
Disodium phosphate, dihydrate	USP, Ph. Eur.
Propylene glycol	USP, JP, Ph. Eur.
Phenol	USP, JP, Ph. Eur.
Hydrochloric acid	USP, JP, Ph. Eur.
Sodium hydroxide	USP, JP, Ph. Eur.
Water for injections	USP, JP, Ph. Eur.

Evaluation results

The formulation including active ingredient and excipients is complied with USP, JP, Ph.Eur and in-house specification that show formulation has standard and acceptable. Moreover, they have no use novel excipients in the formulation.

3.2.2 Manufacture

3.2.2.1 Manufacturer (s)

Ozempic was manufactured by Novo Nordisk A/S, Denmark.

3.22..2 Description of Manufacturing Process and Process Controls

Semaglutide solution for injection filled in a cartridge is manufactured by Novo Nordisk A/S, Denmark. The description of manufacturing process and process controls was satisfy provided.

Evaluation result

Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark is suitable and acceptable manufacturer. They show valid certificate of GMP compliance of a manufacturer from by Lægemiddelstyrelsen Danish Medicines Agency, Denmark and certified CPP from Danish Medicines Agency. The process is considered to a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable for producing the finished product of intended quality in a reproducible manner.

3.2.2.3 Controls of Critical Steps and Intermediates

The critical steps together with limits and actions for critical in-process controls for semaglutide finished product are provided.

3.22..4 Process Validation and/or Evaluation

Validation activities have been performed to confirm that the manufacturing process for semaglutide finished product is capable of consistently and reproducibly producing finished product of the required quality in commercial manufacturing scale.

The process justification program was designed based on a risk assessment of the semaglutide finished product manufacturing process summarising the experience from productions of clinical trial batches and development studies. The process justification was performed.

The process performance qualification programme (PPQ) was designed based on the conclusions from the process justification. Consecutive batches of semaglutide finished product have been manufactured in commercial scale.

Based on the results from the PPQ, it can be concluded that the manufacturing process for semaglutide finished product is in a validated state and suited commercial production.

Sterile filtration and aseptic filling are generally considered critical process steps, as both steps directly affect product sterility. These process steps are not considered specific for semaglutide drug product. Filter validation and aseptic validation have been performed and therefore identified parameters with impact on product sterility are not in the process justification specific for semaglutide drug product.

Based on the process justification studies and the risk assessment performed upon completion of process justification it is concluded that the defined commercial process for manufacturing of semaglutide results in a drug product of acceptable quality when operated within the established inprocess ranges.

3.2.3 Control of Excipients

The excipients are complied with Ph.Eur, USP and JP that show formulation has standard and acceptable. Moreover, they have no use novel excipients in the formulation.

3.2.4 Control of Drug Product

3.2.4.1 Specification (s)

The drug product specification including control of identity and other general test has been provided.

3.2.4.2 Analytical Procedures

The analytical procedures which comply with Ph. Eur., USP and JP are described.

3.2.4.3. Validation of Analytical Procedure

The analytical procedures are validated according to relevant ICH guidelines or reference is made to compendial requirements (*Ph. Eur.*).

Evaluation result

There are specification, analytical method, and process validation. All of them conducted by acceptable standard. Manufacturing processes of drug product follow Ph.Eur. and in-house verified by analytical validation. Moreover, Manufacturer identify in process control in each step for consistency. Overall, we can summarise that manufacturing process of drug product is suitable, reliable, consist and acceptable.

3.2.4.4 Batch Analyses

An extensive overview of the batch analysis testing results of drug product batches used during development is provided. Overall, results shown in-range of acceptable criteria.

3.2.4.5 Characterization of Impurities

A characterisation study was conducted to characterise the semaglutide related impurities generated during the manufacture and storage of semaglutide finished product.

No new impurities of semaglutide were found to be generated during the manufacturing of semaglutide finished product.

3.2.4.6 Justification of Specifications

The specification takes into consideration the consistency in the manufacturing process and the analytical procedure. After phase 3 and before submission, the acceptance criteria for impurities have been narrowed where justified.

Elemental impurities in semaglutide finished product have been assessed in alignment with ICH Q3D.

A number of issues were raised on the justification of specifications and were adequately addressed. A systematic and risk-based approach has been used to establish the control strategy of semaglutide finished product.

3.2.5 Reference Standards or Materials

For information on the reference materials for semaglutide drug product please refer to semaglutide drug substance.

3.2.6 Container Closure System

The container closure system for semaglutide solution for injection comprises the primary packaging, glass cartridge complies with the European Pharmacopoeia (Ph. Eur.) (type I glass), and the PDS290 pen-injector that is currently approved for delivery of several insulin and GLP-1 products in the EU.

The PDS290 pen-injector can deliver doses of 0.25 mg, 0.5 mg or 1.0 mg that is intended to function with a standard needle thread or a needle with a bayonet coupling. The PDS290 pen-injector is the device part of a drug device combination product according to the Council Directive 93/42/EEC concerning Medical Devices, Article 1 (3). Such products are regulated according to Directive 2001/83/EC relating to medicinal products for human use. The PDS290 pen-injector for semaglutide complies with ISO 11608-1 (Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems).

Evaluation result

Quality of container closure system of drug product complies with Ph.Eur. MAHs attached certificate of analysis data for considering, all results comply with the proposed specification. Then we can summarize that container closure of drug product is suitable and acceptable.

3.2.7 Stability

The proposed shelf life for semaglutide is 36 months when stored in a refrigerator (2°C to 8°C) and kept away from the cooling element, protected from light.

The studies were performed according to current ICH guidelines, where guidelines apply. The primary container closure systems used in the presented studies are identical to the ones intended for market.

Data from the photo stability study shows that the PDS290 pen-injector for semaglutide with the cap on provides a suitable protection of semaglutide solution for injection from light exposure.

Adventitious agents

The cell line has been tested for microbial purity. As no further raw materials or excipients of human or animal origin are used for the manufacture of semaglutide, the finished product is evaluated to be safe with regards to TSE agents and there is no risk of contaminating the product with mammalian viruses.

Evaluation result

Stability test of drug product including number of batch, condition, duration and parameter is suitable. Drug product stability protocol conforms to ASEAN Guideline. So, the proposed shelf-life of 36 months at the recommended storage temperature of 2-8°C and storage for 42 days at below 30°C is acceptable.

Assessor's conclusions on Quality

The evaluation result of un-redacted assessment report from EMA and analyzing in Thai-Asian environment and regulation can summarize that the critical points involving efficacy and safety had been clarified already. Moreover, the expert committee meeting on 24th October 2019 summarized in the similarly results. Then overall in the quality data on manufacturing and quality control of drug substances and drug product is acceptable.

Part 4 :Non-clinical documentation

4.1 Pharmacokinetics (ADME)

The pharmacokinetics were dose-proportional and there was no gender dependency.

4.1.1 Absorption

- The absorption of Semaglutide from the SC injection site was rapid in mouse and rat, but slower in rabbit, monkey and minipig.
- 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-normalized 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 hr in the mouse, 11 hr in the rat, 28 hr in the rabbit, 51 hr in the monkey and 148 hr in human.
- Comparison of single dose pharmacokinetics in monkey after subcutaneous and intravenous dosing indicated that elimination is not limited by the absorption rate from subcutis.

4.1.2 Distribution

- The Vd 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.
- 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 SC administration of [$_3$H]-Oct- or [$_3$H]-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 CNS (brain and spinal cord) and white fat.
    - The distribution and concentrations of [$_3$H]-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.

4.1.3 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 - 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 was capable of forming 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%).

4.1.4 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.

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.

4.2 Pharmacodynamics

4.2.1 Primary pharmacodynamics

- In normal male rats, the *in vivo* potency was estimated by dosing semaglutide subcutaneously (sc) followed by an i.v. glucose infusion 3 hrs later. Semaglutide stimulated plasma insulin secretion and lowered blood glucose at a dose of 123 µg/kg (~6 nM plasma exposure) and a trend towards stimulation was observed at 41 µg/kg.

- In male diabetic db/db mice, upon single or repeated 4-week sc dosing, semaglutide lowered blood glucose dose-dependently and had a long duration of action. The ED_{50} for lowering of blood glucose (6 hours post dosing) was estimated to be 1.2 µg/kg for semaglutide, whereas it was about 20-fold higher for liraglutide indicating that semaglutide was more potent *in vivo* than liraglutide. The maximal effect on blood glucose lowering was comparable for semaglutide and liraglutide, and was obtained at 4 - 8 µg/kg for semaglutide in the 4-week study. The effect on body weight was maximal at a dose of 21 µg/kg.

- The beta-cell-reduced Göttingen minipig is a model, in which the human conditions of impaired glucose tolerance are mimicked, and has more resemblance to humans than rodent models. This model was used for evaluation of duration of action of GLP-1R agonists. In a hyperglycaemic clamp study in betacell- reduced minipigs, semaglutide stimulated insulin secretion for up to 7 days after the last dose (8.2 µg/kg) was administered.

- GLP-1 and its analogues are, among other effects, able to reduce food intake, which is an important aspect in the treatment of obesity and diabetes. The subchronic efficacy of semaglutide on body weight reduction was evaluated in diet-induced obese (DIO) aged female rats, which were given chocolate in addition to normal chow for 9 months. Subcutaneous doses of 1.2 and 4.1 µg/kg once-daily for 77 days led to a dose-dependent, significant decrease in body weight, primarily from fat. Furthermore, semaglutide dose dependently decreased overall food intake, which mainly consisted of chocolate.

Leptin, total cholesterol and free fatty acids were significantly decreased after treatment with semaglutide while plasma glucose, HbA1c, insulin, glucagon and triglycerides were not changed.

- The effects of semaglutide on hypothalamic appetite signals were evaluated in high fat diet obese (DIO) mice. Dosing of semaglutide for 18 days (0.15 mg/kg, s.c., daily) significantly lowered body weight. This was associated with increased mRNA expression of the satiety peptide

cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus (ARC) in hypothalamus.

- Expression levels of the hunger peptides neuropeptide Y (NPY) and Agouti-related peptide (AGRP) in the ARC in hypothalamus were not different between semaglutide and vehicle but were lower than in the weight matched vehicle group.

- The effect and duration of semaglutide on lowering of food intake were also studied in young, growing pigs. Steady state plasma levels of semaglutide were achieved by dosing every other day at 21 µg/kg.When steady state had been reached, dosing was stopped and daily food intake was assessed.

- Semaglutide decreased food intake in pigs for at least 2 days after cessation of dosing. The potency of semaglutide for decreasing food intake was in magnitude comparable to liraglutide in pigs, but with a longer duration of action.

- The access and neuronal interaction of semaglutide in the rodent (SD rat, C57BL mice) brain was investigated using peripherally administered fluorescently labelled semaglutide. Semaglutide was shown to have access to discrete brain regions expressing the GLP-1R including some of the welldefined circumventricular organs. Fluorescently labelled semaglutide also gained access to brain regions protected by the blood brain barrier (BBB) such as NTS (nucleus tractus solitarus) in the brain stem and in hypothalamus, where it was present in CART positive neurons in the ARC. The fluorescent signal was lost in the GLP-1R Knock-Out (KO) mouse, suggesting dependence upon binding to the GLP-1 receptor. Electrophysiological measurements of mouse brain slices revealed that semaglutide (100 nM) directly stimulated Pro-opiomelanocortin (POMC)/CART neurons and indirectly inhibited neural activity in neurons expressing NPY.

- The effect of semaglutide on development of atherosclerosis was investigated in two hypercholesterolemic mouse models, the ApoE- and LDL-receptor KO mouse models, at sc doses of 4,12 and 60 µg/kg administered once-daily for 13 or 17 weeks, respectively. These models are widely used to study plaque formation when on a western diet (WD) consisting of high fat and carbohydrate content and 0.2% cholesterol.

- In the LDLr KO mouse model, semaglutide showed a significant, about two-third, reduction of aortic plaque area at all three dose levels tested. This effect was accompanied by a significantly reduced body weight gain and a reduction in plasma TG levels with the highest dose, while plasma cholesterol and cholesterol lipoprotein levels were not changed by semaglutide treatment.

- In the ApoE KO mouse, semaglutide treatment showed a significant attenuation of aortic plaque area at all three dose levels tested after 13 week daily treatment. This effect was accompanied by a significantly reduced body weight gain with all doses.

- In conclusion, the development of WD-induced aortic plaque lesion areas was attenuated by semaglutide in both KO models at all dose levels. The effect was partially independent of reduced body weight gain.

4.2.2 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.

Safety pharmacology

- 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 1 mg/week has been used for exposure comparison in the safety pharmacology section. A value of ~32 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 1.5-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 (>200-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 14-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 (~27-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.

Nonclinical pharmacodynamic drug interaction studies

The 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 Toxicology

Single dose toxicity

- 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.

Repeat dose toxicity

- 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 euthanization. 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.

Genotoxicity

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

Carcinogenicity

- 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 celltumours 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.

Reproduction toxicity

- In the main rat study which combined fertility and embryo-foetal development, there was no effect on male fertility. There were an increased number of females with irregular oestrus cycles, but this did not result in a reduced fertility index. From the mid-dose onward however, there was a reduced number of corpora lutea with reduced implantations and litter size at the high dose. As there was evidence of maternal toxicity at all doses, it is not clear whether these effects are related to treatment or secondary to reduced maternal body weight gain.

- 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 1 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 based on the fact that 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 relies 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, 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 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.

Local tolerance

- 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.

Evaluation result

Non-clinical data could summarize that study design were suitable and the results were reliable. Toxicity study followed by good laboratory practice and unmet unexpected toxicity. The expert committee meeting on 24th October 2019 summarized in the similarly results as un-redacted assessment report from EMA that overall in non-clinical data was suitable and acceptable.

Part 5 :Clinical Study Reports (Main clinical Study Phase 3a)

Table: Clinical study

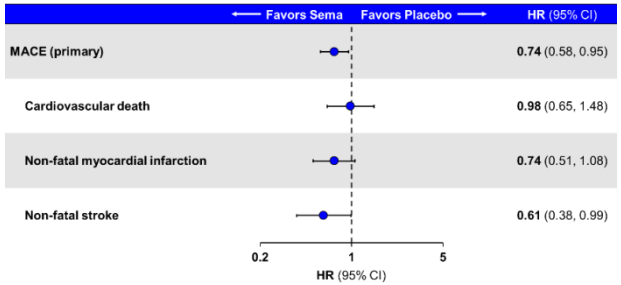
No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
1	**SUSTAIN 1:** Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes	Randomised, double-blind, parallel-group, placebo-controlled, multinational, multicentre, four-armed trial **Duration:** 30 weeks	**Subjects:** 388 T2D adult subjects treated with diet and exercise. **Objective:** Efficacy and safety (vs placebo) **Primary objective**: To demonstrate superiority of once-weekly dosing of two dose levels of semaglutide versus placebo on glycaemic control after 30 weeks of treatment in drug-naïve subjects with T2D. **Secondary objective**: To compare the effects of once-weekly dosing of two dose levels of semaglutide versus placebo after 30 weeks of treatment on: - Inducing and maintaining weight loss - Other parameters of efficacy, safety and tolerability.	1.Semaglutide 0.5 mg 2.Semaglutide 1.0 mg 3.Placebo 0.5 mg 4.Placebo 1.0 mg	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.6 % (-1.5% vs placebo; P<0.0001*) - Semaglutide 0.5 mg QW: -1.5 % (-1.4% vs placebo; P<0.0001*) - Placebo QW: 0% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs placebo. **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 72% - Semaglutide 0.5 mg QW: 74% - Placebo QW: 25% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs placebo. **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 60% - Semaglutide 0.5 mg QW: 59% - Placebo QW: 13% Significantly more subjects receiving semaglutide achieved HbA_{1c} <6.5% vs placebo. **4.Secondary Endpoint**: Weight Change From Baseline - Semaglutide 1 mg QW: -4.5 kg (-3.6 kg vs placebo; P<0.0001*) - Semaglutide 0.5 mg QW: -3.7 kg (-2.7 kg vs placebo;P<0.0001*) - Placebo QW: -1.0 kg Semaglutide was associated with significant reductions in body weight vs Placebo. In the case of semaglutide 1.0 mg, the degree of weight loss was at least twice as great as the respective comparator in each trial.

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
2	**SUSTAIN 2:** Efficacy and safety of semaglutide once-weekly versus sitagliptin once-daily as add-on to metformin and/or thiazolidinedione in subjects with type 2 diabetes	Randomised, double-blind, double-dummy, active-controlled, parallelgroup, multicentre, multinational, four-armed trial **Duration:** 56 weeks	**Subjects:** 1,231 T2D adult subjects who had not achieved adequate glycaemic control on metformin, thiazolidinedione (TZD) or a combination of metformin/TZD. **Primary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily on glycaemic control after 56 weeks of treatment. **Secondary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide versus sitagliptin 100 mg once-daily after 56 weeks of treatment on: - Inducing and maintaining weight loss - Other parameters of efficacy, safety and tolerability	1.Semaglutide 1.0 mg + Sitagliptin placebo 2.Semaglutide 0.5 mg + Sitagliptin placebo 3.Sitagliptin 100 mg + Semaglutide 1.0 mg placebo 4.Sitagliptin 100 mg + Semaglutide 0.5 mg placebo	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.6% (-1.1% vs sitagliptin; P<0.0001*) - Semaglutide 0.5 mg QW:-1.3% (-0.8% vs sitagliptin; P<0.0001*) - Sitagliptin 100 mg QD: -0.6% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs Sitagliptin. **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 78% - Semaglutide 0.5 mg QW: 69% - Sitagliptin QD : 36% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Sitagliptin **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 66% - Semaglutide 0.5 mg QW: 53% - Sitagliptin QD : 20% Significantly more subjects receiving semaglutide achieved HbA_{1c} <6.5% vs Sitagliptin. **4.Secondary Endpoint**: Weight Change From Baseline - Semaglutide 1 mg QW: -6.1 kg (-4.2 kg vs Sitagliptin;P<0.0001*) - Semaglutide 0.5 mg QW: -4.3 kg (-2.3 kg vs Sitagliptin; P<0.0001*) - Sitagliptin QD: -1.9 kg Semaglutide was associated with significant reductions in body weight vs Sitagliptin.

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
3	**SUSTAIN 3:** Efficacy and safety of semaglutide once-weekly versus exenatide ER 2.0 mg once-weekly as add-on to 1-2 oral antidiabetic drugs in subjects with type 2 diabetes.	Randomised, open-label, active-controlled, parallel-group, multinational, multicentre, two-armed, efficacy and safety trial **Duration:** 56 weeks	**Subjects:** 813 adult subjects diagnosed with type 2 diabetes (T2D) inadequately controlled on MET with or without an SU or TZD. **Primary objective:** To compare the effect of semaglutide 1.0 mg once-weekly versus exenatide ER 2.0 mg once-weekly on glycaemic control after 56 weeks of treatment. **Secondary objective:** To compare the effect of semaglutide 1.0 mg once-weekly versus exenatide ER 2.0 mg once-weekly after 56 weeks of treatment on: - Inducing and maintaining weight loss - Other parameters of efficacy, safety and tolerability	1.Semaglutide 1.0 mg 2.Exenatide ER 2.0 mg	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.5% (-0.6% vs Exenatide ER; P<0.0001*) - Exenatide ER 2.0 mg QW: -0.9% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs Exenatide ER 2.0 mg **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 67% - Exenatide ER 2.0 mg QW: 40% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Exenatide ER 2.0 mg **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 47% - Exenatide ER 2.0 mg QW: 22% Significantly more subjects receiving semaglutide achieved HbA_{1c} <6.5% vs Exenatide ER 2.0 mg. **4.Secondary Endpoint**: Weight Change From Baseline - Semaglutide 1 mg QW: -5.6 kg - Exenatide ER 2.0 mg QW: -1.9 kg (-3.8 kg vs Exenatide ER 2.0 mg; P<0.0001*) Semaglutide was associated with significant reductions in body weight vs Exenatide ER 2.0 mg.

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
4	**SUSTAIN 4:** Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonylurea in insulin-naïve subjects with type 2 diabetes	Randomised, open-label, active-controlled, parallel-group, multicentre, multinational, three-armed trial **Duration:** 30 weeks	**Subjects:** 1,089 insulin-naïve adult subjects with type 2 diabetes who had inadequate glycaemic control with MET alone or in combination with an SU **Primary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily on glycaemic control after 30 weeks of treatment in insulin-naïve subjects with type 2 diabetes. **Secondary objective:** To compare the effects of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily after 30 weeks of treatment on: - Inducing and maintaining weight loss - Other parameters of efficacy, safety and tolerability	1.Semaglutide 1.0 mg 2.Semaglutide 0.5 mg 3.Insulin glargine * Patients assigned to insulin glargine U100) were started on a dose of 10 U once daily. Insulin glargine dose adjustments occurred throughout the trial period based on SMPG before breakfast	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.6% (-0.8% vs insulin glargine; P<0.0001*) - Semaglutide 0.5 mg QW: -1.2% (-0.4% vs insulin glargine; P<0.0001*) - Insulin glargine QD: -0.8% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs Insulin glargine. **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 73% - Semaglutide 0.5 mg QW: 57% - Insulin glargine QD: 38% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Insulin glargine. **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 37% - Semaglutide 0.5 mg QW: 54% - Insulin glargine QD: 18% Significantly more subjects receiving semaglutide achieved HbA_{1c} <6.5% vs Insulin glargine. **4.Secondary Endpoint**: Weight Change From Baseline - Semaglutide 1 mg QW: -5.2 kg (-6.3 kg vs Insulin glargine; P<0.0001*) - Semaglutide 0.5 mg QW: -3.5 kg (-4.6 kg vs Insulin glargine; P<0.0001*) - Insulin glargine QD: +1.2 kg Semaglutide was associated with significant reductions in body weight vs Insulin glargine.

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
5	**SUSTAIN 5:** Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes.	Multinational, multi-centre, randomised, double-blind, parallel-group, placebo controlled Trial **Duration:** 30 weeks	**Subjects:** 397 adult subjects with type 2 diabetes (T2D) with inadequately controlled with basal insulin alone or in combination with metformin. **Primary objective:** To demonstrate superiority of once-weekly dosing of two dose levels (0.5 mg and 1.0 mg) of semaglutide versus placebo on glycaemic control in subjects with T2D on basal insulin. **Secondary objective:** To compare the effect of once-weekly dosing of two dose levels of semaglutide (0.5 mg and 1.0 mg) versus placebo in subjects with T2D on basal insulin with regards to: - Inducing and maintaining weight loss - Other parameters of efficacy, safety, tolerability and patient reported outcomes	1.Semaglutide 1.0 mg 2.Semaglutide 0.5 mg 3.Placebo 1.0 mg 4.Plabebo 0.5 mg	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.8% (-1.8% vs placebo; P<0.0001*) - Semaglutide 0.5 mg QW: -1.4% (-1.4% vs placebo; P<0.0001*) - Placebo QW: -0.1% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs Plabebo. **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 79% - Semaglutide 0.5 mg QW: 61% - Placebo QW: 11% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Plabebo. **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 61% - Semaglutide 0.5 mg QW: 41% - Placebo QW: 5% Significantly more subjects receiving semaglutide achieved HbA_{1c} <6.5% vs Plabebo. **4.Secondary Endpoint**: Weight Change From Baseline - Semaglutide 1 mg QW: -6.4 kg (-5.1 kg vs placebo; P<0.0001*) - Semaglutide 0.5 mg QW:-3.7 kg(-2.3 kg vs placebo; P<0.0001*) - Placebo QW: -1.4 kg Semaglutide was associated with significant reductions in body weight vs Placebo

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
6	**SUSTAIN 6:** Long Term Outcomes: To evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.	Randomised, double-blind, placebo-controlled, four-armed, parallel-group trial **Duration:** 104 weeks And follow up 5 weeks.	**Subjects:** 3,297 adult subjects with type 2 diabetes (T2D) at high CV risk with meet inclusion criteria as below: - HbA_{1c} ≥7.0% - Previously on 0–2 OADs, basal or pre-mix insulin ± 0–2 OADs - ≥50 years of age with established CVD (prior CV, cerebrovascular or peripheral vascular disease, chronic heart failure [NYHA Class II–III]), or CKD Stage 3 or worse - ≥60 years of age with at least one CV risk factor **Primary objective:** To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to placebo in adults with T2D. This is done by demonstrating that the upper limit of the two-sided 95% CI of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a MACE **Secondary objective:** To assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once weekly compared to placebo, both added on to standard-of-care, in adults with T2D at high risk of cardiovascular events.	1.Semaglutide 1.0 mg 2.Semaglutide 0.5 mg 3.Placebo 1.0 mg 4.Plabebo 0.5 mg	**1.Primary outcome** The total number of primary component MACE endpoints was 254 (108 [6.6%] with Semaglutide and 146 [8.9%] with placebo). Semaglutide was noninferior to placebo for the primary MACE endpoint. Treatment with Semaglutide resulted in a significant 26% risk reduction in the primary composite MACE outcome vs placebo (hazard ratio 0.74 [95% confidence interval 0.58-0.95]). The risk reduction in the primary composite outcome was mainly driven by a significant (39%) decrease in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no difference in CV death. **2.Secondary outcome**  The risk reduction in the primary composite outcome was mainly driven by a significant (39%) decrease in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal MI, with no difference in CV death.

No.	Trial No.	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
7	**SUSTAIN 7:**	Randomised, open-label, active-controlled, parallel-group, Multinational trial **Duration:** 40 weeks	**Subjects:** 1,201 patients with type 2 diabetes (T2D) inadequately controlled with metformin alone. **Primary objective:** To compare the effect of once-weekly semaglutide 0.5 mg and 1.0 mg versus the corresponding dose level of once-weekly dulaglutide (0.75 mg and 1.5 mg, respectively) on glycaemic control in subjects with T2D inadequately controlled with metformin alone. **Secondary objective:** To compare the effects of once-weekly dosing of two dose levels of semaglutide versus once-weekly dulaglutide (0.75 mg and 1.5 mg, respectively) with regards to: - Inducing and maintaining weight loss - Other parameters of efficacy, safety and tolerability	1.Semaglutide 1.0 mg 2.Semaglutide 0.5 mg 3.Dulaglutide 0.75 mg 4.Dulaglutide 1.5 mg	**1.Primary Endpoint:** HbA_{1c} Change from Baseline - Semaglutide 1 mg QW: -1.8% (-0.4% vs Dulaglutide 1.5 mg ;P<0.0001*) - Duraglutide 1.5 mg QW: -1.4% - Semaglutide 0.5 mg QW: -1.5% (-0.4% vs Dulaglutide 0.75 mg; P<0.0001*) - Duraglutide 0.75 mg QW: -1.1% Semaglutide demonstrated significant and sustained reductions in HbA_{1c} vs Duraglutide. **2.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <7.0% - Semaglutide 1 mg QW: 79% - Duraglutide 1.5 mg QW: 67% - Semaglutide 0.5 mg QW: 68% - Duraglutide 0.75 mg QW: 52% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Duraglutide. **3.Secondary Endpoint:** Percentage of Patients Achieving HbA_{1c} <6.5 % - Semaglutide 1 mg QW: 67% - Duraglutide 1.5 mg QW: 47% - Semaglutide 0.5 mg QW: 49% - Duraglutide 0.75 mg QW: 34% Significantly more subjects receiving semaglutide achieved HbA_{1c} <7.0% vs Duraglutide. **4.Secondary Endpoint**: Weight Change from Baseline - Semaglutide 1 mg QW: -6.5 kg (-3.6 kg vs Duraglutide 1.5 mg; P<0.0001*) - Duraglutide 1.5 mg QW: -3.0 kg - Semaglutide 0.5 mg QW: -4.6 kg (-2.3 kg vs Duraglutide 0.75 mg; P<0.0001*) - Duraglutide 0.75 mg QW: -2.3 kg Semaglutide was associated with significant reductions in body weight vs Placebo

No.	Trial No.	Rationale	Design	Subjects/ Primary Objective(S)	Intervention	Outcome
8	**FOCUS**	FOCUS is a post-authorisation safety study with EMA-approved trial protocol	Plabebo-controlled, double-masked, trial **Duration:** 6 years **Study start:** 08 May 2019 **End of study:** 21 May 2025	**Subjects:** 1,500 patients with inadequately controlled T2D will be randomised to semaglutide or placebo (1:1) both added to standard of care (SOC). **Primary objective:** To assess the long-term effects of treatment with semaglutide compared to placebo, both added to standard-of-care, on diabetic retinopathy development and progression in subjects with T2D. **Secondary objective:** To assess the effects of treatment with semaglutide compared to placebo, both added to standard-of-care, with regards to: - Visual acuity - Diabetic retinopathy manifestations (occurrence of diabetic macular oedema or proliferative diabetic retinopathy) - Diabetic retinopathy treatments (laser photocoagulation, intravitreal agents and vitrectomy) - Modifiable risk factors for diabetic retinopathy (glycaemia, blood pressure and lipids)	**Week 0- 4th** 1.Semaglutide 0.25 mg 2.Placebo 0.25 mg **Week 4th – 8th** 1.Semaglutide 0.5 mg 2.Placebo 0.5 mg **Week 8th – Week 260th** 1.Semaglutide 0.5 mg Or Semaglutide 1 mg 2.Placebo 0.5 mg or Placebo 1 mg	Ongoing trial **End of study:** 21 May 2025

Clinical studies are divided in 4 parts

1. Clinical pharmacodynamic

Semaglutide treatment, as compared with placebo, lowered fasting and postprandial blood glucose by improving multiple aspects of beta-cell function, including insulin secretion, and by reducing both fasting and postprandial glucagon concentrations, all in a glucose dependent manner. The data in the phase 3 trials show improvements in both HOMA-B and HOMA-IR. In the PD trial (3635), there was no apparent improvement in HOMA IR that may be explained by a generally better controlled diabetes (lower HbA1c, lower BMI) in line with the inclusion criteria of this PD trial and may thus have reduced the improvability of insulin resistance in these subjects. The mechanism of postprandial blood glucose lowering also involved a delay in gastric emptying.

Counter-regulation during hypoglycaemia was comparable with semaglutide treatment as compared with placebo. This was based on responses in concentrations of glucagon and C-peptide, and in glucose need during the clamp (AUC_{GIR}). A decreased recognition of hypoglycaemia was also observed. It is not clear if this should be considered favourable or not: on the one hand, it may represent subject's adaptation to normalised glucose levels, on the other hand, it could represent hypoglycaemia unawareness.

The body weight loss observed with semaglutide was primarily from fat tissue. The mechanism of body weight loss involved lowered appetite, both in the fasting and postprandial state, leading to lowered daily energy intake. Semaglutide improved control of eating, reduced food cravings and reduced the preference for high fat foods, as compared to placebo. However, semaglutide reduced energy expenditure as assessed by resting metabolic rate (RMR) using indirect calorimetry/ventilated hood system by appr. 600 kJ per day. The underlying mechanism is not clear.

As evidenced by the QTc trial, semaglutide does not prolong QTc values. However, the effect of semaglutide on pulse rate appears to be larger than with other GLP-1RAs. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects without established CV disease remains difficult. In these subjects the differences in office HR were larger than in the whole population. Consistent with the GLP-1 receptor agonist class effect, a small, persistent increase in resting pulse rate was observed with semaglutide in the clinical trial data available at the time of planning the thorough QT/QTc trial, trial 3652. QTcI, QTcL and QTcF changes were all below regulatory thresholds.

For the observed data, a negative correlation between QTcB and RR interval was found; this association is demonstrated to materialize (albeit weakly) at a heart rate of 60. Consequently, overestimation may be an issue using QTcB in this study. Such association was not present for QTcI and RR intervals. Therefore QTcI (individual heart rate corrected QT interval) was pre-specified as the primary endpoint in this trial; avoiding correction methods for the primary objective that is known to be problematic for compounds with properties to elevate heart rate.

The exposure response model not provide support for the statements made in the report about a better glycaemic control with the 1.0 mg dose compared to the 0.5 mg dose. Both the 0.5 mg and 1.0 mg seem to reach the plateau of the E_{max} curve for HbA_{1c}. The number of GI events and time of GI events increases, whereas HbA_{1c} concentrations already seem to reach plateau at the E_{max} curve. This issue is further discussed in the Clinical Efficacy section.

The population PK analysis also showed a significant effect of body weight on the exposure of semaglutide. Patients with a relatively low body weight, and thus a higher exposure to semaglutide, appear to have a higher incidence of GI events and a lower chance that these adverse events subside over time due to tolerance. The applicant conducted an additional analysis to evaluate the relationship between body weight and the safety and efficacy of semaglutide. In this analysis no clear body weight related trend in the reporting of GI AEs and nausea has been observed across body weight categories and the efficacy (HbA1c change from baseline response) appears to be similar across body weight subgroups with the same dose of semaglutide. It can be concluded that both dose levels of semaglutide can be the safe and efficacious and should be based on individual needs.

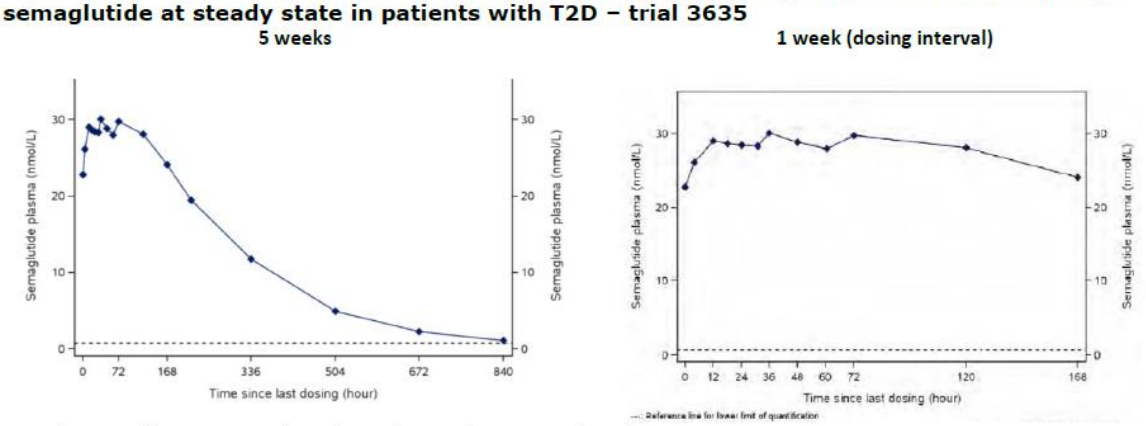
2. Clinical Pharmacokinetic

Absorption:

In the submitted studies it is shown that absorption of semaglutide after subcutaneous injection is slow and Tmax is reached between 24-36 hours post dosing. The slow absorption from the subcutaneous compartment to the systemic circulation is clearly attributing to the prolonged exposure to semaglutide. The absolute bioavailability was estimated to be 89% after abdominal SC administration (study 3687). After a single dose of semaglutide S.C. the systemic concentrations were maintained at the same level for about 7 days. Steady state concentrations were achieved after 4-5 weeks. Fluctuation between $C_{max\ ss}$ and $C_{through}$ was small.

Figure 1 presents a typical concentration-time profile after a 1.0 mg dose of semaglutide administered at steady state in patients with T2D.

Figure 1 Semaglutide concentration versus time profile following administration of 1.0 mg semaglutide at steady state in patients with T2D – trial 3635



Note: horizontal line represent lower limit of quantification. Number of patients= 37.

The differences between injection sites using the thigh or abdomen has been evaluated in studies 3652 and 3684 using steady-state concentrations. This analysis showed similar steady state C_{max} concentrations for the two injection sites.

Furthermore, the applicant evaluated the differences between injection sites on the pharmacokinetics of semaglutide using population PK methods which show that injection site does not affect average exposure (Cavg). The Cavg of upper arm vs abdomen is 0.93[0.90-0.96]90%CI and C_{avg} of thigh vs abdomen is 0.97 [0.93-1.00]90%CI. The number of subjects per injection site is: thigh (n=86), upper arm (n=71) and abdominal skin (n=1454).

Distribution:

The apparent volume of distribution following SC administration of semaglutide was approximately 12- 13 L (Studies 3635, 3684, 3819) and similar (when accounting for differences in BMI) between subjects with T2D and healthy subjects. This volume is small and close to the blood volume, indicating that a high fraction of semaglutide is circulating in the blood. The *in vitro* protein binding, mainly to albumin, was above 99% in human plasma. The unbound fraction was 0.19% and 0.36% in human samples of healthy volunteers (*in vitro* studies 208380 en 213228). The high protein binding prevents semaglutide from being rapidly eliminated from the circulation. Semaglutide passes the placental barrier, blood-brain barrier and is secreted in breast milk, see preclinical section.

Elimination:

The cumulative recovery of total radioactivity was 75% of the administered dose; hereof 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In urine unchanged semaglutide accounted for 3.1% of the administered dose (Study 3789). Mean CL/F was approximately 0.05 L/h in patients with T2D as compared to about 0.035 L/h in healthy subjects. This difference is largely attributable to differences in BMI. Mean t½ was approximately 155 hours (149 to 165 hours) in subjects with T2D and comparable to that in healthy volunteers. Semaglutide is metabolized by proteolytic degradation of the peptide backbone and beta-oxidation of the fatty acid side-chain. Semaglutide is extensively metabolised into many different metabolites. Its most abundant metabolites were P3 that was detected in plasma and U6 and U7 that were detected in urine (study 214379).

Semaglutide is almost completely metabolised and degraded into peptides, amino acids and fatty acid fragments. All metabolites accounted for less than 10% of the total amount of semaglutide related material and are not expected to have any activity. One semaglutide isomer (P3C) has been identified and although it is considered likely that it has some activity it is not expected to be of clinical relevance as its concentration is low (<7.7%).

Because endogenous GLP-1 is metabolised by DPP-IV and NEP, these enzymes are expected to be involved in the metabolism of the structurally related semaglutide. This is confirmed for NEP, which was identified as one of the active metabolic enzymes (*in vitro* study 215514). The pharmacokinetics data do not indicate any influence of polymorphisms of NEP on the pharmacokinetics of semaglutide.

The effects are therefore expected unlikely or minor. The applicant has demonstrated *in vitro* (data on file) that semaglutide was less sensitive to DPP-IV degradation than the endogenous GLP. Therefore DPP-IV degradation is not expected to be a major pathway and genetic polymorphisms of DPP-IV are expected to be negligible.

3. **Clinical efficacy** please find the main study from clinical study reports table as above.

4. **Clinical safety**

The table shows the proportions of patients with AEs, serious adverse events, and adverse events leading to premature treatment discontinuation.

Phase 3a Pool: Overall Safety Profile

	Semaglutide 0.5 mg N=1,373		Semaglutide 1 mg N=1,777		Comparators N=1,657	
	n	%	n	%	n	%
Any AE	1,015	73.4	1,301	72.7	1,136	68.7
SAE	92	6.6	118	6.7	95	5.8
AEs leading to premature treatment discontinuation	84	6.1	156	8.7	51	3.0

SAS, On-treatment. Phase 3a Pool excludes CVOT

The table shows the most frequently reported AEs.

Phase 3a Pool: Most Frequently Reported AEs

	Semaglutide 0.5 mg N=1,373 %	Semaglutide 1 mg N=1,777 %	Comparators N=1,657 %
Gastrointestinal AEs			
Nausea	17.0	19.9	6.3
Diarrhea	12.2	13.3	5.7
Vomiting	6.4	8.4	3.3
Constipation	6.9	6.2	2.7
Dyspepsia	4.1	5.2	2.1
Other AEs			
Nasopharyngitis	14.5	10.7	13.8
Lipase increased	8.7	8.5	6.3
Decreased appetite	6.3	7.2	2.0
Headache	5.3	6.4	5.5
Back pain	3.3	3.4	3.8

SAS, On-treatment. Phase 3a Pool excludes CVOT

Upon review by system organ class, the higher proportions of adverse events, seen with semaglutide, were mainly driven by gastrointestinal disorders, including nausea and diarrhea, as shown in the top part of the table.
In general, these reactions were mild or moderate in severity and of short duration.
An increase in lipase levels was also reported more frequently with semaglutide than with placebo and active comparators. Each of these AEs is consistent with the GLP-1 receptor agonist class.

Phase 3a Pool: Most Frequently Reported SAEs

	Semaglutide 0.5 mg N=1,373 %	Semaglutide 1 mg N=1,777 %	Comparators N=1,657 %
Any SAE	6.6	6.7	5.8
Pancreatitis	0.2	0.2	0
Coronary artery bypass	0	0.2	<0.1
Cholecystitis acute	0	0.2	0
Pneumonia	0.4	0.1	0.1
Ischemic stroke	0.2	0.1	0.2
Cholelithiasis	0.2	0.1	0.1
Coronary arterial stent insertion	0.2	0.1	0
Atrial fibrillation	0.2	<0.1	0.2
Umbilical hernia	0.2	<0.1	<0.1
Cataract	0.2	0	<0.1
Gastritis	0.2	0	<0.1

SAS, On-treatment. Phase 3a Pool excludes CVOT

In the phase 3a pool, the proportion of patients with serious adverse events was low.

Generally, these were slightly higher with semaglutide than with comparator, but there was no increased risk of serious side effects observed with semaglutide 1 mg as compared with .5 mg.

The SAEs were distributed across several MedDRA dictionary system organ classes, in both semaglutide and the comparator groups.

Phase 3a Pool: AEs Leading to Premature Treatment Discontinuation in ≥ 0.5% of Patients

	Semaglutide 0.5 mg N=1,373 %	Semaglutide 1 mg N=1,777 %	Comparators N=1,657 %
Any AE leading to premature treatment discontinuation	6.1	8.7	3.0
Nausea	1.5	2.5	0.5
Vomiting	0.5	1.6	0.1
Diarrhea	1.1	1.5	<0.1
Decreased appetite	0.6	0.8	0
Abdominal pain	0.3	0.5	0.2
Dyspepsia	0.2	0.5	0

SAS, On-treatment. Phase 3a Pool excludes CVOT

Fewer than 10 percent of patients discontinued treatment early, due to adverse events.

Both Semaglutide treatment arms had more patients discontinue treatment due to adverse events than the comparators.

Among the discontinuations, most were in relation to treatment initiation and dose-escalation, and GI adverse events were the main drivers of treatment discontinuation. The highest proportion of the GI events were seen in the initial months, during the escalation period.

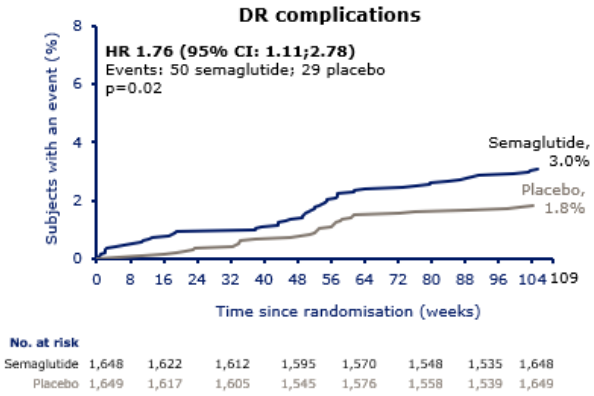
Consistent with the dose-response observed for GI adverse events, the proportion of patients who discontinued early was higher with semaglutide 1 mg than with 0.5 mg.

SUSTAIN 6 (CVOT): Overall Safety Profile

	Semaglutide 0.5 mg N=823		Semaglutide 1 mg N=819		Placebo N=1,644	
	n	%	n	%	n	%
Any AE	732	88.9	722	88.2	1,453	88.4
SAE	264	32.1	240	29.3	574	34.9
AEs leading to premature treatment discontinuation	95	11.5	119	14.5	110	6.7

Similar ADR profile in SUSTAIN 6 as in the phase 3a pool except for diabetic retinopathy complications which was of longer duration than the trials in the phase 3a pool, and which included a heavily comorbid patient population at increased cardiovascular risk.

SUSTAIN 6: Diabetic retinopathy complications (DRC)



DR outcomes	Semaglutide n (%)	Semaglutide Incidence rate per 100 PYR	Placebo n (%)	Placebo Incidence rate per 100 PYR	HR (95% CI)	p value
DR complications	50 (3.0)	1.49	29 (1.8)	0.86	1.76 (1.11;2.78)	0.02
Need for retinal photocoagulation	38 (2.3)	1.13	20 (1.2)	0.59	1.91 (1.11;3.28)	0.02
Need for treatment with intravitreal agents	16 (1.0)	0.47	13 (0.8)	0.38	1.23 (0.59;2.56)	0.58
Vitreous haemorrhage	16 (1.0)	0.47	7 (0.4)	0.21	2.29 (0.94;5.57)	0.07
Onset of diabetes-related blindness*	5 (0.3)	0.15	1 (0.1)	0.03	5.01 (0.59;42.88)	0.14

*Defined as Snellen visual acuity of 20/200 (6/60) or less, or visual field of less than 20 degrees, in the better eye with best correction possible.
CI, confidence interval; DR, diabetic retinopathy; E, number of events. HR, hazard ratio. Four subjects had unknown history of diabetic retinopathy at baseline.
1. Vilsbøll T et al. *Diabetes Obes Metab* 2018;20:889–97. 2. Novo Nordisk. Data on file.

Compared to the overall population, the patients who had events of diabetic retinopathy complications during the trial were characterised by a longer diabetes duration (17.53 years), a higher baseline HbA1c (9.37%), more patients on insulins at baseline (75.9%), andmore patients with pre-existing diabetic retinopathy (83.5%).

Among patients without pre-existing diabetic retinopathy, events of diabetic retinopathy complications were few and there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events).Supporting a lack of effect in those patients without baseline retinopathy, no difference was observed in patients with a baseline fundoscopy evaluated to be normal.

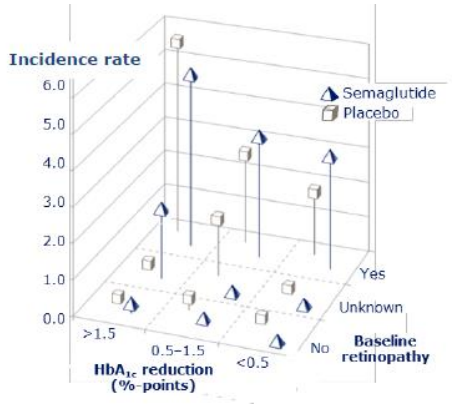
A more specific group with an increased risk of retinopathy complications using semaglutide was identified. This risk of retinopathy complications was only observed in patients with retinopathy at baseline treated with insulin. In patients without retinopathy, there was no effect of semaglutide on the development of retinopathy complications. Numbers needed to treat (3-point MACE) and numbers needed to harm (retinopathy complications) were 45 and 77 respectively for the total population, 19 versus 36 for subjects with baseline retinopathy, and 61 versus 456 for subjects without retinopathy at baseline.

For patients with diabetic retinopathy at baseline and treated with insulin, the number needed to treat is 17 for MACE, whereas the corresponding number needed to harm is 29 for diabetic retinopathy complications.

Rapid improvements in glycaemic control may be associated with a transient worsening of diabetic retinopathy. Semaglutide treatment generally provides a rapid initial decline in blood glucose, e.g., more pronounced and with a faster decline than with a basal insulin.

This initial decline was even more pronounced in the CVOT, likely due to a higher baseline HbA1c. A post-hoc mediator analysis suggests that the effect of semaglutide in patients with pre-existing retinopathy could be explained in part by the HbA1c reduction at week 16, indicating that a rapid initial decline in blood glucose was a likely mechanism causing this effect. Data suggest that semaglutide was associated with increased risk of retinopathy in patients with pre-existent retinopathy and only small HbA1c reductions (HbA1c reduction <0.5%points).

Figure: Mediator analysis of first events of diabetic retinopathy complications by treatment, baseline diabetic retinopathy, and reduction in HbA1c at week 16 - FAS in trial – CVOT



Systematic evaluation of diabetic retinopathy complications was only performed in the CVOT and not in the remaining phase 3a trials. Patients requiring active treatment for known proliferative retinopathy or maculopathy at baseline were excluded from these trials, and overall no safety concerns related to retinopathy were observed.

The applicant plan to conduct a post- authorization safety study (PASS): FOCUS Trial to evaluate the long-term effects of Semaglutide treatment on diabetic retinopathy development, progression and complications. This study was started on 08 May 2019 and will be expected to end on 21 May 2025. Moreover, the applicant will prepare the periodic safety update reports (PSURs) including ongoing updated data related to diabetic retinopathy and prepare the risk management plan (RMP) in which diabetic retinophathy complications are listed and handled as an important identified risk.

Summary of safety profile

Semaglutide safety profile consistent with the well-established GLP-1 RA safety profile.

Most frequent AEs and AEs leading to treatment discontinuation were gastrointestinal disorders, most frequently nausea, diarrhea, and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

Higher incidence of diabetic retinopathy complications observed in SUSTAIN 6.Consistent with the well-known phenomenon of early worsening of pre-existing diabetic retinopathy, secondary to an initial, rapid improvement in glycaemic control.

Assessor's conclusions on clinical

As the information of pharmacokinetic, efficacy and safety clinical data is acceptable. The study design, population and duration are suitable for proposed indication. The safety data show that no reported unexpected pattern of adverse event. The most common are gastrointestinal disorders, including nausea and diarrhea.

There are some concerned points from Thai advisory expert committee on 24th October 2019. The incresing of diabetic retinopathy in patients using this product from SUSTAIN-6 trials leads the requirement of long-term safety data. Applicant plan to conduct a post- authorization safety study (PASS): FOCUS Trial to evaluate the long-term effects of Semaglutide treatment on diabetic retinopathy development, progression and complications. (Expected to end on 21 May 2025)

Moreover, the applicant will prepare the periodic safety update reports (PSURs) including ongoing updated data related to diabetic retinopathy and prepare the risk management plan (RMP) in which diabetic retinophathy complications are listed and handled as an important identified risk.

So, the over all data from the evaluation, the un-redacted assessment report form EMA and the Thai advisory expert committee on 24th October 2019 can conclude that Ozempic 0.25 mg, 0.5 mg, and 1 mg have enough efficacy and safety data that support the proposed indication for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
- In addition to other medicinal products for the treatment of diabetes.

The MAHs also conducted the proper RMP as an RMP from EMA to minimize the risk of usage this medication.

Part 6 :Risk Management Plan

There are some of concerns about Ozempic. For important identified risks, severe hypoglycaemia in combination with other anti-glycaemic agents, acute gallstone disease and diabetic retinopathy complications are concerned. For important potential risks, serious allergic reactions, acute pancreatitis, malignant neoplasm, pancreatic cancer and medullary thyroid cancer are concerned. For missing information, pregnancy and lactation, patients with end-stage renal disease, patients with NYHA Class IV, and patients with severe hepatic impairment are concern. The applicant were conducted the RMP as an RMP from EMA.

Evaluation results

The information of RMP is valid and suitable due to the risk management had been conducted in summary of product characteristic and patient leaflet already.

Label evaluation

Registered label from Novo Nordisk Pharma (Thailand) Ltd. is Unit carton label and inner label following Thai FDA 2009 ANNEX 3 Package insert and labeling rule.

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country’s Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended Daily Allowance)Vitamins and minerals(	n/a	n/a
15	Warning	✓	✓
16	Pack sizes	✓	✓

✓ Available or appropriate

n/a not available

INNER LABEL

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Dosage form*	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date*	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition*	X	✓
10	Country's Registration Number*	X	✓
11	Name and address of Marketing Authorization Holder*	X	✓
12	Name and address of manufacturer*	✓	✓
13	Special labelling*	X	✓
14	Recommended Daily Allowance*	X	✓
15	Warning*	X	✓
16	Pack sizes*	✓	✓

✓ Available or appropriate
n/a not available
* exempted for small ampoule and vial

Patient information leaflet (PIL) evaluation

Patient information leaflet of Ozempic is adapted from SmPC and the originator SmPC .The information in Patient information leaflet is accurate, complete, and consistency with SmPC, quality data, non-clinical data and clinical data .The important information for patient is summarized in this PIL, however, user testing in Thai is required 12 months after receiving registered paper.

Summary of product characteristics (SmPC) evaluation

Summary of product characteristics conform to quality, non**-**clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC conformed to SmPC of Ozempic 0.25 mg solution for injection in pre-filled pen, Ozempic 0.5 mg solution for injection in pre-filled pen, and Ozempic 1 mg solution for injection in pre-filled pen approved in EMA.

Overall Benefit/risk assessment

As evaluation results, the reviewers evaluated the documents submitted to support the quality, efficacy and safety of Semaglutide 1.34 mg/ml. It concluded that quality of Semaglutide is acceptable and pass the standard criteria, non-clinical and clinical data supported proposed indication and no serious adverse event reported during study through post-marketing. The evaluation results of un-redacted assessment report from EMA and Thai advisory expert committee on 24th October 2019 are consistency, overall benefit/risk assessment is positive, so all can summarized Ozempic 0.25 mg solution for injection in pre-filled pen, Ozempic 0.5 mg solution for injection in pre-filled pen, and Ozempic 1 mg solution for injection in pre-filled pen registered indication below is acceptable;

Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications.
- in addition to other medicinal products for the treatment of diabetes.

Semaglutide registered in new biological product. MAHs have to follow up adverse event closely and comply with risk management plan. Then we should approve Semaglutide in special control medicine and the overall benefit/risk assessment supports approval of Semaglutide, under the following 4 requirements

1) This medicine will only be prescribed in hospitals and clinics.

2) Follow the adverse event in post-marketing conducted by SMP protocol submitted in eCTD.

3) Submit the complete version of PIL after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval).

4. Submit data and follow by proposed risk management plan in 1.8.2 Risk management system on eCTD , as attached file

Internal reviewer

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(Kridiphol Janthranant)

Evaluator

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(Worasuda Yoongthong)