

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215256Orig1s000

CLINICAL REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021108
NDA#/Referenced IND for NDA:	215256/126360
Applicant:	Novo Nordisk
Established Name/Trade Name:	Semaglutide
Indication:	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index of 30 kg/m ² or greater (obesity) or 27 kg/m ² or greater (excess weight) in the presence of at least one weight-related comorbid condition.
PDUFA Goal Date:	June 4, 2021
Review Division:	Division of Diabetes, Lipid disorders and Obesity (DDLO)
Clinical Reviewer:	Julie Golden, M.D., Medical Officer, DDLO
Clinical Team Leader (TL)	John Sharretts, M.D., Deputy Director, DDLO
Regulatory Project Manager:	Martin White, MS, Regulatory Project Manager, DDLO
COA Reviewer:	Yasmin Choudhry, M.D., Medical Officer, DCOA
COA TL:	Selena Daniels, PharmD, M.S., Team Leader, DCOA
DCOA Director:	David Reasner, PhD, Director, DCOA
Instruments reviewed:	(b) (4) ☒ Patient-reported outcome (PRO)
	(b) (4) ☒ Patient-reported outcome (PRO)

Table of Contents

1. EXECUTIVE SUMMARY 2

2. REVIEW CONCLUSIONS 2

3. RECOMMENDATIONS FOR FUTURE STUDIES 3

4. BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S) 3

5. CLINICAL OUTCOME ASSESSMENT REVIEW 5

 5.1 CLINICAL TRIAL POPULATION 5

 5.2 CLINICAL TRIAL DESIGN..... 5

 5.3 ENDPOINT POSITION, DEFINITION, AND ASSESSMENT SCHEDULE 5

(b) (4)

1. EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of semaglutide (2.4 mg) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management (b) (4) adult patients with an initial body mass index (BMI) of 30 kg/m² or greater (obesity), or 27 kg/m² or greater (excess weight) in the presence of at least one weight-related comorbid condition. The Applicant proposes (b) (4) from two randomized, double-blind, place-controlled phase 3a clinical trials (Trials NN9536-4373 and NN9536-4374). (b) (4) the applicant submitted a COA evidence dossier (PRO Report). The primary objective of this review is to evaluate from a COA perspective (b) (4).

(b) (4)

The data from Trials NN9536-4373 and NN9536-4374 (here on referred to as Trials 4373 and 4374) demonstrated that semaglutide had statistically significant improvement (b) (4)

(b) (4). Despite achievement of statistical significance in both instruments, there were minimal observed score changes, if any, when looking at the item- and domain-level data at the raw score scale (e.g., some item scores reflect less than one category change on the raw score scale [non-normalized and -transformed scores]). The changes observed in the normalized and transformed scores were also minimal (b) (4)

(b) (4)

From a COA perspective, the (b) (4)

(b) (4)

(b) (4) following additional (b) (4) analyses may help to understand whether there were improvements (b) (4) in a subset of patients (i.e., patients at a certain BMI level):

- Examining the correlations of the COA data with the percentage body weight
- Examining the COA data for participants with select BMI cutoffs

2 REVIEW CONCLUSIONS

The (b) (4) were reviewed for content validity and the other measurement properties. Both instruments measure some important aspects (b) (4). However, the relevancy of some of the items is questionable (b) (4)

- The Applicant established the other measurement properties of the instruments. However, the responsiveness of the instruments may need to be further explored. Based on the response distributions minimal change is observed at the item- and -domain level when looking at the raw score scale, as well as the normalized and transformed scales (b) (4).
(b) (4). Because there is minimal change demonstrated, it is difficult to assess whether the change constitutes a clinically meaningful change. (b) (4).
(b) (4). As such, there is concern that the (b) (4) data would not provide results with clear clinical meaning (b) (4).

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend that sponsors specify and define functional impacts that are relevant and important to patients with obesity or excess weight and that are likely to demonstrate meaningful and interpretable changes in the planned clinical trial(s). Additionally, sponsors seeking to demonstrate clinical benefit of a therapeutic on a particular set of functional impacts should select a sufficiently impaired population for their studies or otherwise plan for stratification or appropriate statistical analyses.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- There have been several communications with the applicant regarding the adequacy of the

clinical outcome assessments (COAs), which included advice on the following:

- Assess the translatability of the items [REDACTED] (b) (4)
- Assess the relevancy of items [REDACTED] (b) (4) for the target population.
- Conduct anchor-based analyses (e.g., using the patient global impression of status [PGI-S] as an anchor) separately in each of the four trials (Trials 4373, 4374, 4375, and 4376). Further, use anchor-based methods supplemented with both empirical cumulative distribution function (eCDF) and probability density function (PDF) curves.²
- Provide a rationale for the proposal to derive a responder threshold using “mean change from baseline to week 68 in the group of subjects that experience a one category improvement in PGI-S.”⁴
- Provide details how responder thresholds 1.93 and 5 were derived [REDACTED] (b) (4)
- Consider score interpretability of the meaningful change threshold(s) for both transformed scores/norm-based scores and the original (raw) scale scores, i.e. the chosen responder threshold(s) based on transformed scores or norm-based scores should exceed at least a 1-unit change on the original (raw) response scale.⁴

Previous COA Reviews:

- C2020150_IND 126360_Patel dated November 24, 2020 [DARRTS Reference ID: 4706383]
- C2020175_IND 126360_Patel dated [DARRTS Reference ID: 4651709]
- C2019409_IND 126360_Patel dated December 31, 2019 [DARRTS Reference ID: 4532607]
- C2019225_IND 126360_Choudhry dated August 8, 2019 [DARRTS Reference ID: 4474870]
- C2018289_IND 126360_Zhou dated January 3, 2019 [DARRTS Reference ID: 4370947]
- C2018098_IND 126360_Choudhry dated June 7, 2018 [DARRTS Reference ID: 4274396]
- C2017266_IND 126360_Chen dated June 7, 2018 [DARRTS Reference ID: 427340]
- C2017241_IND 126360_Chen dated November 1, 2017 [DARRTS Reference ID: 4171462]
- AT 2015-163_IND 126360_Kovacs dated November 24, 2015 [DARRTS Reference ID: 3851394]

Disease Background:

Obesity is a complex health issue resulting from a combination of causes and individual factors such as behavior and genetics. Behaviors can include physical activity, inactivity, dietary patterns, medication use, and other exposures. Obesity is associated with increased risk of a variety of

² Communicated by the Patient-Focused Statistical Support Team in FDA Meeting Minutes dated November 24, 2020 IND 126360 [DARRTS Reference ID: 4622175]

comorbidities including hyperglycemia, type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, atherosclerosis, osteoarthritis, urinary incontinence, non-alcoholic steatohepatitis, cardiovascular diseases, certain types of cancer, and risk of early death.

Investigational Product:

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue and classified as a GLP-1 receptor agonist (GLP-1 RA). GLP-1 RA is a physiological regulator of appetite and GLP-1 receptors are present in several areas of the brain involved in appetite regulation.

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

Trial 4373

The target population for Trial 4373 are adults (≥ 18 years) who are obese ($BMI > 30 \text{ kg/m}^2$) or overweight ($BMI > 27 \text{ kg/m}^2$) with the presence of at least one of the following weight-related comorbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease. Eligible participants had history of at least one self-reported unsuccessful dietary effort to lose body weight. Participants with Type 2 diabetes were excluded from this trial.

Trial 4374

The target population for Trial 4374 are adults (≥ 18 years) who are overweight ($BMI > 27 \text{ kg/m}^2$) and diagnosed with Type 2 diabetes. Eligible participants had history of at least one self-reported unsuccessful dietary effort to lose body weight. Participants treated with insulin were excluded from the trial as insulin promotes weight gain.

A complete list of the inclusion and exclusion criteria is summarized in section 4 of the clinical study protocols for Trials 4373 and 4374.

5.2 Clinical Trial Design

Trial 4373

Trial 4373 was a 68-week, randomized, double-blind, placebo-controlled, two-armed, parallel group, multi-center, multinational phase 3 trial.

Trial 4374

Trial 4374 was a 68-week, randomized, double-blind, double dummy, three-armed, placebo-controlled, multi-center, multinational phase 3 trial.

Refer to the clinical study protocols for more details on the clinical trial designs of Trials 4373 and 4374.

5.3 Endpoint Position, Definition, and Assessment Schedule

Table 1 describes the intended placement of the COAs in the endpoint hierarchy, including the endpoint definition and assessment schedule for Trials 4373 and 4374.

Table 1. Endpoint Position, Definition, and Assessment Schedule for Trials 4373 and 4374

Endpoint Position	Assessment (If COA, specify Name and Type)	Endpoint Definition	Assessment Frequency
Primary	Body weight	Percentage change from baseline to week 68	Screening; Baseline, and every 2 weeks until Week 20; then every 4 weeks until Week 68

(b) (4)



(b) (4)

Reviewer's comment(s):

The data from Trials 4373 and 4374 demonstrated that semaglutide had statistically significant improvement (b) (4)

(b) (4)

Despite achievement of statistical significance in both instruments, there was minimal observed score changes, if any, when looking at the item- and domain-level data at the raw score scale (e.g., some item scores reflect less than one category change on the raw score scale [non-normalized and -transformed scores]). The changes observed in the normalized and transformed scores were also minimal (b) (4)

(b) (4)

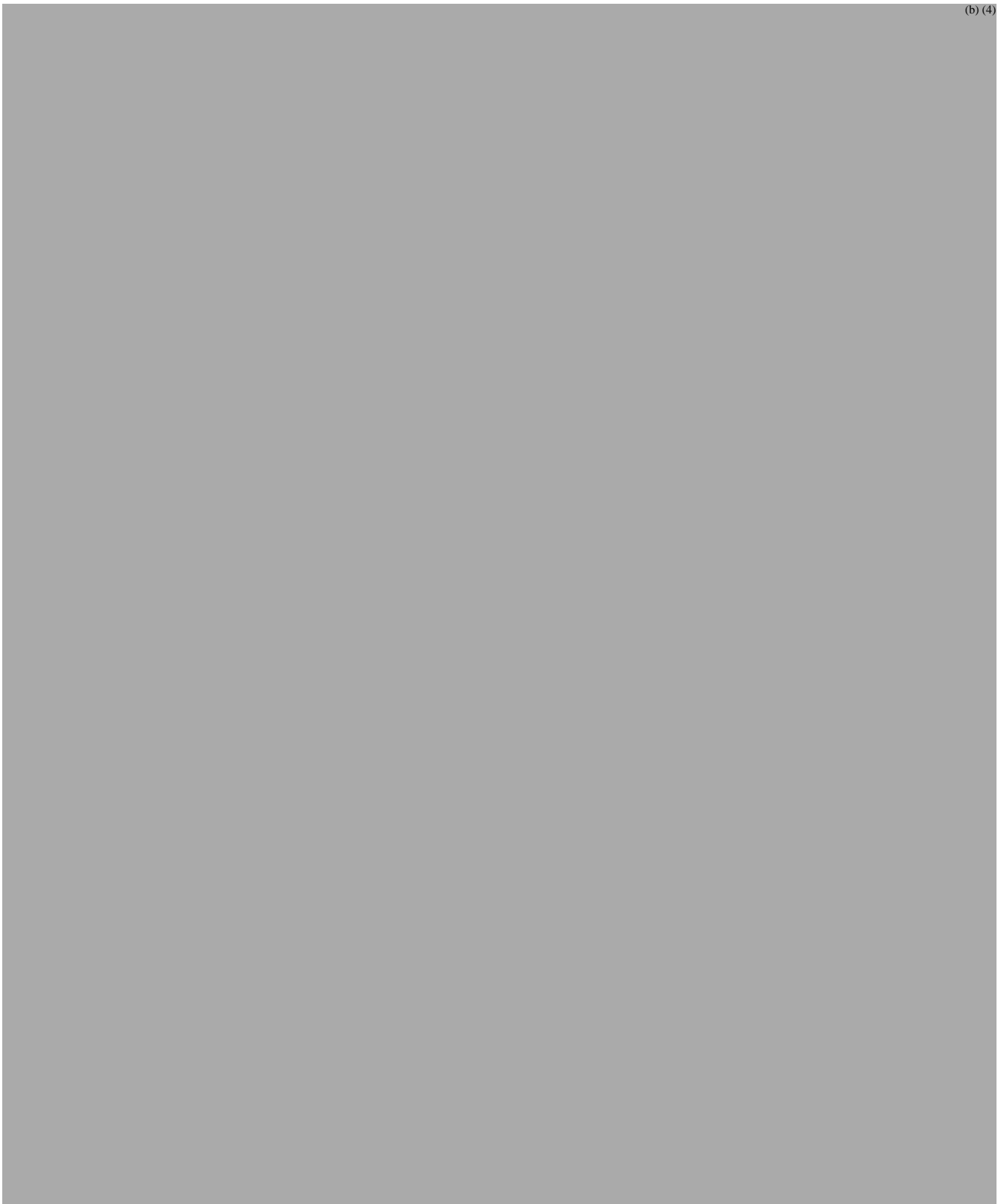
(b) (4), there is concern that (b) (4) the data would not provide results with clear clinical meaning (b) (4)

(b) (4)

An information request was submitted to the Applicant on April 21, 2021 to explain the observed minimal changes in the PRO data. The Applicant noted that the observed floor effects are consistent to the qualitative findings and that the floor effects do not limit the validity of the observed improvements but make it more difficult to detect and demonstrate improvements. This reviewer agrees that the findings are consistent to the qualitative findings and that the floor effects make it difficult to demonstrate improvements. This reviewer is not questioning the

validity of the instruments. The concern is with regard to the interpretability of the observed data.

(b) (4)



This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YASMIN A CHOUDHRY
06/07/2021 10:45:56 AM

SELENA R DANIELS
06/07/2021 10:47:29 AM

DAVID S REASNER
06/07/2021 12:58:31 PM

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

CLINICAL REVIEW

Application Type	Original 505b1 NDA
Application Number	215256
Priority or Standard	Priority (pediatric voucher)
Submit Date	December 4, 2020
Received Date	December 4, 2020
PDUFA Goal Date	June 4, 2021
Division/Office	DDLO/OCHEN
Reviewer Name	Julie Golden
Review Completion Date	June 3, 2021
Established/Proper Name	Semaglutide
Proposed Trade Name	Wegovy
Applicant	Novo Nordisk Inc.
Dosage Form	Subcutaneous injection
Applicant Proposed Dosing Regimen	2.4 mg once-weekly • 0.25 mg/week starting dose • escalating every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg/week
Applicant Proposed Indication/Population	WEGOVY is indicated as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) in adult patients with an initial body mass index (BMI) of • 30 kg/m² or greater (obesity), or • 27 kg/m² or greater (excess weight) in the presence of at least one weight-related comorbid condition
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	WEGOVY is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m² or greater (obese) or • 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)

Table of Contents

Glossary	16
1. Executive Summary	18
1.1. Product Introduction.....	18
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	18
1.3. Benefit-Risk Assessment	19
1.4. Patient Experience Data.....	24
2. Therapeutic Context.....	25
2.1. Analysis of Condition.....	25
2.2. Analysis of Current Treatment Options	26
3. Regulatory Background	34
3.1. U.S. Regulatory Actions and Marketing History.....	34
3.2. Summary of Presubmission/Submission Regulatory Activity	34
3.3. Foreign Regulatory Actions and Marketing History	35
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	36
4.1. Office of Scientific Investigations (OSI)	36
4.2. Product Quality	36
4.3. Clinical Microbiology.....	36
4.4. Nonclinical Pharmacology/Toxicology	37
4.5. Clinical Pharmacology	37
4.6. Devices and Companion Diagnostic Issues	39
4.7. Consumer Study Reviews.....	39
5. Sources of Clinical Data and Review Strategy	40
5.1. Table of Clinical Studies	40
5.2. Review Strategy	46
6. Review of Relevant Individual Trials Used to Support Efficacy	46
6.1. NN9536-4373 (STEP 1): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity.....	46
CDER Clinical Review Template	2
<i>Version date: September 6, 2017 for all NDAs and BLAs</i>	

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

6.1.1. Study Design	46
6.1.2. Study Results	53
6.2. NN9536-4374 (STEP 2): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes	72
6.2.1. Study Design	72
6.2.2. Study Results	76
6.3. NN9536-4375 (STEP 3): Effect and safety of semaglutide 2.4 mg once-weekly as adjunct to intensive behavioral therapy in subjects with overweight or obesity.....	97
6.3.1. Study Design	97
6.3.2. Study Results	100
6.4. NN9536-4376 (STEP 4): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during run-in period ...	114
6.4.1. Study Design	114
6.4.2. Study Results	116
7. Integrated Review of Effectiveness.....	137
7.1. Assessment of Efficacy Across Trials	137
7.1.1. Primary Endpoints	137
7.1.2. Secondary and Other Endpoints	139
7.1.3. Subpopulations	140
7.1.4. Dose and Dose-Response	149
7.1.5. Onset, Duration, and Durability of Efficacy Effects.....	154
7.2. Additional Efficacy Considerations.....	155
7.2.1. Considerations on Benefit in the Postmarket Setting.....	155
7.2.2. Other Relevant Benefits.....	158
7.3. Integrated Assessment of Effectiveness	158
8. Review of Safety	158
8.1. Safety Review Approach	158
8.2. Review of the Safety Database	161
8.2.1. Overall Exposure	161
8.2.2. Relevant characteristics of the safety population:	163
8.2.3. Adequacy of the Safety Database	164

8.3.	Adequacy of Applicant’s Clinical Safety Assessments	165
8.3.1.	Issues Regarding Data Integrity and Submission Quality.....	165
8.3.2.	Categorization of Adverse Events.....	165
8.3.3.	Routine Clinical Tests.....	167
8.4.	Safety Results.....	168
8.4.1.	Deaths.....	168
8.4.2.	Serious Adverse Events.....	176
8.4.3.	Dropouts and/or Discontinuations Due to Adverse Effects.....	187
8.4.4.	Significant Adverse Events.....	194
8.4.5.	Treatment Emergent Adverse Events and Adverse Reactions	194
8.4.6.	Laboratory Findings	199
8.4.7.	Vital Signs.....	209
8.4.8.	Electrocardiograms (ECGs)	212
8.4.9.	QT	213
8.4.10.	Immunogenicity.....	215
8.5.	Analysis of Submission-Specific Safety Issues	231
8.5.1.	Gallbladder-Related Disorders.....	231
8.5.2.	Acute Pancreatitis.....	238
8.5.3.	Cardiovascular Disorders	249
8.5.4.	Neoplasms	266
8.5.5.	Hepatic Disorders	276
8.5.6.	Acute Renal Failure.....	297
8.5.7.	Hypoglycemia	304
8.5.8.	Retinal Disorders.....	312
8.5.9.	Psychiatric Disorders.....	320
8.5.10.	Gastrointestinal Disorders.....	329
8.5.11.	Rare Events.....	341
8.6.	Safety Analyses by Demographic Subgroups	347
8.7.	Specific Safety Studies/Clinical Trials.....	351
8.8.	Additional Safety Explorations.....	351
8.8.1.	Human Carcinogenicity or Tumor Development	354

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

8.8.2. Human Reproduction and Pregnancy	354
8.8.3. Pediatrics and Assessment of Effects on Growth	357
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	357
8.9. Safety in the Postmarket Setting	360
8.9.1. Safety Concerns Identified Through Postmarket Experience	360
8.9.2. Expectations on Safety in the Postmarket Setting.....	366
8.9.3. Additional Safety Issues From Other Disciplines	366
8.10. Integrated Assessment of Safety.....	366
9. Advisory Committee Meeting and Other External Consultations	370
10. Labeling Recommendations	370
10.1. Prescription Drug Labeling	370
10.2. Nonprescription Drug Labeling.....	372
11. Risk Evaluation and Mitigation Strategies (REMS)	372
12. Postmarketing Requirements and Commitments.....	372
13. Appendices.....	373
13.1. References.....	373
13.2. Financial Disclosure	373

Table of Tables

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication.....	27
Table 2: Bioequivalence Assessment Via Pharmacokinetic Endpoints of Semaglutide 2.4 mg at Steady State, Study 4590.....	39
Table 3. Listing of Clinical Trials Relevant to this NDA.....	41
Table 4: List of Endpoints for Each Trial 4373 Objective.....	48
Table 5: Assessment Classification, Trial 4373.....	51
Table 6: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 1950 Subjects, Trial 4373.....	52
Table 7: Subject Disposition, Trial 4373.....	53
Table 8: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4373.....	55
Table 9: Demographic Characteristics of the Primary Efficacy Analysis, Trial 4373.....	57
Table 10: Baseline Characteristics, Trial 4373.....	58
Table 11: Medical History and Concomitant Illness, Selected Events, Trial 4373.....	59
Table 12: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68, Trial 4373.....	61
Table 13: In-Trial Dose Summary, Semaglutide-Treated Subjects.....	68
Table 14: Selected Supportive Secondary Endpoints, Trial 4373.....	70
Table 15: DEXA Substudy Summary Results, Trial 4373.....	71
Table 16: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 1200 Subjects (400 Per Arm), Trial 4374.....	75
Table 17: Subject Disposition, Study 4374.....	77
Table 18: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4374.....	78
Table 19: Demographic Characteristics of the Primary Efficacy Analysis, Trial 4374.....	79
Table 20: Baseline Characteristics, Trial 4374.....	80
Table 21: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68.....	82
Table 22: Diastolic Blood Pressure, Trial 4374.....	92
Table 23: Lipids, Trial 4374.....	92
Table 24: Albuminuria Shift Table, Trial 4374.....	96
Table 25: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 600 Subjects, Trial 4375.....	99
Table 26: Subject Disposition, Trial 4375.....	101
Table 27: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4375.....	102
Table 28: Demographic Characteristics of the Primary Efficacy Analysis.....	103
Table 29: Baseline Characteristics.....	104
Table 30: Medical History and Concomitant Illness, Selected Events.....	104
Table 31: Subjects Receiving Antihypertensive or Lipid-Lowering Medication During the Trial.....	106
Table 32: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68.....	106

Table 33: Selected Supportive Secondary Endpoints, Trial 4375.....	113
Table 34: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 600 Subjects, Trial 4376.....	116
Table 35: Subject Disposition, Study 4376.....	117
Table 36: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4376.....	119
Table 37: Demographic Characteristics at Start of Run-In (Week 0), Trial 4376.....	120
Table 38: Demographic Characteristics of the Primary Efficacy Analysis (Randomized Population), Trial 4376.....	121
Table 39: Baseline Characteristics, Run-In Period, Trial 4376.....	122
Table 40: Baseline Characteristics, Randomized Period, Trial 4376.....	123
Table 41: Medical History and Concomitant Illness at Screening, Selected Events, Randomized Groups, Trial 4376.....	124
Table 42: Primary Endpoint: Percent Body Weight Change from Baseline (Week 20) at Week 68, Trial 4376.....	126
Table 43: Percent Body Weight Change from Start of Semaglutide Run-In (Week 0) to Week 68, Trial 4376.....	127
Table 44: Selected Supportive Secondary Endpoints, Trial 4376.....	137
Table 45: Percent Body Weight Change Primary Endpoint, Phase 3 Trials.....	138
Table 46: Selected Secondary Endpoints, Phase 3 Trials.....	139
Table 47: Lipids, Phase 3 Trials.....	140
Table 48: Percent Weight Change from Start of Run-in (Week 0) to Week 68 by Start of Randomization (Week 20) Weight Loss, Trial 4376.....	156
Table 49: Safety Database.....	162
Table 50: Duration of Exposure in Phase 3 Trials.....	162
Table 51: Exposure in Pools and Individual Trials.....	163
Table 52: Selected Baseline Characteristics of the Phase 3 Pool.....	164
Table 53: Selected Miscategorized AEs (as Identified by Reviewer), Phase 3 Program.....	166
Table 54: Clinical Laboratory Testing in the Phase 3 Trials.....	167
Table 55: Listing of Deaths in Weight Management Program, In-Trial.....	168
Table 56: Blinded Fatal AEs, Ongoing Trials, Data Lock 01 September 2020.....	173
Table 57: Blinded Fatal AEs from Ongoing SELECT Trial, 01 September 2020 until 01 February 2021.....	174
Table 58: Study 4153, SAEs, On-Treatment.....	178
Table 59: SAEs, Study 4373, On-Treatment.....	180
Table 60: SAEs Study 4374, On-Treatment.....	181
Table 61: SAEs, Study 4375, On-Treatment.....	183
Table 62: SAEs, Study 4376, On-Treatment, Run-In Period.....	184
Table 63: SAEs, Study 4376, On-Treatment, Randomized Period.....	185
Table 64: Phase 3 Pool, SAEs, On-Treatment.....	186
Table 65: Adverse Events Leading to Premature Discontinuation of Trial Product.....	189

Table 66: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4373, On-Treatment.....	190
Table 67: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4374, On-Treatment.....	191
Table 68: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4375, On-Treatment.....	192
Table 69: AEs Leading to Permanent Trial Product Discontinuation, On-Treatment, Trial 4376 Run-In Period.....	192
Table 70: AEs Leading to Permanent Trial Product Discontinuation, On-Treatment, Trial 4376 Randomized Period	193
Table 71: Overview of Selected AEs, Phase 3 Pool	194
Table 72: Most Frequent AEs in the Semaglutide Arm ($\geq 5\%$) and Greater Than Placebo, Phase 3 Pool, On-Treatment.....	195
Table 73: Most Frequent AEs in the Semaglutide Arm ($\geq 2\%$) and Greater Than Placebo, Phase 3 Dose Escalation Group, On-Treatment.....	196
Table 74: Most Frequent AEs ($\geq 4\%$), Trial 4376, Run-In Period.....	197
Table 75: Most Frequent AEs In the Semaglutide Arm ($\geq 3\%$), Trial 4376, Randomized Period.....	198
Table 76: Adverse Events “Possibly” or “Probably” Related to Trial Product, On-Treatment... ..	198
Table 77: Selected Biochemistry Data, Minimum and/or Maximum Post-Baseline Values, Phase 3 Dose-Escalation Group, On-Treatment.....	200
Table 78: Electrolyte-Related AEs, Phase 3 Pool, On-Treatment.....	201
Table 79: Muscle- and CK-Related AEs, Phase 3 Pool, On-Treatment	205
Table 80: Hematology Minimum Post-Baseline Values, Phase 3 Dose Escalation Group, On-Treatment.....	206
Table 81: Hematology-Related AEs, Phase 3 Pool, On-Treatment	209
Table 82: Vital Sign-Related AEs, Phase 3 Pool, On-Treatment	210
Table 83: Increased Blood Pressure and Hypertension AEs	212
Table 84: QT-Related AEs, Phase 3 Pool, On-Treatment	213
Table 85: QTcF Interval and ECG Interpretation, Subjects with Outlier Results for Average Semaglutide Concentrations	214
Table 86: Antibody Sample Collection Time-Points, Weight Management Program	217
Table 87: Body Weight Percent Change from Baseline (Trials 4373 and 4374) and HbA1c Change from Baseline (Trial 4374) by Occurrence of Anti-Semaglutide Antibodies, On-Treatment	220
Table 88: Allergic Reaction AEs, Trial 4153, On-Treatment	223
Table 89: Allergic Reaction AEs, Phase 3 Pool, On-Treatment	224
Table 90: Allergic Reaction AEs, Trial 4376, Run-In Period.....	226
Table 91: On-Treatment AEs by SOC in Semaglutide-Treated Subjects with and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374	227
Table 92: On-Treatment Allergic Reactions in Semaglutide-Treated Subjects With and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374.....	228

Table 93: Selected Injection Site Reaction Terms, Phase 3 Dose Escalation Group	230
Table 94: On-Treatment Injection Site Reactions in Semaglutide-Treated Subjects With and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374	231
Table 95: Gallbladder AEs, Study 4153	232
Table 96: Selected Baseline Characteristics of Subjects with Gallbladder Events, Phase 3 Pool	233
Table 97: Gallbladder-Related Disorders, Phase 3 Pool.....	233
Table 98: Gallbladder-Related Disorders (MedDRA Search), Trials 4373, 4374, and 4375	234
Table 99: Gallbladder AEs by Weight Loss, On-Treatment, Phase 3 Dose-Escalation Group	236
Table 100: Pancreatitis Events Confirmed by Adjudication, Study 4153	241
Table 101: Proportion with at Least One Post-Baseline Abnormal Lipase and Amylase Value Meeting Cut-Off, Study 4153.....	243
Table 102: Acute Pancreatitis – Diagnostic Criteria and Severity	244
Table 103: Acute Pancreatitis, EAC-Confirmed and Not Confirmed, On-Treatment, Phase 3 Pool	245
Table 104: Details of EAC-Confirmed Acute Pancreatitis Events, On-Treatment (Including Run-In Period)	246
Table 105: Categorical Summary of Lipase and Amylase, Phase 3 Dose-Escalation Group.....	248
Table 106: Cases with Amylase and/or Lipase $\geq$ 3x ULN.....	249
Table 107: EAC-Confirmed CV Events, Study 4153	251
Table 108: CV Events, MedDRA Search, Study 4373, In-Trial	252
Table 109: CV Events, MedDRA Search, Study 4374, In-Trial	253
Table 110: CV Events MedDRA Search, Study 4375, In-Trial	253
Table 111: CV Events, MedDRA Search, Study 4376, In-Trial	254
Table 112: Adjudication of CV Events, Phase 3 Program.....	255
Table 113: EAC-Confirmed CV Events (Not Including CV Death), Phase 3 Pool, In-Trial.....	256
Table 114: Subjects with EAC-Confirmed CV Events (Not Including CV Death), By Trial	257
Table 115: CV Events Sent for Adjudication, Not Confirmed, Study 4373.....	258
Table 116: EAC-Confirmed MACE, Phase 3 Pool, In-Trial.....	260
Table 117: Cardiac Arrhythmias HLGT by Phase 3 Trial	261
Table 118: Heart Rate, Change from Baseline at Week 68.....	264
Table 119: Neoplasms AEs, Trial 4153, MedDRA Search, In-Trial.....	267
Table 120: Neoplasms Summary (Benign and Malignant), Phase 3 Pool and By Trial, In-Trial Period	269
Table 121: Malignant Neoplasms, Phase 3 Pool and By Trial, In-Trial Period.....	270
Table 122: Malignant Neoplasms by PT, Phase 3 Pool, In-Trial Period.....	271
Table 123: Calcitonin, Outlier Post-Baseline Values	276
Table 124: Calcitonin AEs, Phase 3 Pool	276
Table 125: Hepatic Disorders, Predefined MedDRA Search, Phase 3 Pool.....	279
Table 126: Hepatic Disorders AEs from Trial 4376 Run-In Period.....	280
Table 127: Subject NN9536-4373/ (b) (6), ALT Values (Including from Local Labs)	284

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 128: Concomitant Medications, Subject NN9536-4373/ (b) (6)	285
Table 129: Subject (b) (6) (Trial 4153), Liver Parameters	286
Table 130: Maximum Post-Baseline Liver Parameter Values, On-Treatment, Trials 4373, 4374, and 4375	288
Table 131: Liver Parameter Values, On-Treatment, Trial 4376 at Randomization (Post Semaglutide Run-In Period)	289
Table 132: Liver Parameter Values, On-Treatment, Trial 4376 at Week 68	290
Table 133: Details of ALT/AST Outliers, Phase 3 Trials	291
Table 134: Subjects with Abnormal Liver Enzymes Based on Local Laboratory Data	293
Table 135: Cases Meeting the Biochemical Definition of Hy's Law, Ongoing (Blinded) Weight Management Trials	295
Table 136: Liver Labs for Subject (b) (6) in SELECT Trial	296
Table 137: Acute Renal Failure, MedDRA Predefined Search, Phase 3 Pool and By Trial, On-Treatment	299
Table 138: Categorical Summary of eGFR, Phase 3 Trials, On-Treatment	301
Table 139: Renal Investigations AEs, Phase 3 Pool, On-Treatment	302
Table 140: Serum Creatinine Outliers (>2 mg/dL), Phase 3 Program	302
Table 141: 'Dehydration' SAEs	303
Table 142: AEs by Baseline Renal Function, Phase 3 Pool, On-Treatment	304
Table 143: ADA 2018 and IHSG 2017 Classification of Hypoglycemia	305
Table 144: Hypoglycemic Episodes by Classification, Trial 4374, On-Treatment	307
Table 145: Hypoglycemia Episodes (ADA 2018, Level 2 or 3), Subject Characteristics, Trial 4374	308
Table 146: Hypoglycemic Episodes, Trial 4153, On-Treatment	310
Table 147: Hypoglycemia AEs, Phase 3 Trials in Subjects without Type 2 Diabetes, On-Treatment	311
Table 148: Hypoglycemia AEs by Glycemic Status at Baseline, Phase 3 Trials in Subjects without Type 2 Diabetes, On-Treatment	312
Table 149: Characteristics in Subjects with and without Diabetic Retinopathy Events, Trial 4374, In-Trial Period	314
Table 150: Eye Examinations at Baseline and End-of-Treatment, Trial 4374, In-Trial Period	315
Table 151: Eye Examinations by Week, Shift Table, Trial 4374, In-Trial Period	316
Table 152: Overview of Semaglutide T2D Trial Design Features Relevant for the Evaluation of Diabetic Retinopathy	317
Table 153: Psychiatric AEs, Trial 4153, On-Treatment	321
Table 154: Psychiatric Disorders ($\geq 0.2\%$ of Subjects in the Semaglutide Arm), Pre-Defined MedDRA Search, Phase 3 Pool, On-Treatment	322
Table 155: C-SSRS, Proportions of Subjects with Suicidal Ideation and/or Behavior, Dose-Escalation Group (Trials 4373, 4374, and 4375), In-Trial Period	325
Table 156: PHQ-9 Maximum Total Score, Phase 3 Dose-Escalation Group, In-Trial Period	328
Table 157: Gastrointestinal AEs, Study 4153, On-Treatment	330

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 158: Gastrointestinal AEs in the Phase 3 Dose-Escalation Group and by Trial, On-Treatment Period	332
Table 159: Gastrointestinal SAEs, Dose-Escalation Group.....	333
Table 160: "Rare Events" by Pre-Defined MedDRA Search, Phase 3 Pool, On-Treatment.....	343
Table 161: AEs by Body Weight at Baseline, Phase 3 Pool, On-Treatment	353
Table 162: AEs by Weight Loss at Week 68, Phase 3 Dose-Escalation Group, On-Treatment...	354
Table 163: Pregnancies Reported in Phase 3 Trials	355
Table 164: Pregnancies Reported in Phase 2 Trial 4153.....	356
Table 165: Post-Marketing Hepatic-Related Adverse Drug Reactions Identified for Semaglutide Products.....	360
Table 166: Acute Pancreatitis Post-Marketing Reports, Ozempic.....	364
Table 167: Acute Pancreatitis Post-Marketing Reports, Rybelsus.....	364

Table of Figures

Figure 1: Trial 4373 Design	46
Figure 2: Diet and Physical Activity by Week, Trial 4373	59
Figure 3: Percent Body Weight Change from Baseline by Week, Missing Data Plot, Trial 4373 ..	61
Figure 4: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4373, In-Trial.....	62
Figure 5: Mean Waist Circumference by Week, Trial 4373	63
Figure 6: Mean Systolic Blood Pressure Change from Baseline by Week, Trial 4373	64
Figure 7: Mean SF-36 Physical Functioning by Week, Trial 4373.....	65
Figure 8: Mean IWQOL-Lite CT Physical Function by Week, Trial 4373.....	66
Figure 9: Mean Percent Change in Body Weight from Baseline by Week, Trial 4373	68
Figure 10: Trial 4374 Design	72
Figure 11: Mean Body Weight Change from Baseline, Missing Data Pattern, Trial 4374.....	82
Figure 12: Proportion of Subjects Achieving Body Weight Loss Response Criteria Since Baseline at Week 68, Trial 4374.....	83
Figure 13: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4374, In-Trial	84
Figure 14: Mean Waist Circumference by Week, Trial 4374	85
Figure 15: HbA1c by Week, Trial 4374, In-Trial.....	86
Figure 16: Mean Systolic Blood Pressure by Week, Trial 4374.....	87
Figure 17: Mean SF-36 Physical Functioning by Week, Trial 4374.....	88
Figure 18: Mean IWQOL-Lite-CT Physical Function by Week, Trial 4374	89
Figure 19: Percent Body Weight Change from Baseline by Week, Trial 4374	90
Figure 20: Fasting Plasma Glucose Change from Baseline by Week, Trial 4374	92
Figure 21: Proportion of Subjects Achieving $\leq 6.5\%$ or $\leq 7\%$ HbA1c at Week 68, Trial 4374.....	93
Figure 22: Proportion of Subjects Achieving Both Weight Loss and HbA1c Reduction, Trial 4374	93
Figure 23: Change from Baseline in 6-Minute Walk Test, Trial 4374, Sensitivity Analysis	94
Figure 24: Trial 4375 Design	97
Figure 25: Mean Percent Body Weight Change from Baseline by Week, Missing Data Pattern, Trial 4375.....	106
Figure 26: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4375, In-Trial	107
Figure 27: Mean Waist Circumference by Week, Trial 4375	108
Figure 28: Mean Systolic Blood Pressure by Week, Trial 4375.....	109
Figure 29: Mean Change in SF-36 Physical Functioning from Baseline by Week, Trial 4375.....	110
Figure 30: Percent Body Weight Change from Baseline by Week, Trial 4375	111
Figure 31: Trial 4376 Design	113
Figure 32: Antihypertensive Medication During Randomized Portion of Trial 4376.....	125

Figure 33: Proportions of Subjects with Weight Gain (<0%) or Categorical Weight Loss (≥5%, 10%, 15%, 20%) Since Start of Run-In (Week 0) at Week 68, Trial 4376 127

Figure 34: Percent Body Weight Change from Start of Run-In (Week 0) to Week 68, Cumulative Distribution Figure, Trial 4376, In-Trial 128

Figure 35: Percent Body Weight Change from Baseline (Week 20) to Week 68, Cumulative Distribution Plot, Trial 4376, In-Trial 129

Figure 36: Mean Body Weight Change from Baseline (Week 20) by Week, Missing Data Pattern, Trial 4376 130

Figure 37: Mean Waist Circumference by Week, Randomized Period, Trial 4376 131

Figure 38: Mean Systolic Blood Pressure by Week, Randomized Period, Trial 4376 132

Figure 39: Mean SF-36 Physical Functioning by Week, Randomized Period, Trial 4376 133

Figure 40: Mean Body Weight Change from Baseline (Week 20) by Week, Trial 4376 134

Figure 41: Percent Body Weight by Week, Trial 4376 135

Figure 42: Proportions of Subjects Achieving Selected Categories of Weight Loss at Week 68, Trials 4373, 4374, and 4375 137

Figure 43: Forest Plot of Covariate Effects for Semaglutide Exposure, Trials 4373 and 4374 ... 140

Figure 44: Percent Body Weight Change by Age Group, Trials 4373, 4374, and 4375 141

Figure 45: Percent Body Weight Change by Age Group, Trial 4376 141

Figure 46: Percent Body Weight Change by Sex, Trials 4373, 4374, and 4375 142

Figure 47: Percent Weight Change by Sex, Trial 4376 142

Figure 48: Percent Weight Change by Race, Trials 4373, 4374, and 4375 143

Figure 49: Percent Weight Change by Race, Trial 4376 144

Figure 50: Percent Weight Change by Ethnicity, Trials 4373, 4374, and 4375 144

Figure 51: Percent Weight Change by Ethnicity, Trial 4376 145

Figure 52: Percent Weight Change by Baseline Body Weight, Trials 4373, 4374, and 4375 146

Figure 53: Percent Weight Change by Baseline Body Weight, Trial 4376 146

Figure 54: Percent Weight Change by Region, Trials 4373, 4374, and 4375 147

Figure 55: Percent Change in Weight by Region, Trial 4376 147

Figure 56: Trial 4153 Design 148

Figure 57: Change in Percent Body Weight by Treatment Week, Trial 4153 149

Figure 58: Percent Change in Body Weight from Baseline at Week 52, Trial 4153 150

Figure 59: Percent Change in Body Weight from Baseline at Week 52, Primary Efficacy Analysis, Trial 4153 151

Figure 60: Percent Body Weight Change from Baseline Versus Exposure of Semaglutide, Trial 4153 152

Figure 61: Percent Body Weight Change from Baseline Versus Exposure, Trials 4373 and 4374 153

Figure 62: Week 68 5% Weight Response / Non-Response by Week 20 Weight Response 156

Figure 63: Week 68 5% Weight Response / Non-Response by Week 20 Non-Response 156

Figure 64: Observation Periods for Safety Evaluations Across the Phase 3 Trials 160

Figure 65: Subject NN9536-4376 (b) (6) CK (top panel) and AST (bottom panel) Values 203

Figure 66: Eosinophils by Week, Phase 3 Dose Escalation Group, On-Treatment	206
Figure 67: Hemoglobin by Week, Phase 3 Dose Escalation Group, On-Treatment	207
Figure 68: Semaglutide Trough Concentrations by Week for Subjects with Average Concentration Outlier Values	214
Figure 69: Tiered Antibody Assay Approach	216
Figure 70: Semaglutide Pharmacokinetic Concentration by Occurrence of Anti-Semaglutide Antibodies, Trials 4373 and 4374, On-Treatment	218
Figure 71: Body Weight Percent Change from Baseline by Occurrence of Anti-Semaglutide Antibodies, Spaghetti Plot, Trials 4373 and 4374, On-Treatment	220
Figure 72: Events of Cholelithiasis, Cholecystitis, and Cholecystitis Acute Over Time, On-Treatment, Phase 3 Dose-Escalation Group	234
Figure 73: Events of Cholelithiasis, Cholecystitis, and Acute Cholecystitis and Body Weight Change Over Time, Phase 3 Dose-Escalation Group	235
Figure 74: Cholelithiasis, Cholecystitis, and Acute Cholecystitis Events Over Time, Trial 4376, On-Treatment, Randomized Period	237
Figure 75: Adjudication of Pancreatitis, Study 4153	239
Figure 76: Change in Lipase from Baseline by Treatment Week, Study 4153	241
Figure 77: Change in Amylase from Baseline by Treatment Week, Study 4153	242
Figure 78: Change in HR from Baseline by Treatment Week, MMRM	262
Figure 79: Pulse by Week, On-Treatment, Phase 3 Trials	264
Figure 80: Calcitonin by Week and Minimum and Maximum Values, Trials 4373, 4374, and 4375	273
Figure 81: Calcitonin by Week and Minimum and Maximum Values, Trial 4376 (Randomized Period)	274
Figure 82: Serum Creatinine by Treatment Week, Subject NN9536-4153/ (b) (6)	297
Figure 83: ADA 2013 Classification of Hypoglycemia	305
Figure 84: Hypoglycemic Episodes (ADA 2018, Level 2 or 3), Plot Over Time, Trial 4374	306
Figure 85: AEs of Diabetic Retinopathy, MedDRA Search, SUSTAIN and PIONEER Programs	318
Figure 86: Gastrointestinal AEs, Time-to-Onset, Phase 3 Dose-Escalation Group, On-Treatment	336
Figure 87: Gastrointestinal AEs, Prevalence Plot, Phase 3 Dose-Escalation Group	337
Figure 88: Timing and Duration of Common Gastrointestinal AEs, Phase 3 Dose-Escalation Group	338
Figure 89: Gastrointestinal AEs, Time-to-Onset, Randomized Period of Trial 4376, On-Treatment	339
Figure 90: Gastrointestinal AEs by Severity, Prevalence Plot, Randomized Period of Trial 4376, On-Treatment	340
Figure 91: Most Frequent AEs by Sex and PT, Phase 3 Pool, On-Treatment	347
Figure 92: Most Frequent AEs by Baseline Age and PT, Phase 3 Pool, On-Treatment	348
Figure 93: Most Frequent AEs by Race, Phase 3 Pool, On-Treatment	349
Figure 94: Most Frequent AEs by Ethnic Origin, Phase 3 Pool, On-Treatment	350

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Figure 95: Adverse Events Over Time, Phase 3 Dose Escalation Group 351

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Semaglutide (proposed proprietary name: Wegovy) is a glucagon-like peptide-1 (GLP-1) receptor agonist (RA) that has been developed as a once-weekly subcutaneous (SC) injection as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of

- 30 kg/m² or greater (obesity), or
- 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition

The proposed dosing regimen is 2.4 mg once weekly. To reduce the likelihood of gastrointestinal symptoms, a dose-escalation regimen is proposed, with a starting dose of 0.25 mg once weekly for 4 weeks and then dose increases every 4 weeks to 0.5, 1.0, 1.7, and 2.4 mg/week.

The applicant has developed a single-dose pen-injector with an integrated prefilled syringe, with a 0.5 mL dose volume for the 3 lower doses and a 0.75 mL dose volume for the 2 higher doses. The semaglutide drug product will be available in 5 concentrations for the 5 respective doses: 0.5 mg/mL, 1.0 mg/mL, 2.0 mg/mL, 2.27 mg/mL, and 3.2 mg/mL.

Semaglutide SC injection at doses of 0.5 mg and 1 mg once-weekly is currently approved in the US for treatment of type 2 diabetes (T2D) and for cardiovascular (CV) risk reduction in people with T2D and established cardiovascular disease (NDA 209637, Ozempic). Oral semaglutide is also approved in the US at daily doses of 7 mg and 14 mg for treatment of T2D (NDA 213051, Rybelsus).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Semaglutide 2.4 mg met the statutory standard for effectiveness, with all 4 phase 3 trials demonstrating statistically and clinically meaningful changes from baseline in body weight. Placebo-subtracted weight loss from baseline after 1 year at the maintenance semaglutide dose was 10.3-12.4% in a non-diabetic population and 6.2% in a population with T2D. The majority (68.8-86.6%) of subjects on semaglutide 2.4 mg achieved at least 5% body weight loss at the end of the trial, and this was 2- to 3-times the proportions of subjects randomized to placebo.

The statistically significant treatment effects observed with semaglutide in this program are larger in magnitude than has been seen with any currently approved drug for chronic weight

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

management. Weight loss with semaglutide was associated with improvements in glycemia, blood pressure, and lipids in most trials.

1.3. Benefit-Risk Assessment

See the table below.

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

Obesity and overweight impact millions of Americans and excess weight is a risk factor for many health conditions including hypertension, dyslipidemia, type 2 diabetes (T2D), coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers. Individuals with obesity report impaired physical functioning, mental health conditions such as depression, and a decreased quality of life. Standard-of-care for treatment is lifestyle therapy, such as reduced calorie, nutritionally complete diets, increased physical activity, and behavioral modification. Patients with morbid obesity (BMI ≥ 40 kg/m² or ≥ 35 kg/m² with weight-related comorbidities) can have good outcomes with bariatric surgery. The medical treatments approved to-date for chronic weight management do not have widespread use, possibly because of issues such as lack of insurance coverage, limited weight loss, safety issues, or because of historical concerns about the benefit-risk balance that have led numerous obesity drugs to be removed from the U.S. market.

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is currently approved in the U.S. as a subcutaneous injection at doses up to 1 mg weekly and as an oral tablet at doses up to 14 mg daily for the treatment of type 2 diabetes (T2D). In addition to the glycemic control indication, the subcutaneous injection product is also approved to reduce the risk of major adverse cardiovascular events in patients with T2D and established cardiovascular disease.

Semaglutide was studied at a dose of 2.4 mg weekly as a subcutaneous injection in a large phase 3 program that meets the recommendations for size and scope outlined in the 2007 FDA draft guidance for weight management. Semaglutide 2.4 mg was shown to be effective for weight management in patients with obesity and overweight with co-morbidities. Weight loss was achieved at the maintenance dose of 2.4 mg and continued for up to a year in all populations studied (with and without T2D). The majority of subjects on semaglutide 2.4 mg achieved at least 5% body weight loss at 68 weeks. The treatment effects observed with semaglutide in this program are larger in magnitude than has been seen with any currently approved drug for chronic weight management and are clinically meaningful. Weight loss with semaglutide was associated with improvements in glycemia, blood pressure, lipids, and physical functioning in most trials.

Semaglutide and other GLP-1 RAs have a well-characterized safety profile. There is a boxed warning for thyroid c-cell tumors/medullary thyroid carcinoma based on nonclinical data. Other described or theoretical safety concerns from the weight management or diabetes programs (or based on knowledge of the GLP-1 RA class) include: gastrointestinal adverse events, increase in heart rate, hypoglycemia, orthostatic hypotension and syncope, acute kidney injury, gallbladder disease, pancreatitis, hypersensitivity reactions, potential hepatic disorders, diabetic retinopathy, and psychiatric disorders.

In summary, the most common risks of semaglutide currently are monitorable and can be mitigated with labeling. The weight loss efficacy appears substantial at least in some patients. On balance, the benefit-risk for semaglutide 2.4 mg once-weekly for chronic weight management in a population of obese and overweight individuals appears favorable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Obesity and overweight impacts millions of Americans • Obesity is a chronic, relapsing health condition • Obesity is difficult to treat • Obesity increases the risk of chronic health outcomes, including hypertension, dyslipidemia, type 2 diabetes (T2D), coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers • Weight loss of 5-10% in patients with obesity is generally accepted as beneficial on cardiometabolic health biomarkers. • The cardiovascular benefit of pharmacologic-induced weight loss has not been demonstrated in clinical trials to date	Patients at risk from excess weight who would benefit from weight loss medication include those with BMI ≥ 30 kg/m² (obese) and those with BMI ≥ 27 kg/m² (overweight) with weight-related co-morbidities (e.g., hypertension, dyslipidemia, type 2 diabetes).
Current Treatment Options	• Standard-of-care is lifestyle treatment (reduced calorie diet, increased physical activity) • Bariatric surgery is effective but given risks, is reserved for patients with morbid obesity • Current medications for chronic weight management suffer from poor acceptance and limited use • The most frequently used medication for weight loss is generic phentermine, which has very limited long-term data for safety or	The effort to treat obesity with drugs has been plagued with safety concerns and has led some drugs to never be approved in the U.S. or to be removed from the U.S. market after approval due to serious toxicities. Four drugs are currently approved in the U.S. for chronic weight management in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	efficacy and is only approved for short-term use	treatment of obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide. Phentermine and other amphetamine congeners were approved in the U.S. primarily in the 1950s and 60s with a short-term use limitation. However, this class continues to be the most frequently used for prescription weight loss, despite a lack of long-term safety and efficacy data.
Benefit	• Placebo-subtracted weight loss from baseline after 1 year at the maintenance semaglutide dose was 10.3-12.4% in a non-diabetic population and 6.2% in a population with T2D. • The majority (68.8-86.6%) of subjects randomized to semaglutide 2.4 mg achieved at least 5% body weight loss at the end of the trial, and this was 2 to 3 times the proportions of subjects randomized to placebo. • Weight loss with semaglutide was associated with improvements in glycemia, blood pressure, and lipids in most trials. • Cardiovascular and other outcomes benefits of semaglutide in the obese patient population without T2D are unknown. • Long-term benefits (beyond 68 weeks) are unknown.	The weight management program demonstrated that semaglutide 2.4 mg leads to robust, durable weight loss in obese and overweight patients over the study period, and the weight loss was associated with improvements in cardiometabolic parameters. An ongoing CVOT should clarify the long-term CV benefit of semaglutide in an obese population without T2D.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Adverse events that are known or theoretical include: gastrointestinal AEs, increase in heart rate, hypoglycemia, orthostatic hypotension and syncope, acute kidney injury, gallbladder disease, pancreatitis, hypersensitivity reactions, potential hepatic disorders, diabetic retinopathy, and psychiatric disorders. ○ All GLP-1 RAs include a boxed warning for MTC based on nonclinical data ○ Pancreatitis is labeled as a class warning but was infrequently seen in this program ○ Diabetic retinopathy was identified as a novel safety concern in the semaglutide CVOT in T2D ○ Drug-induced liver injury has been reported with semaglutide and other GLP-1 RAs in the post-marketing setting ○ Suicidality has been observed with other obesity drugs ○ Whether the increase in HR translates to a CV risk in the obesity population is unknown ○ Hypoglycemia is most likely a safety concern for patients with T2D on sulfonylureas or insulin • 37 pregnancies were reported in the phase 2 and 3 trials	The most common adverse reactions are monitorable and can be mitigated with labeling. Studies ongoing or planned will help to understand some of these risks: • Ongoing CVOTs in weight management and diabetes • 2-year safety trial in weight management • Pediatric trials in weight management • A trial to evaluate the long-term effects of semaglutide versus placebo on diabetic retinopathy development and progression when added to standard-of-care in subjects with T2D • MTC registry • Pregnancy studies A post-marketing evaluation is ongoing regarding possible DILI and GLP-1 RA drugs

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
x	Clinical outcome assessment (COA) data, such as	
	x Patient reported outcome (PRO)	Section 6.1.2, 6.2.2, 6.3.2, 6.4.2
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
	□ Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
	□ Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

According to the 2013 American Heart Association / American College of Cardiology guidelines on the management of overweight and obesity, obesity raises the risk of morbidity from, and is also associated with increased risk of all-cause and cardiovascular (CV) disease mortality.¹ Obesity affects millions of American adults, affects patients' health and quality-of-life, is notoriously difficult to treat, and is therefore a significant public health issue.

As described in the FDA draft guidance for developing weight management drugs,² weight change is the endpoint of interest in clinical trials for the development of obesity drugs. Among individuals with overweight or obesity, weight is an easily measured surrogate for body adiposity, and long-term weight loss in the range of 5 to 10% is associated with improved glycemic control, blood pressure, and lipid parameters.³

It is presumed that salutary changes in cardiovascular and metabolic risk factors will translate into CV benefit, such as reductions in the incidence of myocardial infarction and stroke. Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, weight loss (at least at the magnitude seen in trials of most other weight management drugs; see Table 1) has not been established as a surrogate for CV benefit. The Look AHEAD (Action for Health in Diabetes) trial⁴ was a randomized controlled trial in over 5000 patients with T2D comparing an intensive lifestyle intervention (including weight loss) to standard-of-care for a follow-up of 10 years. The trial was stopped early (9.6 years) for futility of the composite primary outcome (first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalized angina); HR 0.95 (95% CI 0.83, 1.09). Weight loss was greater in the intervention group (8.6% at 1 year, 6.0% at study end) as compared to the control group (0.7% at 1 year, 3.5% at study end).

¹ Jensen MD, et al. Executive summary: Guidelines (2013) for the management of overweight and obesity in adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Obesity* 2014. 22(S2): S5-39.

² FDA Draft Guidance for Industry: Developing Products for Weight Management. February 2007.

³ Van Gaal LF, et al. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord* 1997 Mar; 21 Suppl 1: S5-9.

⁴ The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013; 369: 145-54.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Weight loss drugs with sympathomimetic effects may also cause CV harm.⁵ While not necessarily applicable to semaglutide, it is worth remembering that drugs may have safety concerns that mitigate weight loss benefits (see Section 2.2, below).

Although semaglutide for T2D (Ozempic) has been approved to reduce the risk of major adverse CV events (CV death, non-fatal myocardial infarction or non-fatal stroke) in adults with T2D and established CV disease, the use of Ozempic specifically as a therapy for T2D versus standard-of-care is important is interpreting the CV outcomes for semaglutide.⁶

An ongoing CV outcomes trial with semaglutide in subjects with obesity and without T2D (trial EX9536-4388, 'SELECT'; discussed elsewhere in this review) will help to clarify its CV benefits.

2.2. Analysis of Current Treatment Options

The effort to treat obesity with drugs has been plagued with safety concerns and has led some drugs to never be approved in the United States (rimonabant) or to be removed from the U.S. market after approval (fenfluramine, dexfenfluramine, phenylpropanolamine, sibutramine, and most recently, lorcaserin) due to serious toxicities.

As of this writing there are 4 agents approved in the U.S. for chronic weight management in the treatment of obesity: orlistat, phentermine/topiramate, naltrexone/bupropion, and liraglutide (see Table 1).

Phentermine and other amphetamine congeners were approved in the U.S. primarily in the 1950s and 60s with a short-term use limitation. However, this class continues to be the most frequently used for prescription weight loss,⁷ despite a lack of long-term safety and efficacy data (Table 1).

⁵ James WPT, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010; 363:905-17.

⁶ See also: Golden J, Saxenda (liraglutide for weight management) efficacy supplement clinical review, dated 12 Oct 2018 [to include CV data from Victoza (liraglutide for T2D) in its labeling]; NDA 206321 SDN 424

⁷ Borders-Hemphill V, Drug Utilization Trends of Anti-Obesity Products in the Outpatient Setting Y1991-2011, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, March 28-29, 2012

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed)
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
Xenical (orlistat)	XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m ² or ≥ 27 kg/m ² in the	1999	one 120-mg capsule three times a day with each main meal containing fat	After 1 year of treatment, the mean percent weight loss difference between XENICAL-treated patients and placebo-treated patients was 3%.	Decreased absorption of fat-soluble drugs (e.g., cyclosporine) and vitamins Liver injury Increases in urinary oxalate Cholelithiasis GI symptoms (oily stool)	Label includes onset of type 2 diabetes data from 4-year study Approved at a lower dose for over-the-counter weight loss

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

	presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).					
Qsymia (phentermine/topiramate XR)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m ² or greater (obese), or 27 kg/m ² or greater (overweight) in the presence of at least one weight related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia	2012	Start treatment with Qsymia 3.75 mg/23 mg daily for 14 days; after 14 days increase to the recommended dose of Qsymia 7.5 mg/46 mg once daily. Evaluate weight loss after 12 weeks of treatment with Qsymia 7.5 mg/46 mg. If a patient has not lost at least 3% of baseline body weight on Qsymia 7.5 mg/46 mg, discontinue Qsymia or escalate the dose, as it is unlikely that the patient will achieve and sustain clinically	After 1-year of treatment, the difference in mean weight loss between Qsymia and placebo was -9.4% (Qsymia 15/92, obese patients, study 1), -6.6% (Qsymia 7.5/46, overweight and obese, study 2), and -8.6% (Qsymia 15/92, overweight and obese, study 2)	Embryo-fetal toxicity Increase in HR Suicidal behavior and ideation Acute myopia and secondary angle closure glaucoma Mood and sleep disorders Cognitive impairment Metabolic acidosis Elevation in creatinine Hypoglycemia in T2D on anti-diabetic therapy Hypotension in	Product is approved with a REMS for embryo-fetal toxicity Study 2 included patients with and without T2D Both components are approved drugs

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

			meaningful weight loss at the Qsymia 7.5 mg/46 mg dose. To escalate the dose: Increase to Qsymia 11.25 mg/69 mg daily for 14 days; followed by dosing Qsymia 15 mg/92 mg once daily. Evaluate weight loss following dose escalation to Qsymia 15 mg/92 mg after an additional 12 weeks of treatment. If a patient has not lost at least 5% of baseline body weight on Qsymia 15 mg/92 mg, discontinue Qsymia as directed, as it is unlikely that the patient will achieve and sustain clinically meaningful weight		patients treated with antihypertensive medications CNS depression with CNS depressants Potential seizures with abrupt withdrawal Dose adjustment in renal and hepatic impairment Kidney stones Oligohidrosis and hypothermia Hypokalemia Monitoring labs: bicarbonate, creatinine, potassium, glucose	

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

			loss with continued treatment.			
Contrave (naltrexone HCl and bupropion HCl)	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m ² or greater (obese), or 27 kg/m ² or greater (overweight) in the presence of at least one weight related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)	2014	Start at one CONTRAVE 8 mg/90 mg tablet once daily for one week and dose escalate to a total daily dosage of two CONTRAVE 8 mg/90 mg tablets twice daily (32 mg/360 mg) at the start of Week 4.	After 1 year of treatment, CONTRAVE %weight loss difference from placebo -4.1% (study 1), -3.2% (study 2), -2.0% (study 3, T2D)	Suicidal behavior and ideation Neuropsychiatric AEs and suicide risk in smoking cessation treatment Seizures Vulnerability to opioid overdose and precipitated opioid withdrawal Increase in BP and HR Allergic reactions Hepatotoxicity Activation of mania Angle-closure glaucoma Hypoglycemia in T2D on anti-diabetic therapy	Both components are approved drugs

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Saxenda (liraglutide)	SAXENDA is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in: Adult patients with an initial body mass index (BMI) of: 30 kg/m ² or greater (obese), or 27 kg/m ² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)	2014	Initiate at 0.6 mg SC once daily for 1 week, dose escalate weekly for 4 weeks until maintenance dose of 3 mg once daily is reached	Difference in % weight change at week 56, Saxenda – placebo: -4.5% (study 1), -3.7% (study 2, T2D), -5.2% (study 3)	Risk of thyroid C-cell tumors Acute pancreatitis Acute gallbladder disease Hypoglycemia HR increase Renal impairment Hypersensitivity reactions Suicidal behavior and ideation Most common AEs are GI (nausea, vomiting, diarrhea)	Also approved for (b) (4) T2D (b) (4) (b) (4) Only weight management product with a pediatric indication

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

	Pediatric patients aged 12 years and older with: body weight above 60 kg and an initial BMI corresponding to 30 kg/m ² or greater for adults (obese) by international cut-offs					
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Phentermine and other amphetamine congeners	Indicated as a short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity for patients with an initial body mass index greater than or equal to 30 kg/m ² , or	1959	Depends on product: typical oral dosage is individualized to obtain an adequate response with the lowest effective dose	In relatively short-term clinical trials, adult obese subjects instructed in dietary management and treated with “anorectic” drugs lost more weight on the average than those treated with placebo and diet. The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest	Coadministration with other weight loss products not recommended Primary pulmonary hypertension Valvular heart disease Development of tolerance Effect on the ability to engage in potentially hazardous tasks	These short-term products are a hold-over from before the era of chronic use treatment for obesity

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

	greater than or equal to 27 kg/m ² in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia)			in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks.	Risk of abuse and dependence Usage with alcohol Use in patients with hypertension Use in patients on insulin or oral hypoglycemic medications for T2D	

Source: U.S. approved drug labels

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Semaglutide is marketed in the U.S. as Ozempic⁸ at doses of 0.5 and 1 mg once weekly subcutaneously (SC), and Rybelsus⁹ at doses of 7 and 14 mg once daily orally (PO), for glycemic control in patients with T2D. Ozempic also has an indication to reduce major adverse cardiovascular (CV) events in patients with T2D and established CV disease.¹⁰

There are 2 ongoing PMRs for Ozempic:

- 3294-2: Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Ozempic (semaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Ozempic (semaglutide).¹¹
- 3294-5: Conduct a 52-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of semaglutide for the treatment of type 2 diabetes mellitus in pediatric subjects ages 10 to 17 years (inclusive). Background therapy will consist of either metformin, insulin, or metformin plus insulin.

3.2. Summary of Presubmission/Submission Regulatory Activity

Semaglutide for weight management IND 126360 was opened June 2015, with the submission of a phase 2, placebo-controlled, dose-finding trial of semaglutide for chronic weight management (trial 4153).

An end-of-phase 2 meeting was held on 23 October 2017. The following was discussed:

- Phase 3 trial design, eligibility criteria, and endpoints: The Division agreed with the scope, size, design, and endpoints of the trial. The applicant was encouraged to loosen some of the eligibility restrictions to broaden and generalize the patient population.

⁸ NDA 209637, approved 05 December 2017

⁹ NDA 213051, approved 20 September 2019

¹⁰ NDA 209637 supplement 3, approved 16 January 2020

¹¹ This MTC registry collects data from all approved GLP-1 RA products in the U.S.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- CV safety: Based on the expected event rate, the applicant clarified that it was unlikely that the phase 3 trials would be powered to rule out a hazard ratio of 2. The applicant was encouraged to explore the feasibility of an outcomes trial and the applicant suggested that they would propose a separate meeting to discuss.
- Safety monitoring: Specifically discussed were issues regarding diabetic retinopathy (seen in excess in the Ozempic CV outcomes trial (CVOT)), pancreatitis, neoplasms, gallbladder, pregnancy, and general safety monitoring.
- Dose and dosing regimen: See discussion in Section 7.1.4.
- Statistical issues: FDA agreed that the proposed hierarchical testing procedure adequately controls the type 1 error probability. The applicant was informed, however, that (b) (4) would be a review issue.
- Clinical pharmacology: FDA agreed that the QTc study could be cross-referenced (see Section 8.4.9). It was recommended that the 2.4 mg/week dosage on gastric emptying be separately addressed. FDA recommended that the to-be-marketed drug product be used in at least 1 of the phase 3 trials.
- Stopping rule: The applicant agreed to investigate subgroup analyses based on the amount of weight lost during the run-in period of trial 4376 (see Section 7.2.1).
- Immunogenicity: FDA agreed that the proposal for antibody sampling seemed reasonable.

3.3. Foreign Regulatory Actions and Marketing History

Semaglutide 0.5 mg and 1 mg for once-weekly SC injection is approved worldwide (Ozempic) for treatment of T2D, and in the U.S. and Russia for CV risk reduction in people with T2D and established CV disease. Oral semaglutide at daily doses of 7 mg and 14 mg (Rybelsus) is approved in the U.S., Canada, the E.U. and Japan for the treatment of T2D.

The weight management program was designed to meet regulatory requirements in other countries. To my knowledge, semaglutide has not been approved for use for weight management anywhere in the world to date.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The scope of the site inspections was reduced (from 5 domestic inspections to 2) because of the ongoing COVID-19 pandemic. The following 2 sites were inspected in support of this application:

- Domenica Rubino (trial 4375)
- Andrew Brockmyre (trial 4376)

No Form FDA-483, Inspectional Observations, was issued for either site.

See the Clinical Inspection Summary from Dr. Cynthia Kleppinger, Office of Scientific Investigations (OSI) for more details.

4.2. Product Quality

This NDA cross-references the approved Ozempic NDA 209637 for all drug substance information.

The drug product contains 0.5 mg/mL, 1.0 mg/mL, 2.0 mg/mL, 2.27 mg/mL, or 3.2 mg/mL of the active ingredient semaglutide as an injectable solution as a prefilled syringe in a single-dose pen-injector. The semaglutide single dose pen-injector comes in five variants, one for each of the doses 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, and 2.4 mg.

Excipients in the drug product include disodium phosphate, dihydrate; sodium chloride; hydrochloric acid; sodium hydroxide; and water for injections.

The Office of Pharmaceutical Quality (OPQ) recommends approval. Refer to the integrated quality assessment, OPQ for more details.

4.3. Clinical Microbiology

Semaglutide is not an antimicrobial.

(b) (4)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

There are no microbiology deficiencies. Refer to the integrated quality assessment, OPQ for more details.

4.4. Nonclinical Pharmacology/Toxicology

This NDA cross-references the approved Ozempic NDA 209637 for standard nonclinical information.

The nonclinical summary for the weight management program included the following: 1) updated animal-to-human exposure ratios due to the higher clinical dose for weight management (2.4 mg/week) compared to the clinical dose for T2D (1 mg/week), and 2) a summary of the body weight-related effects of semaglutide occurring within the brain based on current literature and 2 additional animal pharmacology studies.

Refer to the review from Dr. Elena Braithwaite, Division of Pharmacology-Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPT-CHEN) for more details. Dr. Braithwaite recommends approval.

4.5. Clinical Pharmacology

Some of the key findings from the clinical pharmacology program are as follows. Except where noted, these are the applicant's conclusions.¹² Refer to the review from Dr. Sang Chung, Office of Clinical Pharmacology (OCP) for more details. Dr. Chung recommends approval.

- Steady-state pharmacokinetics (PK) showed that semaglutide has an elimination half-life ($t_{1/2}$) of approximately one week. Exposure of semaglutide increased in a dose-proportional manner up to 2.4 mg once weekly.
- Body weight was the most important covariate resulting in lower exposure with higher body weight and vice versa. Other investigated covariates (sex, age, race, ethnicity, renal function, injection site, and glycemic status) had a minor or no influence on semaglutide exposure. (Also see Figure 43 in Section 7.1.3, Subpopulations.)
- Exposure-response assessments showed that the body weight lowering response increased with increasing semaglutide exposure within the concentration range obtained with semaglutide 2.4 mg.
- The proportion of subjects reporting gastrointestinal adverse events, in particular nausea or vomiting, increased to a minor extent with increasing semaglutide exposure and appeared

¹² Module 2.7.2, Summary of Clinical Pharmacology

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

to plateau so that it was almost constant over the studied exposure range for semaglutide 2.4 mg.

- Gastric emptying was evaluated in a dedicated study. No apparent effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, although these results may have been confounded by body weight change.¹³
- In a supportive secondary analysis in study 4455, body weight loss was associated with reduced appetite due to increases in satiety and fullness, leading to lower energy intake.
- No prolongation of the QTc interval and no semaglutide exposure-QTc relationship was observed in the thorough QT/QTc study conducted for Ozempic (maximum semaglutide dose 1.5 mg).
- Semaglutide anti-drug antibodies do not appear to affect PK. See Immunogenicity, Section 8.4.10 for more details.
- All clinical trials evaluated semaglutide drug product delivered in a PDS290 pen-injector. In trial 4590, bioequivalence between the *to-be-marketed* drug product in a single-dose pen-injector and the drug product in a PDS290 pen-injector was assessed. The estimated treatment ratios and 90% CIs for AUC_{0-168h} and C_{max} were within the acceptance interval of [0.80, 1.25], Table 2.

¹³ Personal communication, Dr. Chung.

Table 2: Bioequivalence Assessment Via Pharmacokinetic Endpoints of Semaglutide 2.4 mg at Steady State, Study 4590

	FAS	N	Estimate	95% CI	90% CI
AUC, 0-168h (nmol*h/L)					
Mean					
Semaglutide D, DV3396	33	29	14572	[13937 ; 15236]	
Semaglutide B, PDS290	31	30	13827	[13234 ; 14446]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.0539		[1.0003 ; 1.1104]
Cmax (nmol/L)					
Mean					
Semaglutide D, DV3396	33	29	118	[112 ; 125]	
Semaglutide B, PDS290	31	30	102	[96.8 ; 108]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.1556		[1.0800 ; 1.2365]

FAS: Number of subjects in full analysis set

N: Number of subjects contributing to analysis, CI: Confidence interval

The endpoint is logarithmically transformed and analysed using an ANCOVA model with treatment and stratification as factors and logarithm of body weight as covariate. Subject (b) (6) was excluded from this analysis due to trial product spillage during injection at V15. Subject (b) (6) was excluded from this analysis due to insufficient data to derive endpoints at 2.4 mg dose. Subjects (b) (6) did not take all of the last 3 planned 2.4 mg doses, and thus were excluded from this analysis, as per protocol.

Source: Study 4590 CSR, Table 11-1

4.6. Devices and Companion Diagnostic Issues

Human Factors

Reviewers in the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) found the results of the human factors validation study acceptable. The reviewers evaluated the proposed packaging and labeling and identified areas of vulnerability that may lead to medication errors. Recommendations were sent to the applicant. Please refer to the DMEPA review for more details.

Center for Devices and Radiological Health (CDRH)

Reviewers in CDRH assessed the device performance and have no outstanding deficiencies that preclude approval. Post-approval inspections are required for 2 of the manufacturing firms.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 describes the 8 clinical trials conducted and submitted in the NDA to support the semaglutide chronic weight management program.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 3. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
NN9536-4153	NCT02453711	Randomized (6:1 active:placebo), double-blind, placebo-controlled, 16-armed, parallel group, multi-center, multinational trial with liraglutide 3 mg as active comparator, investigating safety and efficacy of once-daily semaglutide	Semaglutide (1.0 mg/mL) SC, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg once daily Liraglutide (6.0 mg/mL) SC, 3 mg once daily Placebo (matching each of the active treatment arms) SC, once daily	Primary: % change from baseline in body weight	52 weeks	957	Subjects with obesity without diabetes mellitus	71 sites in 8 countries (Australia, Belgium, Canada, Germany, Israel, Russia, UK, US)
NN9536-4373 (STEP 1)	NCT03548935	Randomized (2:1), double-blind, placebo-controlled, 2-arm, parallel group, multi-center, multinational trial assessing the effect and safety of semaglutide SC 2.4 mg once-weekly vs placebo as an adjunct to reduced	Semaglutide (3.0 mg/mL) SC 2.4 mg once-weekly, or placebo	Co-primary: % change from baseline in body weight Subjects who achieve body	68 weeks (extension ongoing)	1961	Subjects with obesity (BMI ≥ 30 kg/m ²), or overweight (BMI ≥ 27 to < 30 kg/m ²) and at least 1	129 sites in 16 countries (Argentina, Belgium, Bulgaria, Canada, Denmark, ,

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		calorie diet and increased physical activity		weight reduction $\geq$ 5% from baseline			weight-related comorbidity	Finland, France, Germany, India, Japan, Mexico, Poland, Russia, Taiwan, UK, US)
NN9536-4374 (STEP 2)	NCT03552757	Randomized (1:1:1), double-blind, double-dummy, placebo-controlled, multi-center, multinational trial assessing the effect and safety of semaglutide SC 2.4 mg once-weekly vs placebo as an adjunct to reduced calorie diet and increased physical activity	Semaglutide (1.34 mg/mL) SC, 1 mg once-weekly Semaglutide (3.0 mg/mL) SC, 2.4 mg once-weekly Placebo (matching each of the 2 active treatment arms) SC, once-weekly	Co-primary: % change from baseline in body weight Subjects who achieve body weight reduction $\geq$ 5% from baseline	68 weeks	1210	Subjects with BMI $\geq$ 27 kg/m ² and T2D (HbA1c 7 – 10%)	149 sites in 12 countries (Argentina, Canada, Germany, Greece, India, Japan, Russia, South Africa, Spain, UAE, UK, US)
NN9536-4375 (STEP 3)	NCT03611582	Randomized (2:1), double-blind, placebo-controlled, 2-arm, parallel-group, multi-center trial assessing the effect and safety of	Semaglutide (3.0 mg/mL; 3.2 mg/mL during last 8	Co-primary: % change from baseline in body weight	68 weeks	611	Subjects with obesity (BMI $\geq$ 30 kg/m ²), or overweight	41 sites in 1 country (US)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		semaglutide SC 2.4 mg once-weekly vs placebo as an adjunct to intensive behavioral therapy	weeks of treatment) SC 2.4 mg once-weekly, or placebo	Subjects who achieve body weight reduction $\geq 5\%$ from baseline			(BMI ≥ 27 to < 30 kg/m ²) and at least 1 weight-related comorbidity	
NN9536-4376 (STEP 4)	NCT03548987	Randomized (2:1), double-blind, placebo-controlled, 2-arm, multi-center, multinational withdrawal trial assessing the effect and safety of semaglutide SC 2.4 mg once-weekly vs placebo in subjects who reached maintenance dose during run-in period	Semaglutide (3.0 mg/mL) SC 2.4 mg once-weekly, or placebo	Primary: % change from randomization (week 20) to week 68 in body weight	68 weeks	803	Subjects with obesity (BMI ≥ 30 kg/m ²), or overweight (BMI ≥ 27 to < 30 kg/m ²) and at least 1 weight-related comorbidity, who had reached the maintenance dose of 2.4 mg at randomization	73 site in 10 countries (Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine, US)
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
NN9535-4588	NCT04152915	Randomized (1:1), single-center, parallel-group, multiple-dose, open-label trial to demonstrate bioequivalence between semaglutide formulations for the single-dose pen-injector and for	Semaglutide D (0.5 mg/mL and 2.0 mg/mL), 0.25 mg and 1 mg once-weekly SC	PK/PD Bioequivalence	7 weeks	66	Subjects with BMI 25.0 – 34.9 kg/m ²	1 site in Germany

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		the PDS290 semaglutide pen-injector	administration with single-dose pen-injector Semaglutide B (1.34 mg/mL), 0.25 mg and 1 mg once-weekly SC administration with PDS290 pen-injector					
NN9536-4590	NCT04187300	Randomized (1:1), single-center, parallel-group, 2-armed, open-label, multiple-dose trial to demonstrate bioequivalence between semaglutide formulations for the single-dose pen-injector and for the PDS290 pen-injector	Semaglutide D (2.0 mg/mL and 3.2 mg/mL), 1 mg and 2.4 mg once-weekly SC administration with single-dose pen-injector Semaglutide B (3.0 mg/mL), 1 mg and 2.4 mg once-weekly SC	PK/PD Bioequivalence	21 weeks	64	Subjects with BMI 27.0 – 34.9 kg/m ²	1 site in Germany

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			administration with PDS290 pen-injector					
NN9536-4455	NCT03842202	Randomized (1:1), single-center, parallel-group, multiple-dose, double-blind, placebo-controlled trial to assess the effect of semaglutide 2.4 mg once-weekly on gastric emptying	Semaglutide (3.0 mg/mL) SC 2.4 mg once-weekly, or placebo	Primary: paracetamol AUC	21 weeks	72	Subjects with BMI 30 – 45 kg/m ²	1 site in Germany

Source: Module 5.2, Tabular listing of all clinical studies; and Modules 5.3.1, 5.3.4, and 5.3.5, Study synopses

5.2. Review Strategy

I reviewed all the information contained in this document.

I focused my efficacy assessment on the 4 phase 3 clinical study reports, the Summary of Clinical Efficacy (SCE), and the Integrated Summary of Efficacy (ISE). The efficacy review defers to some of the analyses and assessments conducted by reviewers from the Office of Biostatistics, the Clinical Outcomes Assessment (COA) staff, and the Office of Clinical Pharmacology.

My strategy for safety is detailed in Section 8; in summary, I reviewed the safety from the 8 clinical trials in the weight management program, focusing on the phase 3 trials as well as pooling and grouping conducted by the sponsor in the Summary of Clinical Safety (SCS) and the Integrated Summary of Safety (ISS). Blinded data, including data in the 120-day safety update, clinical trial 15-day safety reports under IND 126360, and post-marketing information were reviewed in selected sections of the safety review. The safety review defers to some of the analyses and assessments conducted by reviewers from the Office of Surveillance and Epidemiology, the Office of Biotechnology Products, the Division of Pediatrics and Maternal Health, the Division of Pharmacology/Toxicology, and the Office of Clinical Pharmacology.

Not all endpoints that were submitted in the NDA were discussed in this document. My focus was on those endpoints that informed the assessment of benefit-risk of the product, and particularly those endpoints that are being considered for inclusion in product labeling.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. NN9536-4373 (STEP 1): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity

6.1.1. Study Design

Overview and Objective

Trial 4373 is the largest safety and efficacy trial in the STEP program, designed to demonstrate that semaglutide 2.4 mg administered subcutaneously (SC) once-weekly as an adjunct to reduced-calorie diet and increased physical activity, is effective (reduces body weight) and safe for the treatment of patients with overweight or obesity. Secondary objectives were to assess the effect of semaglutide 2.4 mg on cardiovascular risk factors, clinical outcome assessments, glucose metabolism, and other factors related to body weight.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

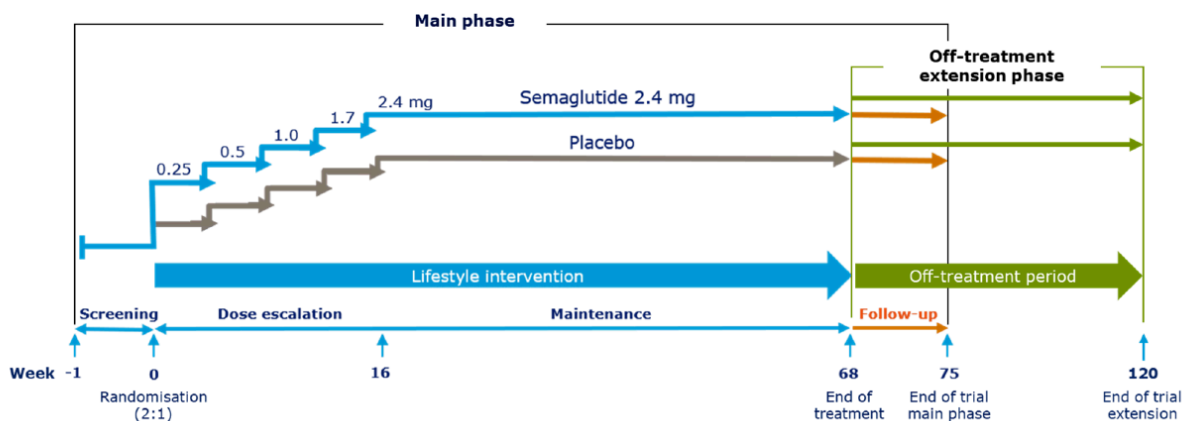
Trial Design

This was a multicenter, multinational trial that included a 68-week randomized, double-blind, 2-arm, placebo-controlled main phase and an open-label, 52-week off-treatment extension phase. Only the main phase was reported in the trial report.

Semaglutide was dose-escalated over 16 weeks to the 2.4 mg once-weekly maintenance dose for GI tolerability (i.e., the following doses were given once-weekly for 4 weeks each: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg).

A follow-up visit was scheduled 7 weeks after end-of-treatment to account for the long half-life.

Figure 1: Trial 4373 Design



Source: Study 4373 CSR, Figure 9-1

Subjects in the trial were at least 18 years of age, with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with the presence of at least 1 of the following weight-related co-morbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Subjects were excluded with type 1 or type 2 diabetes, a HbA1c $\geq 6.5\%$, or body weight change > 5 kg within 90 days before screening. In order to be randomized, subjects must have had a PHQ-9 score < 15 and no suicidal behavior or ideation between screening and randomization.

A subpopulation of 140 subjects in the U.S. (135 planned) underwent DEXA scanning for body composition monitoring; subjects eligible for the DEXA sub-study must have had a BMI ≤ 40 kg/m² at screening.

Study Endpoints

The 2 co-primary efficacy endpoints were:

- Percent change in body weight from baseline to week 68
- Proportion of subjects achieving a weight loss of $\geq 5\%$ from baseline to week 68

Secondary endpoints were:

- Proportion of subjects achieving a weight loss of $\geq 10\%$ from baseline to week 68
- Proportion of subjects achieving a weight loss of $\geq 15\%$ from baseline to week 68
- Waist circumference change from baseline to week 68
- Systolic blood pressure change from baseline to week 68
- SF-36 Physical Functioning score change from baseline to week 68
- IWQOL-Lite-CT Physical Function score change from baseline to week 68

Additional endpoints and the objectives they address are outlined in the following table:

Table 4: List of Endpoints for Each Trial 4373 Objective

Objectives	Endpoints
Primary objective	Primary endpoints
• To compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on body weight	• Change from baseline at week 0 to week 68 in body weight (%) • Subjects who after 68 weeks achieve (yes/no): • Body weight reduction $\geq 5\%$ from baseline (week 0) Confirmatory and supportive secondary endpoints (confirmatory secondary endpoints are marked with an #) • Subjects who after 68 weeks achieve (yes/no): • Body weight reduction $\geq 10\%$ from baseline (week 0)[#] • Body weight reduction $\geq 15\%$ from baseline (week 0)[#] • Body weight reduction $\geq 20\%$ from baseline (week 0) • Change from baseline at week 0 to week 68 in: • Body weight (kg) • BMI (kg/m²)

Objectives	Endpoints
Secondary objectives – related to efficacy • To compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on: • Cardiovascular risk factors • Clinical outcome assessments • Glucose metabolism • Other factors related to body weight	Confirmatory and supportive secondary endpoints - efficacy endpoints (confirmatory secondary endpoints are marked with an #) Cardiovascular risk factors • Change from baseline at week 0 to week 68 in: • Systolic blood pressure (mmHg)# • Diastolic blood pressure (mmHg) • Lipids (mmol/L and mg/dL) ○ Total cholesterol ○ HDL cholesterol ○ LDL cholesterol ○ VLDL cholesterol ○ Free fatty acids ○ Triglycerides • CRP (mg/L) • PAI-1 activity (AU/mL) Clinical outcome assessments • Change from baseline at week 0 to week 68 in: • Physical functioning score (SF-36)# • Physical function domain (5-items) score (IWQOL-Lite-CT)# • SF-36 ○ Role-physical score ○ Bodily pain score ○ General health score ○ Vitality score ○ Social functioning score ○ Role-emotional score ○ Mental health score ○ Physical component summary ○ Mental component summary • IWQOL-Lite-CT ○ Physical domain score ○ Psychosocial domain score ○ Total score • Subjects who after 68 weeks achieve (yes/no): • Responder definition value for SF-36 physical functioning score • Responder definition value for IWQOL-Lite-CT physical function domain (5-items) score Glucose metabolism • Change from baseline at week 0 to week 68 in: • HbA_{1c} (% and mmol/mol) • FPG (mmol/L and mg/dL) • Fasting serum insulin (mIU/L) Other body weight-related endpoints • Waist circumference (cm)# • Soluble leptin receptor (ng/mL) • Leptin (ng/mL) • Body composition (as assessed by DEXA in a subset of subjects): ○ Total fat mass (kg and %) ○ Lean body mass (kg and %) ○ Visceral fat mass (kg and %) • Body weight (kg and %) in the DEXA subset of subjects

Objectives	Endpoints
Secondary objectives – related to safety To compare the safety and tolerability of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity	Supportive secondary endpoints - safety endpoints - Number of TEAEs from baseline at week 0 to week 75 - Number of SAEs from baseline at week 0 to week 75 - Change from baseline at week 0 to week 68 in: - Pulse (bpm) - Amylase (U/L) - Lipase (U/L) - Calcitonin (ng/L)
Exploratory objectives - To compare the effect of semaglutide s.c. 2.4 mg once weekly versus placebo as an adjunct to a reduced-calorie diet and increased physical activity in subjects with overweight or obesity on: - Glycaemic status - Use of medication for hypertension and dyslipidaemia - Work productivity - Treatment discontinuation - Liver indices - Urinary incontinence - Diet and physical activity	Exploratory endpoints Glycaemic status - Change from baseline at week 0 to week 68 in glycaemic category (normo-glycaemia, pre-diabetes, T2D) Use of medication for hypertension and dyslipidaemia - Change from baseline at week 0 to week 68 in: - Antihypertensive medication (decrease, no change, increase) - Lipid-lowering medication (decrease, no change, increase) Work productivity - Change from baseline at week 0 to week 68 in the SPS-6, total score Treatment discontinuation - Subjects who from randomisation at week 0 to week 68 have permanently discontinued randomised trial product (yes/no) - Time to permanent discontinuation of randomised trial product (weeks) Liver indices - Change from baseline at week 0 to week 68 in fatty liver index score category (<30, ≥30 and <60, ≥60) Urinary incontinence - Change from baseline at week 0 to week 68 in ICIQ-UI-SF, sum score (assessed in female subjects) Diet and physical activity - Number of days per week with at least one entry in the food diary from baseline at week 0 to week 68 - Number of minutes per week of physical activity from baseline at week 0 to week 68

Source: Study 4373 CSR, Table 9-8

Note that not all endpoints are discussed in this document.

Statistical Analysis Plan

The primary estimand quantified the treatment effect of semaglutide in all randomized subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

therapies.

The classification of endpoints for each subject based on whether it is available or missing is described in the following table:

Table 5: Assessment Classification, Trial 4373

Assessment at week 68	Subjects on randomised treatment at week 68	Type description	Type Abbreviation
Available	Yes	Available on randomised treatment: Subjects who complete the trial on randomised treatment with an assessment at week 68: Includes those that stop and restart trial product.	AT
	No	Available but discontinued Subjects who discontinued randomised treatment prematurely but returned to have an assessment at week 68. These are also called retrieved subjects	AD
Missing	Yes	Missing on randomised treatment: Subjects who complete the trial on randomised treatment without an assessment at week 68: Includes those that stop and restart trial product.	MT
	No	Missing and discontinued: Subjects who discontinued randomised treatment prematurely and did not return to have an assessment at week 68. These are also called non-retrieved subjects	MD

Source: Study 4373 SAP, Table 1

In the analysis approach addressing the primary estimand, week 68 assessments from retrieved subjects (AD) were used. These data were also used to impute missing measurements at week 68 for non-retrieved subjects (MD). The imputation was done separately within each treatment arm.

Given an anticipated total of 1950 subjects in the trial, power calculations were as follows:

Table 6: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 1950 Subjects, Trial 4373

Order	Endpoint	Assumed mean ($\pm$ SD) or proportion for completers		Expected mean ($\pm$ SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight change #	14 ($\pm$ 10)	3 ($\pm$ 10)	12.5 ($\pm$ 11)	9.5%-points	> 99	> 99
2	5% responders	82%	42%	76%	1.8	> 99	> 99
3	10% responders	66%	24%	60%	2.5	> 99	> 99
4	15% responders	46%	12%	41%	3.4	> 99	> 99
5	WC change (cm) #	11 ($\pm$ 10)	4 ($\pm$ 10)	10 ($\pm$ 10)	6 cm	> 99	> 99
6	sBP change (mmHg) #	6.2 ($\pm$ 13)	1.5 ($\pm$ 13)	5.5 ($\pm$ 13)	4 mmHg	> 99	> 99
7	SF-36 PF score change	6 ($\pm$ 10)	2 ($\pm$ 10)	5.4 ($\pm$ 11)	3.4 score-points	> 99	> 99
8	IWQoL-Lite PFD score change	[24] ($\pm$ 20)	[13] ($\pm$ 20)	22.5 ($\pm$ 21)	9.5 score-points	>99	>99

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number

All tests in the hierarchy are based on the primary estimand

Source: Study 4373 SAP, Table 2

Protocol Amendments

There were 2 global amendments:

- Amendment 3, dated 21 Dec 2017:
 - Implemented genetic biosamples for future analysis
 - Removed criteria for discontinuation of trial treatment for subjects included in the trial in violation of eligibility criteria if considered safe to continue
 - Risks associated with semaglutide were to be removed from the protocol and instead referred to the IB
- Amendment 6, dated 04 Jun 2018:
 - Extended the trial for an additional 45-weeks off-treatment period after the last visit in the main phase without structured lifestyle intervention in selected countries/sites

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

6.1.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and FDA 21 CFR 312.120. The FDA 21 CFR, parts 312, 50, and 56 were followed.

Financial Disclosure

See Section 13.2.

Subject Disposition

All subjects randomized in the trial were exposed to treatment (1306 semaglutide-treated subjects and 655 placebo-treated subjects), and therefore were included in the full analysis set (FAS) and the safety analysis set.

Disposition is as follows:

Table 7: Subject Disposition, Trial 4373

	Semaglutide N=1306	Placebo N=655
Treatment Completion		
On-treatment at week 68 (treatment completers)	1083 (82.9)	508 (77.6)
After at least 1 temporary interruption	119 (9.1)	58 (8.9)
Attended end-of-treatment visit without permanent discontinuation of trial product	1080 (82.7)	506 (77.3)
Trial product permanently discontinued	223 (17.1)	147 (22.4)
Adverse event	91 (7.0)	21 (3.2)
Protocol violation	3 (0.2)	5 (0.8)
Pregnancy	7 (0.5)	3 (0.5)
Lack of efficacy	1 (<0.1)	16 (2.4)
Investigator discretion	4 (0.3)	1 (0.2)
Safety concern as judged by the investigator	15 (1.1)	0
Withdrawal of consent	9 (0.7)	10 (1.5)
Lost to follow-up	26 (2.0)	25 (3.8)
Other	67 (5.1)	66 (10.1)
Attended end-of-treatment visit after permanent discontinuation of trial product	161 (12.3)	95 (14.5)
Trial Completion		

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Attended end-of-trial visit (trial completion)	1240 (94.9)	609 (93.0)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	1072 (82.1)	506 (77.3)
Withdrawn from trial	66 (5.1)	46 (7.0)
Withdrawal by subject	26 (2.0)	17 (2.6)
Lost to follow-up	39 (3.0)	28 (4.3)
Death	1 (<0.1)	1 (0.2)
Withdrawn from trial before week 68	43 (3.3)	35 (5.3)
Withdrawn from trial without prior permanent discontinuation of trial product	3 (0.2)	4 (0.6)
Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).		

Source: Study 4373 CSR, Table 10-1

Protocol Violations/Deviations

There were no important trial-level protocol deviations (PDs) in the trial.

There were 4 important country-level PDs in the trial:

- 3 occurred in the US and concerned not submitting safety reports in accordance with regulatory requirements to sites and to the IRB. When the deviations were discovered, the safety reports were reconciled and submitted.
- 1 occurred in Argentina and concerned unintentional unblinding of a subject to site staff and NN staff. The deviation occurred due to an internal email containing information related to a SUSAR that was intended for health authorities.

The 82 important site-level PDs and 500 important subject-level PDs are summarized in the table below.

Table 8: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4373

Protocol deviation category	Site-level PDs (n)	Subject-level PDs (n)			Total site and subject-level PDs (n)	
		Screening failures (n)	Semaglutide 2.4 mg (n)	Placebo (n)		Total subject-level PDs (n)
Total	82	2	325	173	500	582
Informed consent	5	2	28	1	31	36
Inclusion/exclusion criteria ^a		0	21	10	31	31
Treatment administration	9	0	28	14	42	51
Trial procedures/assessments	61	0	139	75	214	275
Concomitant medication	0	0	0	0	0	0
Subject visit schedule	5	0	95	68	163	168
SAE notification/safety procedures	0	0	13	4	17	17
Privacy and data protection	1	0	1	1	2	3

^a also includes randomisation criteria
Source: Study 4373 CSR, Table 10-4

The most common protocol deviations were in the categories of trial procedures/assessments and subject visit schedule.

In the trial procedures/assessments category (total 275):

- 17 deviations were related to the primary endpoint(s) and 33 to the confirmatory secondary endpoint(s). The majority were due to missing assessments at week 68 (end-of-treatment) and/or inadequate calibration of scales.
- 15 deviations were related to documentation/delegation of tasks and 210 were related to other reasons. Thirty-five (35) site-level and 58 subject level PDs concerned end-of-trial visits (week 75) being converted to phone visits due to the COVID-19 pandemic. The remaining PDs included site staff performing diet and physical exercise counseling or other tasks without certification or delegation,¹⁴ and missing calcitonin, PHQ-9, and C-SSRS assessments, and pregnancy tests.¹⁵

¹⁴ The applicant notes that upon discovery of the deviations, staff was either retrained or new qualified staff was allocated.

¹⁵ Subsequent pregnancy tests in the affected subjects were negative.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In the subject visit schedule category (total 168):

- The majority of the PDs comprised subjects attending the end-of-treatment visit (week 68) more than 1 week out of visit window (93 PDs) and half (45/93) of these PDs were for subjects who had discontinued trial product permanently.
- The remaining PDs concerned randomization more than 1 week later than the visit window or subjects attending the follow-up visit more than 1 week earlier than scheduled.

Reviewer comment: I reviewed the protocol deviations and do not believe they significantly impacted the safety of the trial subjects or the interpretation of the study results. The applicant appropriately addressed important deviations when found.

Aside from PDs, there were also 48 cases of unintentional unblinding prior to database lock that were identified and reported. All cases were related to AEs, with the majority related to handling of potential SUSARs and sponsor unblinding. In 2 cases, the unblinding was initiated by the investigator (both were cases of maternal exposure during pregnancy). The applicant notes that all intentional unblinding cases were handled according to internal procedures and did not affect the trial data integrity.

Regarding the impact of the COVID-19 pandemic, almost all subjects had completed their last visits at the time of the pandemic. The main trial procedures affected by COVID-19 were as follows:

- Source data verification was abolished for the last part of the trial (as of 23 March 2020). According to the applicant, all data were still entered into the electronic data capture system and checked for completeness. Furthermore, data cleaning and casebook sign-off was ensured.
- Approximately 213 subjects had their follow-up visits (week 75) converted to phone visits (ensuring AE reporting and safety follow-up).
- Some blood samples were not being able to be sent from the site to the central laboratory for a period of time, but all samples were eventually received and analyzed, and the delay did not impact subject safety as the samples were for PK and antibody follow-up.
- One subject (semaglutide 2.4 mg) had a COVID-19 related AE (PT: 'Corona virus infection'), that was non-serious and of mild severity.
- No subjects discontinued treatment or withdrew from the trial due to COVID-19.

Demographic Characteristics

Demographic characteristics were well-balanced among groups. Overall, 74% were female and mean age was 46 years. As only 39% of subjects were from the United States (U.S.), the population was somewhat underrepresented for subjects who are Black (5.7%) and of Hispanic

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

or Latino ethnicity (12.0%) as compared to the general U.S. population (in 2019, 13.4% and 18.5%, respectively¹⁶).

Table 9: Demographic Characteristics of the Primary Efficacy Analysis, Trial 4373

	Semaglutide N=1306	Placebo N=655
Sex		
Male	351 (26.9)	157 (24.0)
Female	955 (73.1)	498 (76.0)
Age		
Mean years (SD)	46 (13)	47 (12)
Median (years)	46	48
Min, max (years)	18, 86	18, 82
Age Group		
18 - < 65 years	1198 (91.7)	607 (92.7)
65 - < 75 years	99 (7.6)	46 (7.0)
75 - < 85 years	8 (0.6)	2 (0.3)
≥ 85 years	1 (<0.1)	0
Race		
White	973 (74.5)	499 (76.2)
Black or African American	72 (5.5)	39 (6.0)
Asian	181 (13.9)	80 (12.2)
American Indian or Alaska Native	17 (1.3)	10 (1.5)
Native Hawaiian or Other Pacific Islander	0	2 (0.3)
Other	25 (1.9)	8 (1.2)
Not Applicable ¹	38 (2.9)	17 (2.6)
Ethnicity		
Hispanic or Latino	150 (11.5)	86 (13.1)
Not Hispanic or Latino	1118 (85.6)	551 (84.1)
Not Applicable ¹	38 (2.9)	17 (2.6)
Unknown	0	1 (0.2)
Region		
United States	505 (38.7)	258 (39.4)
Rest of the World	801 (61.3)	397 (60.6)
Argentina	39 (3.0)	26 (4.0)
Belgium	39 (3.0)	21 (3.2)
Bulgaria	32 (2.5)	13 (2.0)
Canada	39 (3.0)	24 (3.7)
Germany	70 (5.4)	30 (4.6)

¹⁶ <https://www.census.gov/quickfacts/fact/table/US/PST045219>

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Denmark	34 (2.6)	16 (2.4)
Finland	38 (2.9)	22 (3.4)
France	38 (2.9)	17 (2.6)
United Kingdom	135 (10.3)	83 (12.7)
India	82 (6.3)	35 (5.3)
Japan	67 (5.1)	33 (5.0)
Mexico	47 (3.6)	23 (3.5)
Poland	42 (3.2)	18 (2.7)
Russian Federation	73 (5.6)	27 (4.1)
Taiwan	26 (2.0)	9 (1.4)
¹ Data on race and ethnicity were collected as 'Not Applicable' in France		

Source: Study 4373 CSR, Tables 10-2 and 10-3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, mean body weight was 105.3 kg, mean BMI was 37.9 kg/m², mean waist circumference was 114.7 cm, and mean HbA1c was 5.7%. Baseline characteristics were well-balanced among groups.

Table 10: Baseline Characteristics, Trial 4373

	Semaglutide N=1306	Placebo N=655
Body weight		
Mean kg (SD)	105.4 (22.1)	105.2 (21.5)
Median (kg)	102.1	101.3
Min, max (kg)	61.8, 245.6	66.3, 211.0
BMI		
Mean kg/m ² (SD)	37.8 (6.7)	38.0 (6.5)
Median (kg/m ²)	36.7	36.5
Min, max (kg/m ²)	26.5, 83.0	27.5, 67.0
Waist circumference		
Mean cm (SD)	114.6 (14.8)	114.8 (14.4)
Median (cm)	113.0	113.2
Min, max (cm)	85.0, 180.0	83.8, 182.9
HbA1c		
Mean % (SD)	5.7 (0.3)	5.7 (0.3)
Median (%)	5.7	5.7
Min, max (%)	4.1, 6.6	4.6, 6.6
Fasting plasma glucose	n=1291	n=649
Mean mg/dL (SD)	95.4 (10.7)	94.7 (10.5)
Median (mg/dL)	94.4	93.7
Min, max (mg/dL)	68.1, 166.0	66.5, 150.5

Source: Study 4373, Table 10-3

Table 11 presents a summary of past and concomitant illness of subjects at screening.

Table 11: Medical History and Concomitant Illness, Selected Events, Trial 4373

	Semaglutide N=1306	Placebo N=655
Anemias nonhemolytic and marrow depression	71 (5.4)	29 (4.4)
Coronary artery disorders	37 (2.8)	17 (2.6)
Thyroid gland disorders	199 (15.2)	109 (16.6)
Retina, choroid and vitreous hemorrhages and vascular disorders	5 (0.4)	2 (0.3)
Gastrointestinal motility and defecation conditions	264 (20.2)	127 (19.4)
Benign neoplasms gastrointestinal	58 (4.4)	24 (3.7)
Gastrointestinal inflammatory conditions	56 (4.3)	24 (3.7)
Pancreatitis acute	5 (0.4)	1 (0.2)
Hepatic steatosis	71 (5.4)	35 (5.3)
Nonalcoholic fatty liver disease	38 (2.9)	25 (3.8)
Nonalcoholic steatohepatitis	5 (0.4)	1 (0.2)
Gallbladder disorders	76 (5.8)	46 (7.0)
Lipid metabolism disorders	483 (37.0)	221 (33.7)
Glucose metabolism disorders	221 (16.9)	103 (15.7)
Glycosylated hemoglobin increased	113 (8.7)	56 (8.5)
Neoplasms benign, malignant and unspecified	182 (13.9)	90 (13.7)
Psychiatric disorders	397 (30.4)	221 (33.7)
Sleep apnea syndrome	168 (12.9)	75 (11.5)

Source: Study 4373 CSR, Table 14.1.13

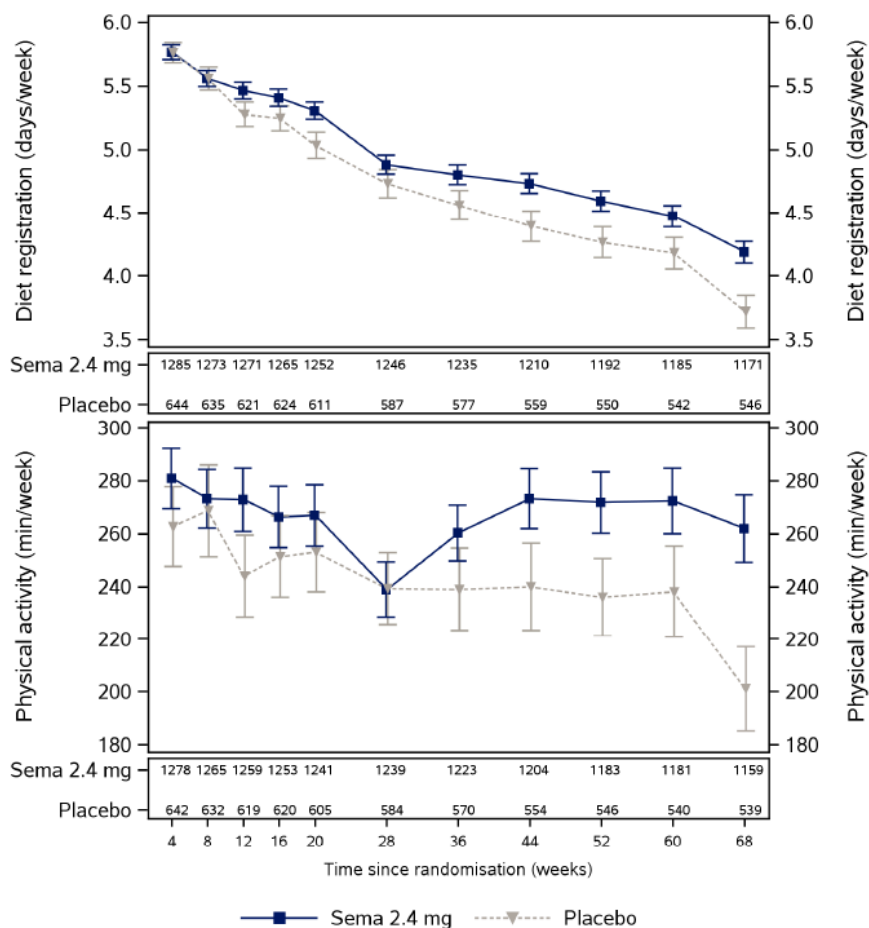
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance of trial product was assessed by asking the subject about missed doses and monitoring of PK dosing diaries. Information about compliance and missed doses was to be documented in the subject's medical record.

Subjects were to record their food intake and physical activity daily. Compliance was assessed by number of days per week with at least one entry in the food diary and number of minutes per week of physical activity.

- For both treatment groups, the compliance of recording food intake daily decreased during the trial. However, on average, subjects treated with semaglutide 2.4 mg recorded food intake on more days than subjects treated with placebo (Figure 2, top panel).
- For both treatment groups, mean number of minutes of physical activity per week was above the encouraged 150 min per week throughout the trial, but generally greater for subjects treated with semaglutide 2.4 mg versus placebo (Figure 2, bottom panel).

Figure 2: Diet and Physical Activity by Week, Trial 4373



Observed data from in-trial period. Error bars are +/- standard error of the mean. Diet registration: Number of days per week with at least one entry in the food diary. Physical activity: Number of minutes per week of physical activity. Note that for both diet and physical activity registration the presented data relates to weeks prior to the actual visit. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4373 CSR, Figure 10-3

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Efficacy Results – Primary Endpoint

Superiority of the co-primary endpoints – percent change in body weight from baseline to week 68 and proportion of subjects achieving a weight loss of $\geq 5\%$ – was confirmed.

Table 12: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68, Trial 4373

Treatment	N	Baseline Mean (SD)	Week 68 Mean (SD) In-trial	% Change from Baseline ANCOVA RD-MI
Semaglutide	1306	105.4 (22.1)	89.0 (22.7)	-14.85
Placebo	655	105.2 (21.5)	101.9 (22.0)	-2.41
Semaglutide vs. Placebo		Between treatment difference (95% CI)		p value
		-12.44 (-13.37, -11.51)		<0.0001

Source: Study 4373 CSR, Tables 14.2.2 and 14.2.9

The proportions of subjects on semaglutide 2.4 mg and placebo achieving 5% body weight loss were 86.4% and 31.5%, respectively, $p < 0.0001$.

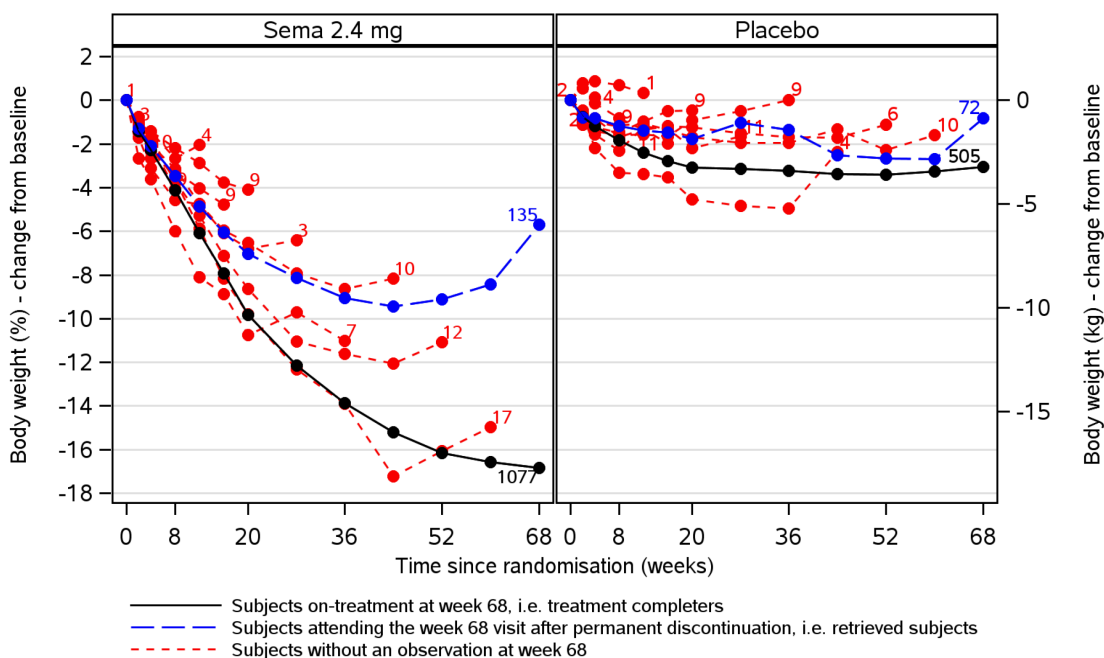
All sensitivity analyses were consistent with the co-primary analyses.

Data Quality and Integrity

Data quality and integrity in this trial are very good. Subjects were encouraged to remain in the trial for data collection, even if trial product was permanently discontinued. A total of 94.3% of the randomized subjects completed the trial; 94.9% semaglutide and 93.0% placebo.

Missing data were evaluated graphically to detect patterns relevant for the interpretation of the primary analysis (Figure 3). Retrieved dropouts; i.e., subjects who discontinued treatment but returned for a week 68 assessment (blue lines), illustrate the differential in weight change as compared to those who remained on-treatment (black line), particularly in the semaglutide group.

Figure 3: Percent Body Weight Change from Baseline by Week, Missing Data Plot, Trial 4373



Observed data. Subjects with missing data at week 68 (dashed red line) are grouped by last available observation (LAO). Numbers shown are subjects contributing to the mean.

Source: Study 4373 CSR, Figure 11-4

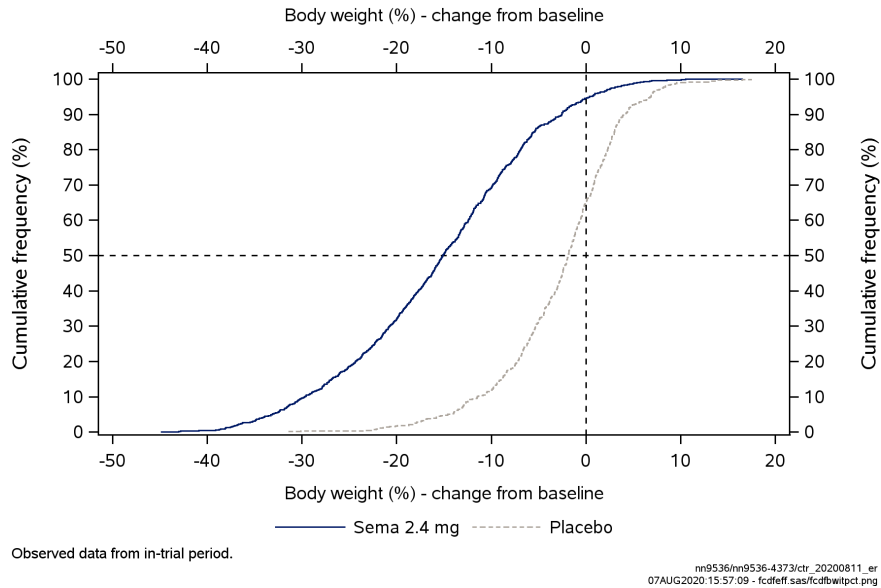
Reviewer comment: These patterns as shown in Figure 3 are not unexpected. Given that the overall number of subjects with missing data that contributed to the primary analysis was relatively low, missing data are not likely to substantially impact the interpretation of the primary analysis.

Efficacy Results – Secondary and other relevant endpoints

Superiority of semaglutide versus placebo was confirmed for all secondary confirmatory endpoints in the hierarchical testing procedure: proportions of subjects who lost $\geq 10\%$ and $\geq 15\%$ body weight at week 68, as well as change from baseline at week 68 in waist circumference, systolic blood pressure, SF-36 physical functioning score, and IWQOL-Lite-CT physical function score.

- The proportions of subjects on semaglutide 2.4 mg and placebo achieving 10% body weight loss were 69.1% and 12.0%, respectively, and those achieving 15% weight loss were 50.5% and 4.9%, respectively; all $p < 0.0001$. In addition (not in the hierarchy), those achieving 20% weight loss were 32.0% and 1.7%, respectively. Figure 4 presents the cumulative distribution for percent body weight change, which shows a left shift for semaglutide for all proportions of weight change from baseline.

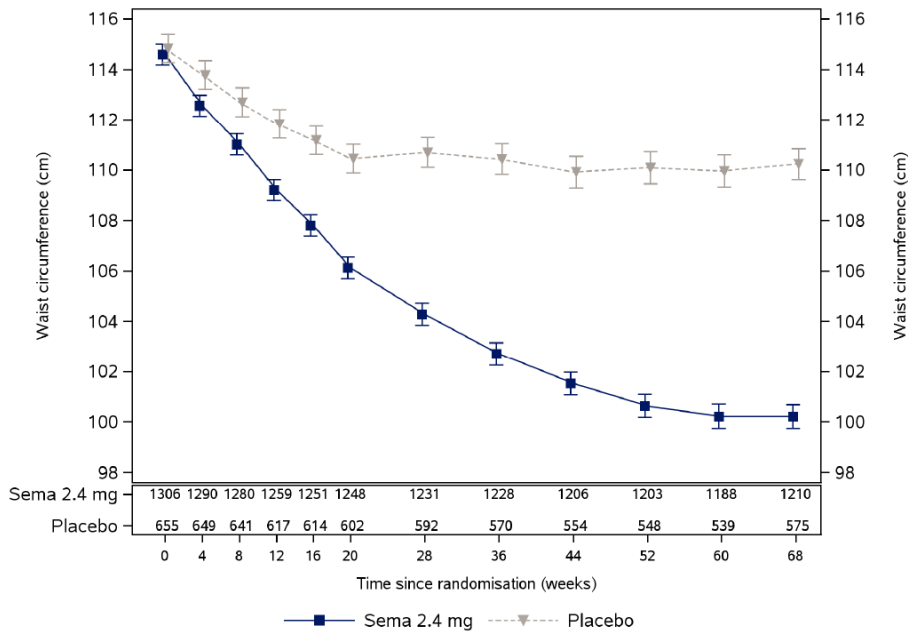
Figure 4: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4373, In-Trial



Source: Study 4373 CSR, Figure 14.2.5

- At baseline, mean waist circumference was 114.7 cm. Mean changes in waist circumference from baseline at week 68 were -13.5 cm for semaglutide 2.4 mg and -4.1 cm for placebo, for an estimated treatment difference (ETD) of -9.4 cm (95% CI -10.3, -8.5), $p < 0.0001$.

Figure 5: Mean Waist Circumference by Week, Trial 4373

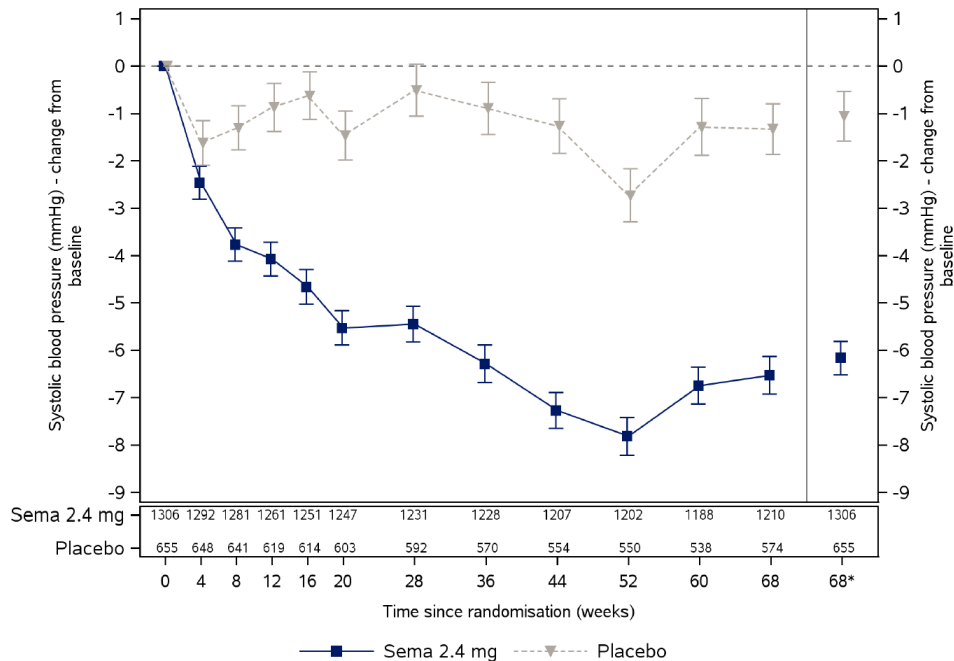


Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4373 CSR, Figure 11-10

- At baseline, mean systolic blood pressure (SBP) was 126 mmHg. Mean changes in SBP were -6.2 mmHg for semaglutide 2.4 mg and -1.1 mmHg for placebo, for an ETD of -5.1 mmHg (95% CI -6.3, -3.9), $p < 0.0001$.

Figure 6: Mean Systolic Blood Pressure Change from Baseline by Week, Trial 4373



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the confirmatory secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4373 CSR, Figure 14.2.86

Reviewer comment: Changes in SBP of the magnitude observed in this trial are likely to be beneficial for cardiovascular health.¹⁷

- The Short Form 36 v2.0 acute measures overall health-related quality-of-life.^{18,19} The physical functioning domain of the SF-36 (SF-36 physical functioning score) was prespecified in this program as an endpoint of interest that could be sensitive to weight change.²⁰

¹⁷ Ettehad D, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*, 2016. 387: 957-67.

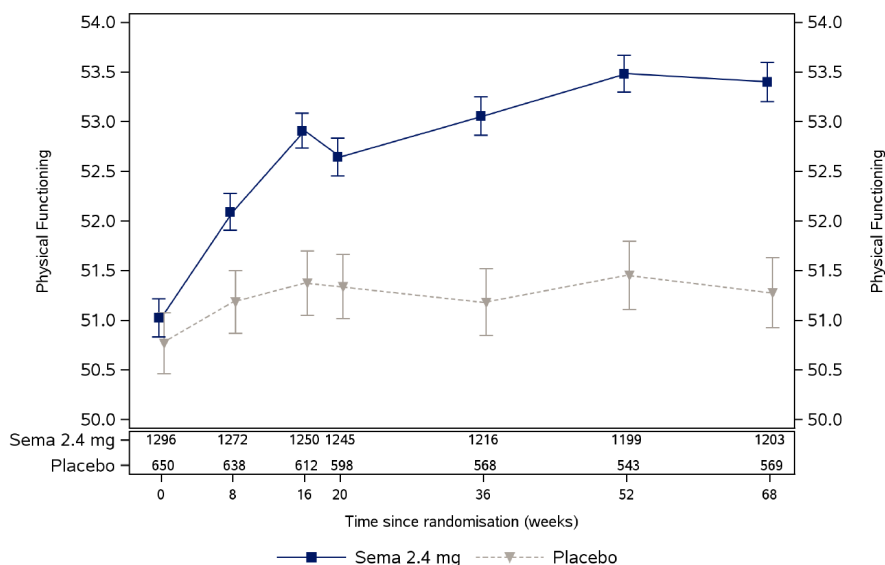
¹⁸ Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-83.

¹⁹ The SF-36 for adults with a 1-week recall period contains 36 items: a total of 35 items measure 8 domains of functional health and well-being: physical functioning (10 items), role limitation due to physical health problems (4 items), bodily pain (2 items), general health perceptions (5 items), vitality (4 items), social functioning (2 items), role limitations due to emotional problems (3 items) and general mental health (5 items). An additional single item gives information on health change over the past week. Furthermore, 2 component summary scores are created: mental component summary (MCS) score and physical component summary (PCS) score.

²⁰ The scores for SF-36 physical functioning are norm-based scores, i.e., scores transformed to a scale where the 2009 U.S. general population has a mean of 50 and an SD of 10. The range of possible scores for the SF-36 PF score is 19.03–57.60.

Higher scores indicate better physical functioning. At baseline, mean SF-36 physical functioning score was 50.9. Mean changes in SF-36 physical functioning scores were +2.2 for semaglutide 2.4 mg and +0.4 for placebo, for an ETD of +1.8 (95% CI +1.2, +2.4), $p < 0.0001$.

Figure 7: Mean SF-36 Physical Functioning by Week, Trial 4373



SF-36: Short Form 36 v2.0 acute.
Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

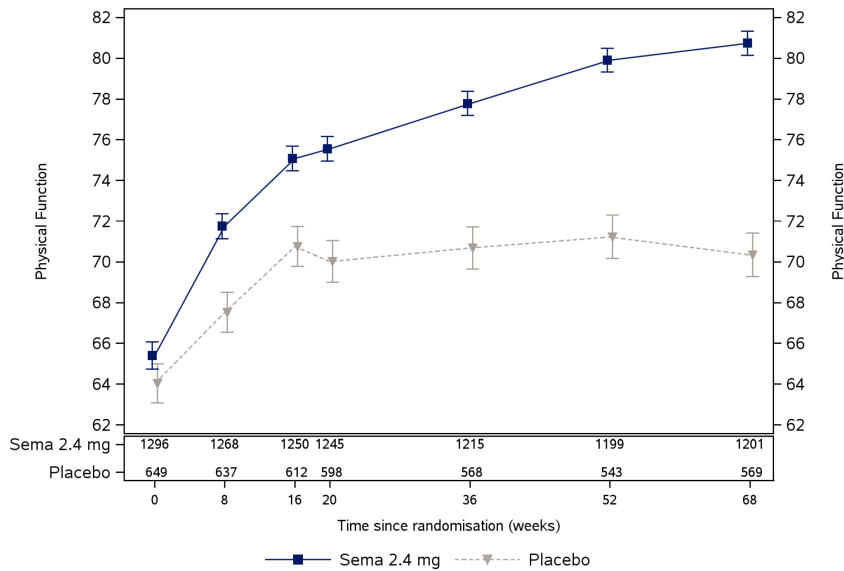
Source: Study 4373 CSR, Figure 11-22

- Impact of Weight on Quality of Life-Lite for Clinical Trials version (IWQOL-Lite for CT), version 3.0 is a 20-item modified version of a questionnaire tool designed to assess the weight-related quality of life.²¹ The IWQOL-Lite for CT physical function score²² was developed based on recommendations from FDA and was prespecified as an endpoint of interest in this program. Higher scores indicate better physical function. At baseline, the IWQOL-Lite physical function score was 65.0. Mean changes in IWQOL-Lite physical function scores were +14.7 for semaglutide 2.4 mg and +5.2 for placebo, for an ETD of +9.4 (95% CI +7.5, +11.4), $p < 0.0001$.

²¹ Kolotkin RL, et al. Development of a clinical trials version of the Impact of Weight on Quality of Life-Lite questionnaire (IWQOL-Lite Clinical Trials Version): results from two qualitative studies. Clin Obes. 2017;7(5):290-9.

²² The range of possible scores for the IWQOL-Lite-CT Physical function is 0-100.

Figure 8: Mean IWQOL-Lite CT Physical Function by Week, Trial 4373



IWQOL-Lite-CT: Impact of Weight on Quality of Life-Lite for Clinical Trials.
 Observed data from in-trial period. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4373 CSR, Figure 11-27

Reviewer comment: While the results based on the mean difference between groups were statistically significant for these instruments, the clinical significance of these results is uncertain. As Dr. Yasmin Choudhry, reviewer in the Division of Clinical Outcome Assessment notes in her review, there were minimal observed score changes, if any, when looking at the item- and domain-level data at the raw score scale. Please refer to Dr. Choudhry's review for details.

Dose/Dose Response

Although there was only 1 dose tested in this trial (2.4 mg/week), subjects escalated once weekly from initiation doses of 0.25 mg/week to 0.5 mg, 1 mg, and 1.7 mg/week, until 2.4 mg/week was reached after 16 weeks. Deviations from the recommended dose-escalation could occur at the investigator's discretion, and if a subject did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose. Table 13 presents dose information for subjects in-trial at a particular week; this table shows that in those subjects on semaglutide treatment, the majority were on the 2.4 mg dose.

Table 13: In-Trial Dose Summary, Semaglutide-Treated Subjects

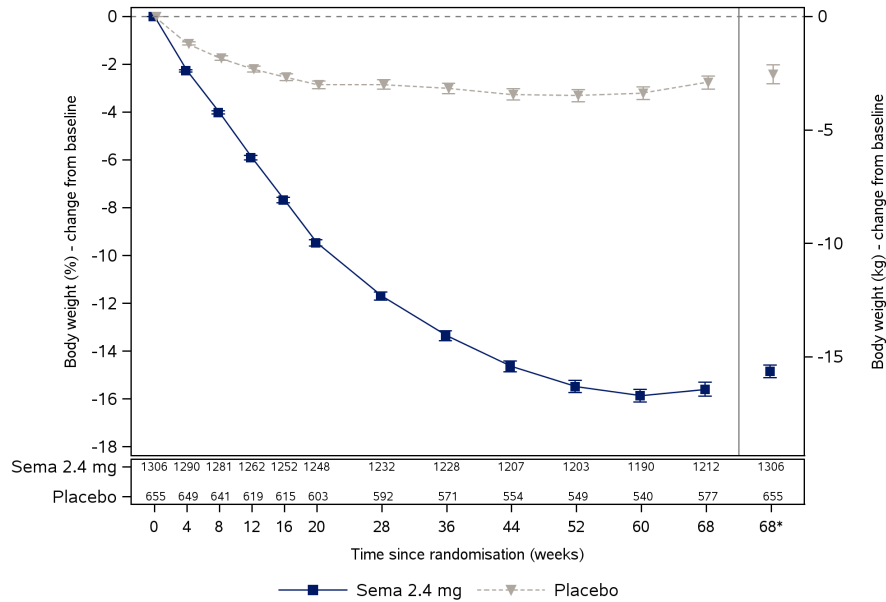
	2.4 mg	<2.4 to 1.7 mg	<1.7 to 1 mg	<1 to 0.5 mg	<0.5 to 0.24 ^a mg	No Dose	Missing/Unknown
Visit 12 / Week 20 N=1291	83.5%	4.1%	2.6%	1.2%	0.5%	7.8%	0.3%
Visit 14 / Week 28 N=1286	81.5%	4.3%	2.3%	0.9%	0.5%	9.9%	0.8%
Visit 20 / Week 52 N=1278	77.5%	4.4%	1.6%	1.9%	0.4%	13.4%	0.9%
Visit 24 / Week 65 ^b N=1274	75.2%	4.2%	1.9%	1.6%	0.9%	15.4%	0.9%
Visit 24 / Week 68 ^b N=1270	65.6%	3.2%	1.7%	1.0%	0.7%	27.6%	0.2%
Percentages are based on subjects with an observation at the visit. a In some weeks, a small number of subjects were administered doses as low as 0.24 mg (instead of 0.25 mg), so that is included in this cell. There were no doses reported less than 0.24 mg. b This table was simplified and does not include all weeks that could have contributed to a visit. For example, for Visit 24, data for weeks 65, 66, 67, and 68 were provided by the applicant. Two representative weeks were chosen for the table; on-treatment numbers might not match disposition information in Table 7.							

Source: Study 4373 CSR, Table 14.2.147

Durability of Response

Figure 9 presents mean percent weight change by week. Separation of the weight curves is apparent as early as week 4. Plateau in the curve in the semaglutide arm occurs around week 60, whereas the plateau occurs in the placebo group around week 20.

Figure 9: Mean Percent Change in Body Weight from Baseline by Week, Trial 4373



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

nn9536/mn9536-4373/ctr_20200811_er
 07AUG2020:15:57:18 - fmeanefax.sas/meanbwchbit.png

Source: Study 4373 CSR, Figure 14.2.8

Persistence of Effect

Persistence of effect was not tested in this trial.

Additional Analyses Conducted on the Individual Trial

In addition to the confirmatory secondary endpoints described above, a number of other supportive secondary cardiometabolic parameters are typically measured in weight management drug trials and are included in Section 14 of product labeling to support the clinical meaningfulness of weight loss in the studied population. The differences (or percent differences) in changes in diastolic blood pressure (DBP), HbA1c, Total cholesterol (Total-C), LDL-C, HDL-C, and triglycerides were all nominally significantly different for semaglutide versus placebo (favoring semaglutide).

Table 14: Selected Supportive Secondary Endpoints, Trial 4373

	Semaglutide		Placebo		Semaglutide minus Placebo (95% CI ^a)
	Baseline	Change from Baseline	Baseline	Change from Baseline	
DBP (mmHg)	80	-2.83	80	-0.42	-2.41 (-3.25, -1.57)
HbA1c (%)	5.7	-0.45	5.7	-0.15	-0.29 (-0.32, -0.26)
	Baseline	% Change from Baseline	Baseline	% Change from Baseline	Relative Difference of Semaglutide to Placebo (95% CI ^a)
Total-C (mg/dL)	189.6	-3.25	192.1	+0.06	-3.31 (-4.77, -1.84)
LDL-C (mg/dL)	110.29	-2.53	112.45	+1.27	-3.76 (-5.94, -1.52)
HDL-C (mg/dL)	49.4	+5.24	49.5	+1.42	+3.77 (+2.20, +5.36)
Triglycerides (mg/dL)	126.21	-21.89	127.94	-7.26	-15.78 (-18.76, -12.69)

^a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error

Source: Study 4373 CSR, Tables 14.2.71, 14.2.74, 14.2.90, 14.2.93, ISE Tables 6.3.127, 6.3.128, 6.3.129, 6.3.132

Reviewer comment: The changes observed in these endpoints support the clinical meaningfulness of the observed difference in weight loss between groups.

A body composition sub-study utilizing dual energy x-ray absorptometry (DEXA) was conducted in a sub-population of 140 subjects from the U.S. Weight loss in the subgroup was consistent with the overall population. An absolute reduction was seen in total and visceral fat mass and lean body mass in the semaglutide group versus the placebo group. When expressed as relative to total body mass, there was a decrease for fat mass and increase for lean mass in the semaglutide group versus the placebo group. A decrease in visceral fat mass relative to total fat mass was also observed in the semaglutide versus placebo group. The results are summarized in Table 15.

Table 15: DEXA Substudy Summary Results, Trial 4373

	Semaglutide N=95		Placebo N=45		Semaglutide minus Placebo (95% CI ^a)
	Baseline	Change from Baseline	Baseline	Change from Baseline	
Body weight (kg)	98.3	-14.73	98.7	-3.26	-11.47 (-15.12, -7.82)
Total fat mass (kg)	42.1	-8.36	43.3	-1.37	-6.99 (-9.79, -4.19)
Total fat mass (% ^b)	43.4	-3.48	44.6	-0.19	-3.29 (-4.94, -1.65)
Lean body mass (kg)	52.4	-5.26	51.5	-1.83	-3.43 (-4.74, -2.13)
Lean body mass (% ^b)	53.9	+3.04	52.7	+0.09	+2.94 (+1.40, +4.49)
Visceral fat mass (kg)	1.3	-0.36	1.5	-0.10	-0.27 (-0.39, -0.15)
Visceral fat mass (% ^c)	33.8	-1.99	36.3	-0.01	-1.98 (-3.69, -0.27)

a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error
b relative to total body mass
c relative to total fat mass

Source: Study 4373 CSR, Tables 14.2.62, 14.2.64, 14.2.69, 14.2.70

Reviewer comment: As discussed in the FDA draft weight management guidance,² measurement of body composition at baseline and follow-up should be conducted in a representative sample of subjects to ensure that semaglutide-induced weight loss is caused primarily by a reduction in fat content, not lean body mass. This substudy showed the intended effect of semaglutide is primarily on body fat loss, however, there is not a benefit shown with these results that the primary endpoint and key secondary endpoints do not already capture.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

6.2. NN9536-4374 (STEP 2): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes

6.2.1. Study Design

Overview and Objective

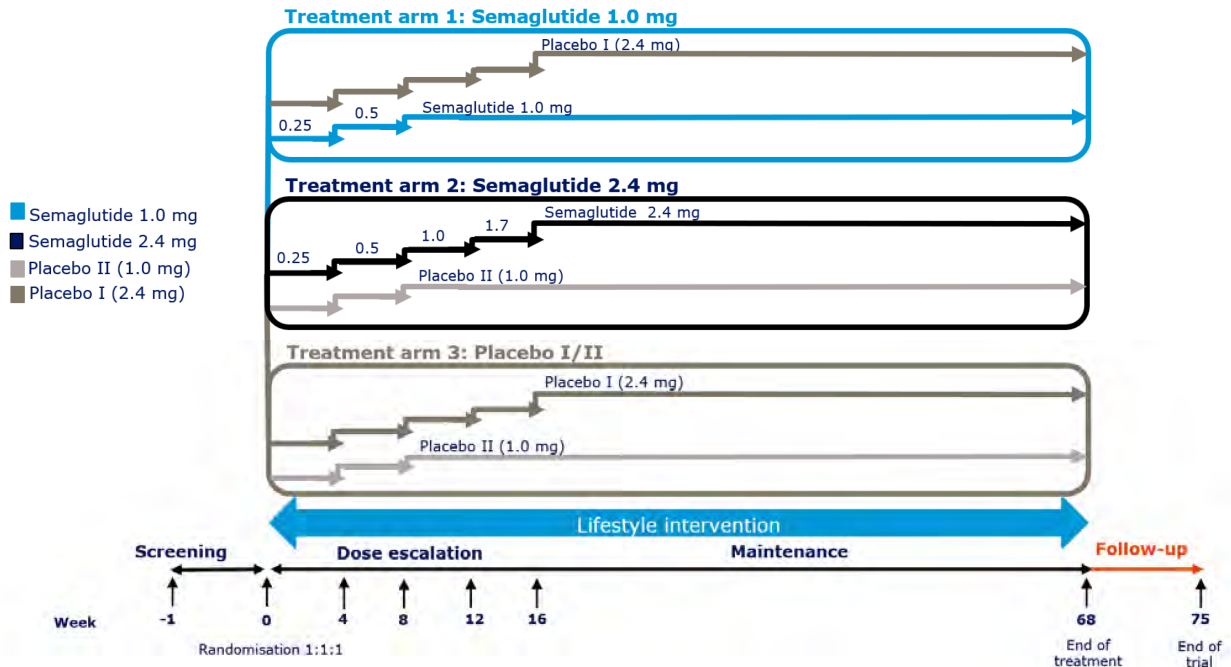
Trial 4374 was designed to demonstrate that semaglutide 2.4 mg administered SC once-weekly as an adjunct to reduced-calorie diet and increased physical activity, is effective (reduces body weight) and safe for the treatment of subjects with overweight or obesity and type 2 diabetes (T2D). Secondary objectives were to assess the effect of semaglutide 2.4 mg on cardiovascular risk factors, clinical outcome assessments, and glycemic control.

Trial Design

The trial was a multicenter, multinational trial that included a 68-week randomized, double-blind, 3-arm, placebo-controlled treatment period and a 7-week off-treatment follow-up period. A total of 1200 subjects were randomized 1:1:1 to semaglutide 2.4 mg, semaglutide 1 mg, or placebo in a double-dummy design (all subjects received 2 injections per week to blind by dose level).

Semaglutide was dose-escalated over 8 weeks for the 1 mg dose and over 16 weeks for the 2.4 mg dose (Figure 10).

Figure 10: Trial 4374 Design



Source: Study 4374 CSR, Figure 9-1

Subjects in the trial were at least 18 years of age, with BMI ≥ 27 kg/m² and T2D treated with either diet and exercise alone or stable treatment with metformin, sulfonylurea (SU), sodium-glucose cotransporter 2 inhibitor (SGLT2i), glitazone as single agent therapy or up to 3 oral antidiabetics (OADs; metformin, SU, SGLT2i or glitazone). Subjects were excluded with a body weight change > 5 kg within 90 days before screening, renal impairment measured as estimated glomerular filtration rate (eGFR) value of < 30 mL/min/1.73 m² (< 60 mL/min/1.73 m² in subjects treated with SGLT2i), or uncontrolled and potentially unstable diabetic retinopathy or maculopathy. In order to be randomized, subjects must have had a PHQ-9 score < 15 and no suicidal behavior or ideation between screening and randomization.

Study Endpoints

All endpoints tested semaglutide 2.4 mg – placebo, unless otherwise specified.

The 2 co-primary endpoints were:

- Percent change in body weight from baseline to week 68
- Proportion of subjects achieving a weight loss of $\geq 5\%$ from baseline to week 68

Confirmatory secondary endpoints were:

- Proportion of subjects achieving a weight loss of $\geq 10\%$ from baseline to week 68

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- Proportion of subjects achieving a weight loss of $\geq 15\%$ from baseline to week 68
- Waist circumference change from baseline to week 68
- Percent change in body weight from baseline to week 68: semaglutide 2.4 mg – semaglutide 1 mg
- HbA1c change from baseline to week 68
- Systolic blood pressure change from baseline to week 68
- SF-36 Physical Functioning score change from baseline to week 68
- IWQOL-Lite-CT Physical Function score change from baseline to week 68

Statistical Analysis Plan

The primary estimand quantified the treatment effect of semaglutide in all randomized subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies.

The classification of endpoints for each subject based on whether it is available or missing is as was described for trial 4373 (Table 5).

In the analysis approach addressing the primary estimand, week 68 assessments from retrieved subjects (AD) were used. These data were also used to impute missing measurements at week 68 for non-retrieved subjects (MD). The imputation was done separately within each treatment arm.

Given an anticipated total of 1200 subjects in the trial (400 per arm), power calculations were as follows:

Table 16: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 1200 Subjects (400 Per Arm), Trial 4374

Order	Endpoint	Assumed mean ($\pm$ SD) or proportion for completers		Expected mean ($\pm$ SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo I/II				
1	% weight change #	11.6 ($\pm$ 10)	1.7 ($\pm$ 10)	10.2 ($\pm$ 11)	8.5%-points	> 99	> 99
2	5% responders	75%	37%	69%	1.8	> 99	> 99
3	10% responders	56%	20%	51%	2.6	> 99	> 99
4	15% responders	37%	9%	33%	3.7	> 99	> 99
5	WC change (cm) #	9.1 ($\pm$ 10)	2.8 ($\pm$ 10)	8.2 ($\pm$ 11)	5.4 cm	> 99	> 99
6	% weight change #, *	11.6 ($\pm$ 10)	8.1 ($\pm$ 10)	10.2 vs 7.2 ($\pm$ 11)	3.0%-points	97	97
7	HbA _{1c} (%) change #	1.4 ($\pm$ 1.0)	0.5 ($\pm$ 1.0)	1.3 ($\pm$ 1.5)	0.8%-points	> 99	96
8	sBP change (mmHg) #	5.1 ($\pm$ 13)	0.4 ($\pm$ 13)	4.4 ($\pm$ 14)	4 mmHg	98	94
9	SF-36 PF score change	6 ($\pm$ 10)	2 ($\pm$ 10)	5.4 ($\pm$ 11)	3.4 score-points	> 99	94
10	IWQoL-Lite PFD score change	24 ($\pm$ 20)	13 ($\pm$ 20)	22.5 ($\pm$ 21)	9.5 score-points	> 99	94

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number; * semaglutide 2.4 mg vs semaglutide 1.0 mg

All tests in the hierarchy are based on the primary estimand.

Source: Study 4374 SAP, Table 2

Protocol Amendments

There was 1 U.S. amendment and 1 global amendment:

- Amendment 2 (U.S.), dated 16 Mar 2018:
 - U.S. specific eye examination requirements were removed; eye examinations were to be performed according to the global standards
- Amendment 4 (global), dated 04 Jun 2018:
 - To implement genetic biosamples for future analysis
 - Removal of criteria for discontinuation of trial treatment for subjects included in the trial in violation of the inclusion and/or exclusion criteria and/or randomization criteria
 - Removal of the persistent criteria from the exploratory endpoint regarding onset of micro- or macroalbuminuria as well as regression to normoalbuminuria (assessment at week 68 should be confirmed with 2 confirmatory assessments after end of treatment)
 - Classifications of risks were removed from the protocol and instead a reference to the IB or any updates hereof was added for further details of the risks associated with semaglutide treatment

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

6.2.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and FDA 21 CFR 312.120. The FDA 21 CFR, parts 312, 50, and 56 were followed.

Financial Disclosure

See Section 13.2

Subject Disposition

A total of 1210 subjects were randomized (full analysis set, FAS), and 1207 were exposed to treatment (safety analysis set).

Disposition is as follows:

Table 17: Subject Disposition, Study 4374

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Randomized, FAS	404	403	403
Exposed, safety analysis set	403	402	402
Treatment Completion			
On-treatment at week 68 (treatment completers) ^a	357 (88.4)	354 (87.8)	347 (86.1)
After at least 1 temporary interruption	34 (8.4)	27 (6.7)	28 (6.9)
Trial product permanently discontinued	47 (11.6)	49 (12.2)	56 (13.9)
Adverse event	26 (6.4)	19 (4.7)	13 (3.2)
Protocol violation	1 (0.2)	5 (1.2)	5 (1.2)
Investigator discretion	0	2 (0.5)	1 (0.2)
Safety concern as judged by the investigator	1 (0.2)	1 (0.2)	0
Withdrawal of consent	2 (0.5)	5 (1.2)	7 (1.7)
Lost to follow-up	5 (1.2)	2 (0.5)	3 (0.7)
Other	12 (3.0)	15 (3.7)	25 (6.2)
Attended end-of-treatment visit after permanent discontinuation of trial product	37 (9.2)	37 (9.2)	42 (10.4)
Trial Completion			
Attended end-of-trial visit (trial completers)	391 (96.8)	390 (96.8)	383 (95.0)
Withdrawn from trial	13 (3.2)	13 (3.2)	20 (5.0)
Withdrawal by subject	5 (1.2)	10 (2.5)	12 (3.0)
Lost to follow-up	7 (1.7)	2 (0.5)	7 (1.7)
Death	1 (0.2)	1 (0.2)	1 (0.2)
a all subjects attended end-of-treatment visit without permanent discontinuation of trial product			

Source: Study 4374 CSR, Table 10-1

Protocol Violations/Deviations

There were no important trial-level protocol deviations (PDs) in the trial.

There was 1 important country-level PD in the trial:

- In Spain, end-of-trial visits (week 75) were converted to phone visits due to COVID-19 for a total of 30 subjects at 8 sites.

The 97 important site-level PDs and 398 important subject-level PDs are summarized in the table below.

Table 18: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4374

Protocol deviation category	Site-level PDs (n)	Subject-level PDs (n)				Total site and subject-level PDs (n)	
		Screening failures (n)	Semaglutide 2.4 mg (n)	Semaglutide 1.0 mg (n)	Placebo (n)		Total subject-level PDs (n)
Total	97	7	111	130	150	398	495
Informed consent	11	4	13	10	10	37	48
Inclusion/exclusion criteria ^a	1	0	17	31	20	68	69
Treatment administration	4	0	14	8	11	33	37
Trial procedures/assessments	74	3	40	49	53	145	219
Concomitant medication	0	0	2	0	6	8	8
Subject visit schedule	4	0	20	29	46	95	99
SAE notification/safety procedures	1	0	3	3	4	10	11
Privacy and data protection	1	0	2	0	0	2	3

^a also includes randomisation criteria

Source: Study 4374 CSR, Table 10-4

Reviewer comment: I reviewed the protocol deviations and do not believe they significantly impacted the safety of the trial subjects or the interpretation of the study results. The applicant appropriately addressed important deviations when found. See the discussion of protocol deviations for trial 4373 for additional information.

Regarding the impact of the COVID-19 pandemic, almost all subjects had completed their end-of-treatment visits at the time of the pandemic. The main trial procedures affected by COVID-19 were as follows:

- Source data verification was abolished for the last part of the trial (as of 23 March 2020). According to the applicant, all data were still entered into the electronic data capture system and checked for completeness, and data cleaning and casebook sign-off was ensured.
- Approximately 230 subjects had their follow-up visits (week 75) converted to phone visits and 1 subject had the end-of-treatment visit (week 68) converted to a phone visit.
- Some blood samples could not be sent from the site to the central laboratory for a period of time, but all samples except samples for 2 subjects were eventually received and analyzed,

and the delay did not impact subject safety as the samples were for PK and antibody follow-up.

- One subject (Subject ID (b) (6), semaglutide 2.4 mg) had a COVID-19 related SAE (PT: 'Corona virus infection'), that was reported as severe.
- One subject (Subject ID: (b) (6), placebo) did not attend the follow-up visit due to COVID-19 and was therefore reported as lost to follow-up and withdrawn from the trial. However, the subject was a treatment completer. No subjects discontinued treatment due to COVID-19.

Demographic Characteristics

Demographic characteristics were well-balanced among groups. Overall, 51% were female and mean age was 55 years. As only 30% of subjects were from the U.S., the population was somewhat underrepresented for subjects who are Black (8.3%) and of Hispanic or Latino ethnicity (12.8%) as compared to the general US population.¹⁶

Table 19: Demographic Characteristics of the Primary Efficacy Analysis, Trial 4374

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Sex			
Male	181 (44.8)	200 (49.6)	213 (52.9)
Female	223 (55.2)	203 (50.4)	190 (47.1)
Age			
Mean years (SD)	55 (11)	56 (10)	55 (11)
Median (years)	56	56	56
Min, max (years)	19, 84	20, 81	20, 82
Age Group			
18 - < 65 years	316 (78.2)	320 (79.4)	317 (78.7)
65 - < 75 years	78 (19.3)	78 (19.4)	78 (19.4)
75 - < 85 years	10 (2.5)	5 (1.2)	8 (2.0)
≥ 85 years	0	0	0
Race			
White	237 (58.7)	272 (67.5)	242 (60.0)
Black or African American	112 (27.7)	97 (24.1)	108 (26.8)
Asian	35 (8.7)	28 (6.9)	37 (9.2)
American Indian or Alaska Native	4 (1.0)	0	2 (0.5)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	0
Other	16 (4.0)	6 (1.5)	13 (3.2)
Ethnicity			
Hispanic or Latino	47 (11.6)	59 (14.6)	49 (12.2)
Not Hispanic or Latino	357 (88.4)	344 (85.4)	354 (87.8)
Region			

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

United States	128 (31.7)	117 (29.0)	116 (28.8)
Rest of the World	276 (68.3)	286 (71.0)	287 (71.2)

Source: Study 4374 CSR, Tables 10-2 and 10-3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, mean body weight was 99.8 kg, mean BMI was 35.7 kg/m², mean waist circumference was 114.6 cm, and mean HbA1c was 8.1%. On average, subjects had diabetes for a duration of 8 years. Baseline characteristics were well-balanced among groups.

Table 20: Baseline Characteristics, Trial 4374

	Semaglutide 2.4 mg N=404	Semaglutide 1 mg N=403	Placebo N=403
Body weight			
Mean kg (SD)	99.9 (22.5)	99.0 (21.1)	100.5 (20.9)
Median (kg)	97.5	96.1	98.3
Min, max (kg)	54.4, 199.2	59.2, 184.8	62.4, 184.6
BMI			
Mean kg/m ² (SD)	35.9 (6.4)	35.3 (5.9)	35.9 (6.5)
Median (kg/m ²)	34.6	33.8	34.6
Min, max (kg/m ²)	27.0, 66.2	26.9, 58.4	26.5, 65.4
Waist circumference			
Mean cm (SD)	114.5 (14.3)	113.9 (14.0)	115.5 (13.9)
Median (cm)	112.0	111.9	113.5
Min, max (cm)	84.0, 172.7	85.0, 162.0	80.0, 174.0
HbA1c			
Mean % (SD)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Median (%)	8.0	8.0	8.0
Min, max (%)	6.7, 10.6	5.8, 10.2	5.7, 10.3
Fasting plasma glucose			
Mean mg/dL (SD)	152.7 (40.9)	155.7 (41.5)	157.9 (42.1)
Median (mg/dL)	146.3	149.2	151.8
Min, max (mg/dL)	72.4, 329.2	70.5, 369.0	55.3, 352.3

Source: Study 4373, Table 10-3

At screening, proportions of subjects with history of diseases of interest were skin cancer, 3.7%, psychiatric disease 19.4%, colon neoplasms, 4.0%, breast cancer, 1.3%, and gallbladder disease, 17.0%.

At screening, proportions of subjects with weight-related co-morbidities of interest were hypertension, 70.1%, dyslipidemia, 68.3%, obstructive sleep apnea, 14.5%, coronary heart disease, 8.2%, knee osteoarthritis, 16.2%, and non-alcoholic fatty liver disease, 21.6%.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

At screening, proportions of subjects with diabetes-related complications were diabetic neuropathy, 20.2%, diabetic nephropathy, 12.7%, and diabetic retinopathy, 10.2%.

A total of 95.5% used OADs at baseline, with biguanides (90.2%), SUs (25.1%), and SGLT2is (23.5%) being the most frequently reported. The proportions of subjects on 1 OAD were 55.0%, 2 OADs 32.9%, 3 OADs 7.3%, and 4 OADs 0.2% (2 subjects who used a combination of metformin, SGLT2i, SU, and glitazone were randomized in error).

Other than OADs, some of the most frequently used medications at baseline were drugs acting on the renin-angiotensin system, 57.9%, statins, 51.8%, antithrombotic agents, 26.3%, and diuretics, 22.6%.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

At the end of the treatment all subjects were asked about their last dose administered. Of the treatment completers, 84.0% of the subjects in the semaglutide 2.4 mg group reported a last dose of 2.4 mg and 94.9% of the subjects in the semaglutide 1 mg group reported a last dose of 1 mg. In the placebo group, 97.1% of the subjects reported a last dose equivalent to 2.4 mg and 97.7% of the subjects reported a last dose equivalent to 1 mg.

Insulin was used as a rescue medication in 2 subjects (0.5%) in the semaglutide 2.4 mg group, 5 subjects (1.2%) in the semaglutide 1 mg group, and 18 subjects (4.5%) in the placebo group. For OAD medication, 4.6%, 4.9%, and 23.0%, respectively, had an increase in intensity from week 0 to week 68.

Concomitant gastrointestinal medications initiated at or after randomization included:

- Drugs for acid-related disorders (21.8% for semaglutide 2.4 mg, 17.4% for semaglutide 1 mg, and 8.9% for placebo); the majority being proton pump inhibitors (13.6%, 10.7%, 5.2%, respectively)
- Drugs for functional gastrointestinal disorders (10.9%, 7.9%, 2.7%)
- Antidiarrheals (9.9%, 6.7%, 4.7%)
- Drugs for constipation (8.7%, 6.5%, 1.7%)
- Antiemetics and antinauseants (5.2%, 4.7%, 1.7%)

Four subjects in the semaglutide 2.4 mg group, 7 subjects in the semaglutide 1 mg group, and 13 subjects in the placebo group initiated concomitant anti-obesity medication; all were after the last trial product. In addition, 1 subject in the placebo group had a bariatric surgery, also after last trial product.

Efficacy Results – Primary Endpoint

Superiority of the co-primary endpoints – percent change in body weight from baseline to week 68 and proportion of subjects achieving a weight loss of $\geq 5\%$ – was confirmed. The weight results of the semaglutide 1 mg dose are presented for completeness (mean percent change in body weight, semaglutide 2.4 mg – semaglutide 1 mg, was a confirmatory secondary endpoint).

Table 21: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68

Treatment	N	Baseline Mean (SD)	Week 68 Mean (SD) In-trial	% Change from Baseline ANCOVA RD-MI
Semaglutide 2.4 mg	404	99.9 (22.5)	89.6 (21.0)	-9.64
Semaglutide 1 mg	403	99.0 (21.1)	92.3 (20.7)	-6.99
Placebo	403	100.5 (20.9)	96.8 (20.3)	-3.42
Between treatment difference (95% CI)				p value
Semaglutide 2.4 vs. Placebo		-6.21 (-7.28, -5.15)		<0.0001
Semaglutide 2.4 vs. Semaglutide 1		-2.65 (-3.66, -1.64)		<0.0001

Source: Study 4374 CSR, Tables 14.2.2 and 14.2.9

The proportions of subjects on semaglutide 2.4 mg, semaglutide 1 mg, and placebo achieving 5% body weight loss were 68.8%, 57.1%, and 28.5%, respectively; semaglutide 2.4 mg versus placebo, $p < 0.0001$ and semaglutide 2.4 mg versus semaglutide 1 mg, $p=0.0012$.

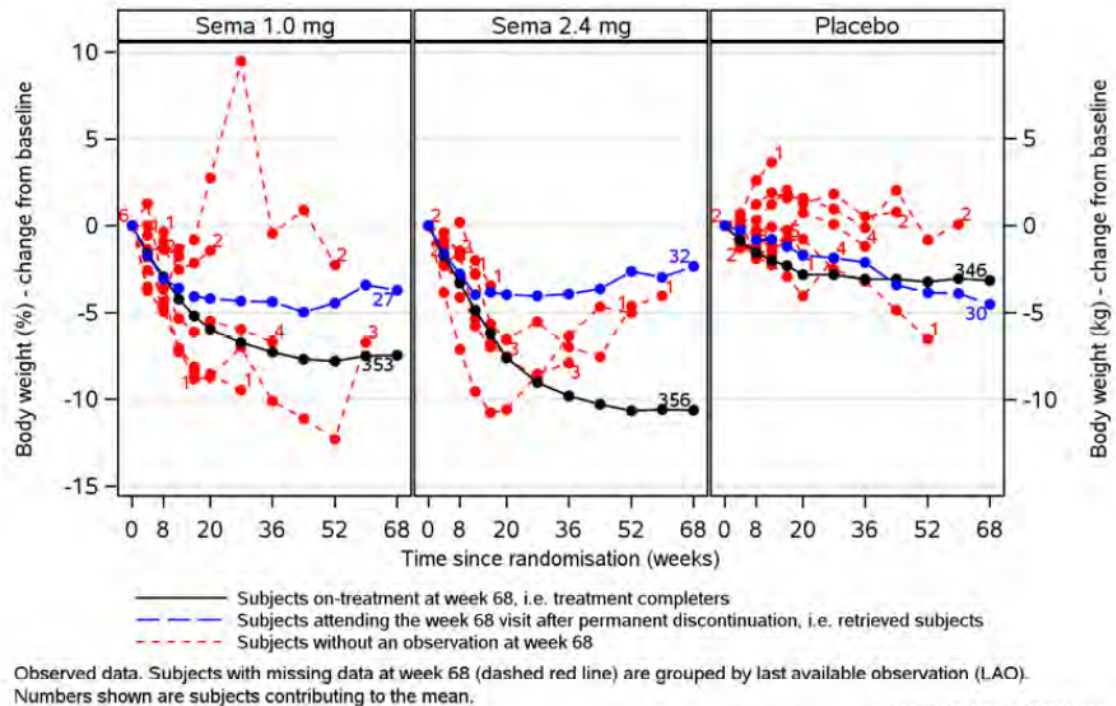
All sensitivity analyses were consistent with the co-primary analyses.

Data Quality and Integrity

Data quality and integrity in this trial are very good. Subjects were encouraged to remain in the trial for data collection, even if trial product was permanently discontinued. A total of 96.2% of the randomized subjects completed the trial; 96.8% semaglutide 2.4 mg, 96.8% semaglutide 1 mg, and 95.0% placebo.

Missing data were evaluated graphically to detect patterns relevant for the interpretation of the primary analysis (Figure 11). Retrieved dropouts; i.e., subjects who discontinued treatment but returned for a week 68 assessment (blue lines), illustrate the differential in weight change as compared to those who remained on-treatment (black line) in the semaglutide groups.

Figure 11: Mean Body Weight Change from Baseline, Missing Data Pattern, Trial 4374



Source: Study 4374 CSR, Figure 14.2.7

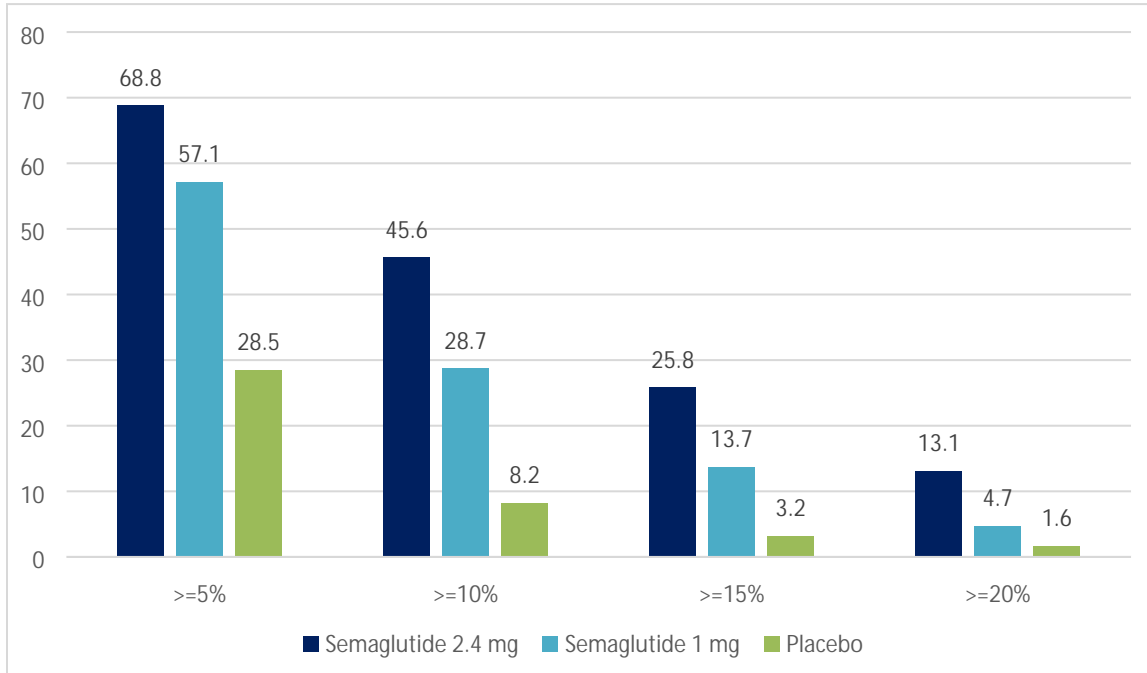
Reviewer comment: Given that the overall number of subjects with missing data that contributed to the primary analysis was relatively low, missing data are not likely to substantially impact the interpretation of the primary analysis. It is noted that retrieved placebo drop-outs did somewhat better than expected (i.e., demonstrated increased weight loss vs. completers), which could have biased the results towards the null.

Efficacy Results – Secondary and other relevant endpoints

Superiority of semaglutide versus placebo was confirmed for all secondary confirmatory endpoints in the hierarchical testing procedure: proportions of subjects who lost $\geq 10\%$ and $\geq 15\%$ body weight at week 68, and change from baseline at week 68 in waist circumference, mean percent body weight change versus semaglutide 1 mg (data shown in Table 21), HbA1c, SBP, SF-36 physical functioning score, and IWQOL-Lite-CT physical function score.

- The proportions of subjects meeting various cut-off criteria for weight loss response is illustrated in Figure 12; the p-values for the 2 endpoints in the statistical testing hierarchy – the odds of achieving $\geq 10\%$ and $\geq 15\%$ body weight at week 68, semaglutide 2.4 mg versus placebo – were <0.0001 for both.

Figure 12: Proportion of Subjects Achieving Body Weight Loss Response Criteria Since Baseline at Week 68, Trial 4374

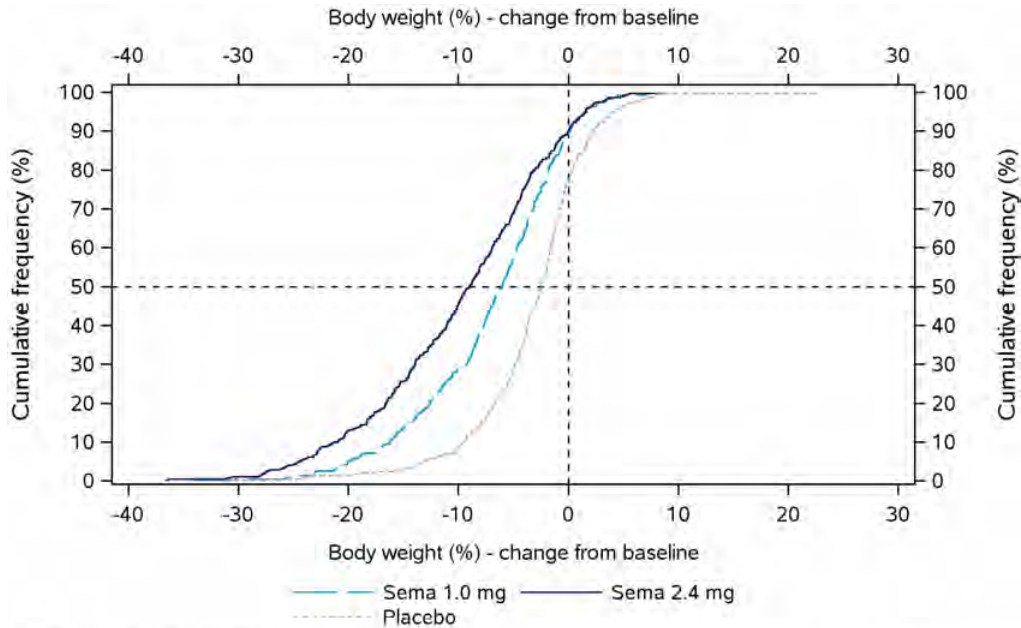


Source: Study 4374 CSR, Figure 14.2.35

Figure 4 presents the cumulative distribution for percent body weight change, which shows a left shift for semaglutide 2.4 mg for all proportions of weight change from baseline.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Figure 13: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4374, In-Trial



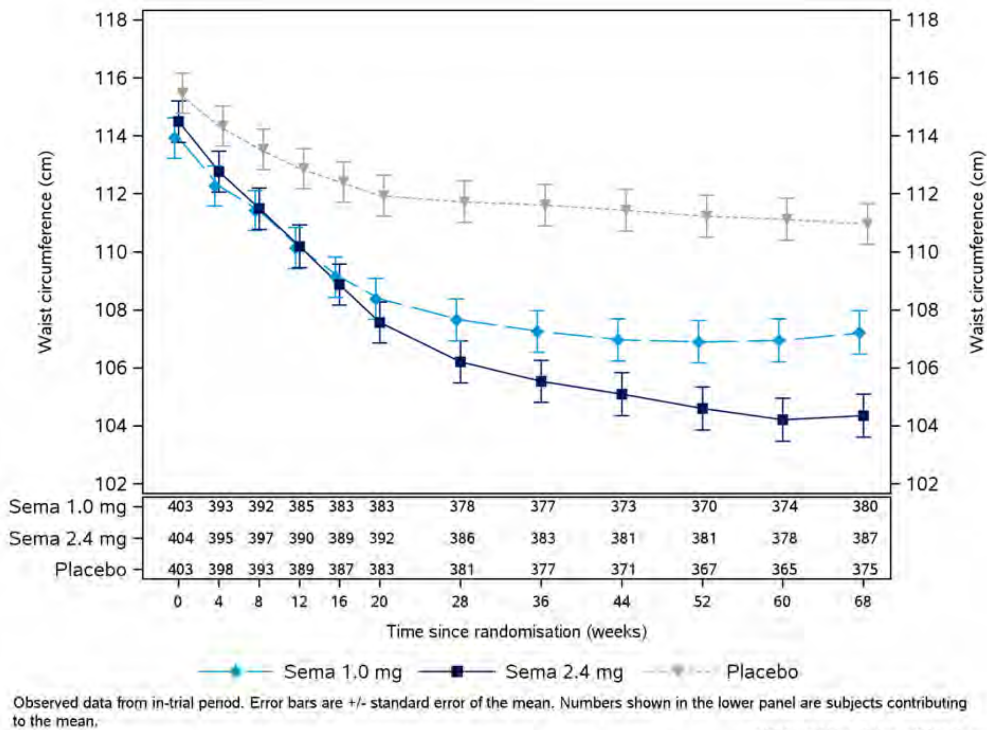
Observed data from in-trial period.

nn9536/nn9536-4374/ctr_20200821_er
25AUG2020,08:32:47 - fcitfeff.sas/fcdblwtipct.png

Source: Study 4374 CSR, Figure 14.2.5

- At baseline, mean waist circumference was 114.6 cm. Mean changes in waist circumference from baseline at week 68 were -9.40 cm for semaglutide 2.4 mg, -6.72 cm for semaglutide 1 mg, and -4.52 cm for placebo, for an ETD for semaglutide 2.4 mg versus placebo of -4.88 cm (95% CI -5.97, -3.79), $p < 0.0001$ and for semaglutide 2.4 mg versus semaglutide 1 mg, -2.69 cm (-3.72, -1.65), $p < 0.0001$.

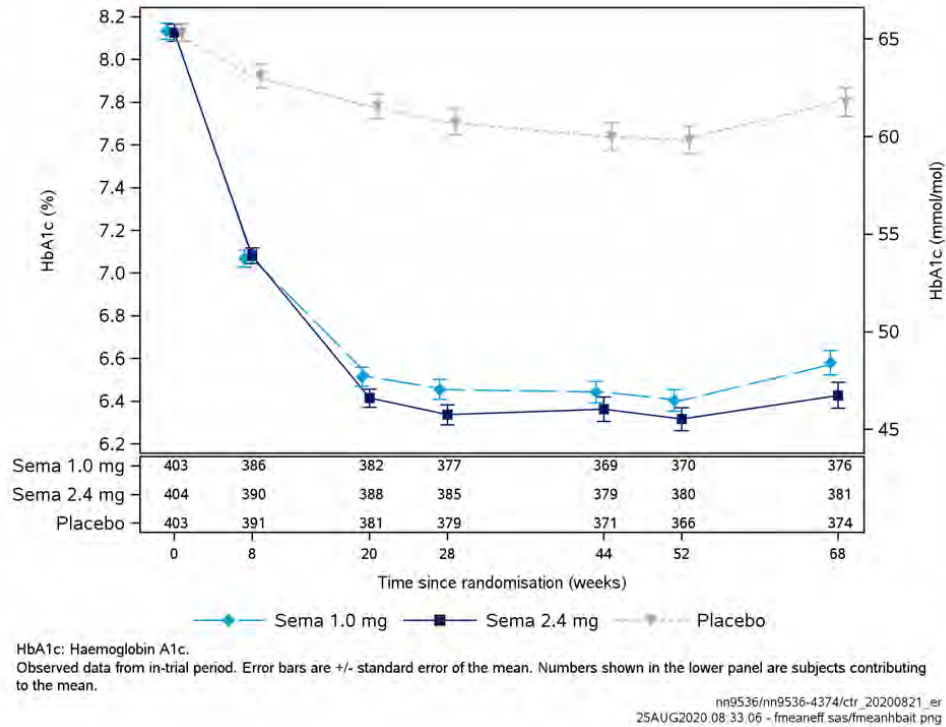
Figure 14: Mean Waist Circumference by Week, Trial 4374



Source: Study 4374 CSR, Figure 11-10

- At baseline, mean HbA1c was 8.1%. Mean changes in HbA1c from baseline at week 68 were -1.60% for semaglutide 2.4 mg, -1.45% for semaglutide 1 mg, and -0.37% for placebo, for an ETD for semaglutide 2.4 mg versus placebo of -1.23% (95% CI -1.42, -1.05), $p < 0.0001$, for semaglutide 1 mg versus placebo, -1.08% (-1.28, -0.89), $p < 0.0001$, and for semaglutide 2.4 mg versus semaglutide 1 mg, -0.15% (-0.34, +0.04), $p = 0.1218$. Change in HbA1c by week is shown in Figure 15.

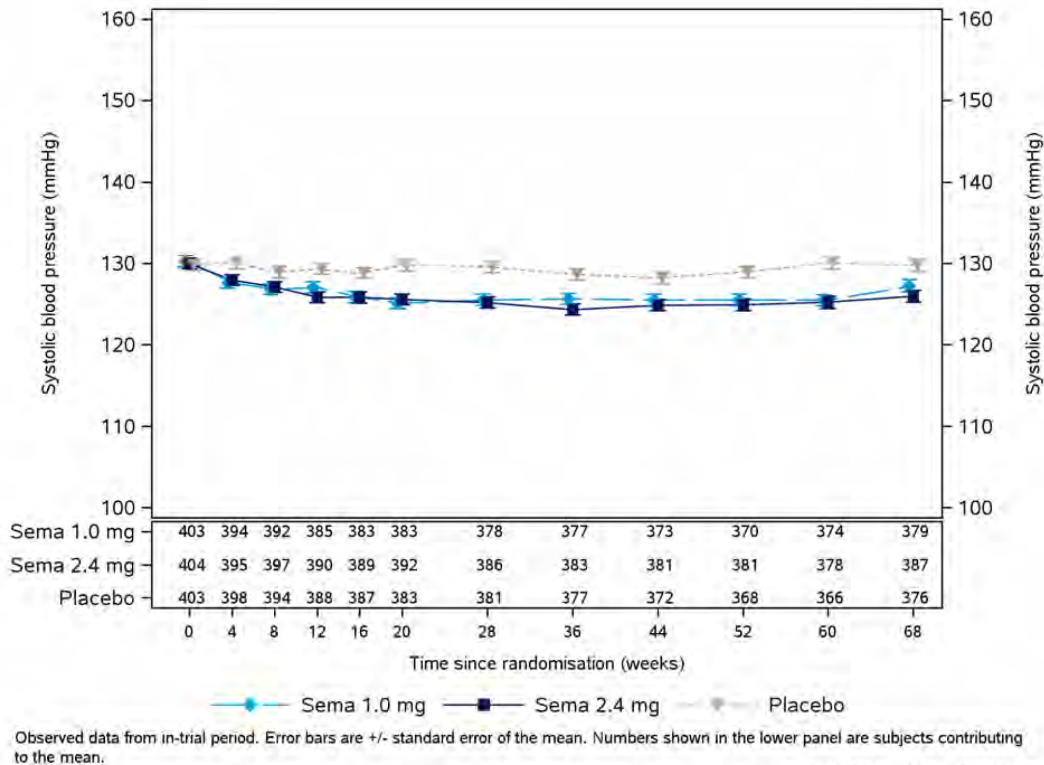
Figure 15: HbA1c by Week, Trial 4374, In-Trial



Source: Study 4374 CSR, Figure 14.2.63

- At baseline, mean SBP was 130 mmHg. Mean changes in SBP were -3.92 mmHg for semaglutide 2.4 mg, -2.88 for semaglutide 1 mg, and -0.49 mmHg for placebo, for an ETD for semaglutide 2.4 mg versus placebo of -3.43 mmHg (95% CI -5.57, -1.30), $p=0.0016$ and for semaglutide 2.4 mg versus semaglutide 1 mg of -1.04 mmHg (-3.33, +1.24), $p=0.3713$.

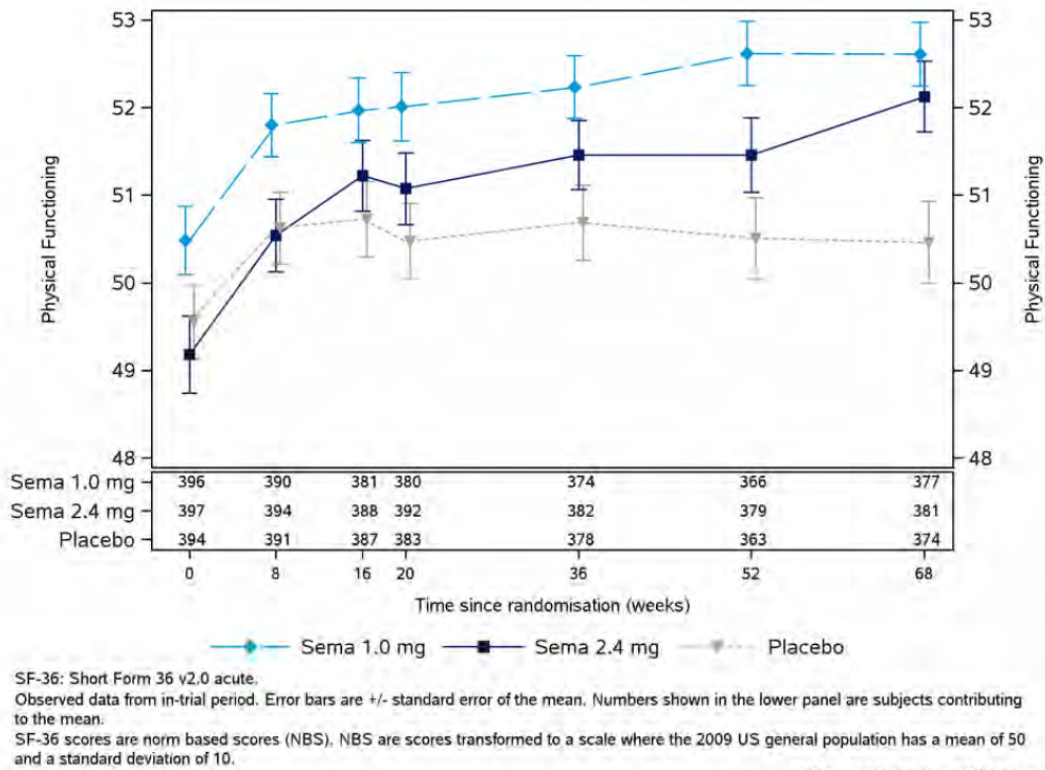
Figure 16: Mean Systolic Blood Pressure by Week, Trial 4374



Source: Study 4374 CSR, Figure 11-20

- At baseline, mean SF-36 physical functioning score was 49.7. Mean changes in SF-36 physical functioning scores were +2.52 for semaglutide 2.4 mg, +2.39 for semaglutide 1 mg, and +0.99 for placebo, for an ETD for semaglutide 2.4 mg versus placebo of +1.52 (95% CI +0.44, +2.61), $p=0.0061$ and for semaglutide 2.4 mg versus semaglutide 1 mg of +0.12 (-0.95, +1.20), $p=0.8235$.

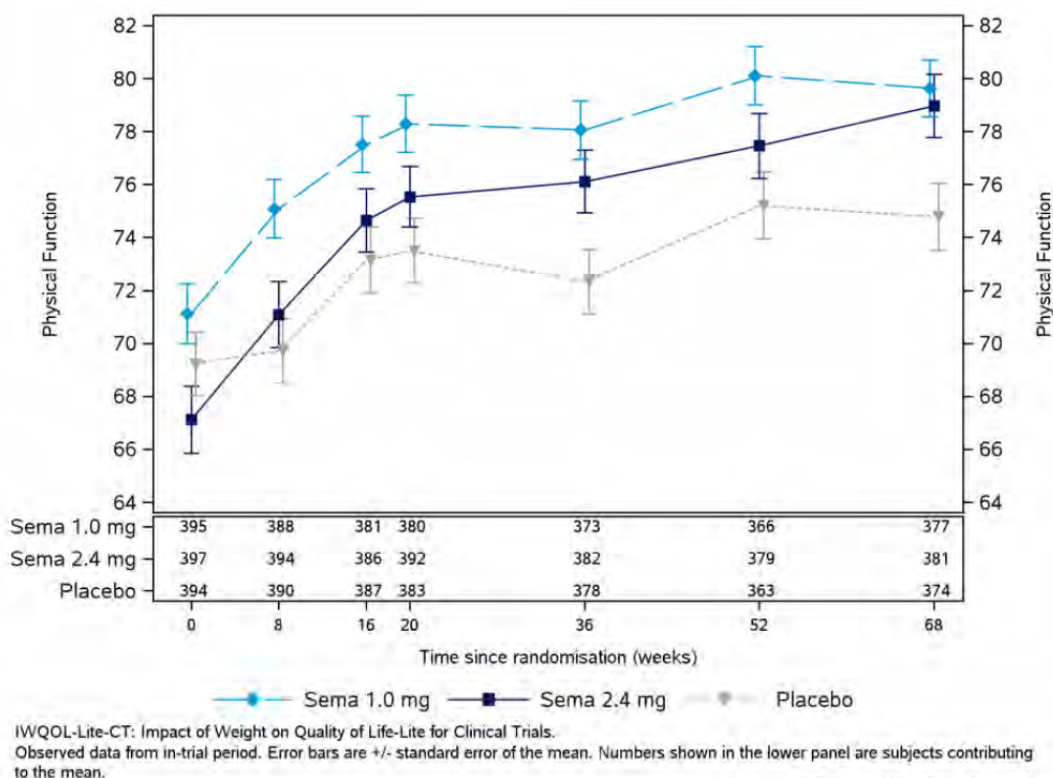
Figure 17: Mean SF-36 Physical Functioning by Week, Trial 4374



Source: Study 4374 CSR, Figure 11-27

- At baseline, the IWQOL-Lite physical function score was 69.2. Mean changes in IWQOL-Lite physical function scores were +10.12 for semaglutide 2.4 mg, +8.72 for semaglutide 1 mg, and +5.29 for placebo, for an ETD for semaglutide 2.4 mg versus placebo of +4.83 (95% CI +1.79, +7.86), $p=0.0018$ and for semaglutide 2.4 mg versus semaglutide 1 mg of +1.41 (-1.50, +4.31), $p=0.3423$.

Figure 18: Mean IWQOL-Lite-CT Physical Function by Week, Trial 4374



Source: Study 4374 CSR, Figure 11-32

Reviewer comment: As discussed with the patient reported outcomes (PROs) for trial 4373, while the results based on the mean difference between groups were statistically significant for these instruments, the clinical significance of these results is uncertain. As Dr. Yasmin Choudhry, reviewer in the Division of Clinical Outcome Assessment notes in her review, there were minimal observed score changes, if any, when looking at the item- and domain-level data at the raw score scale. Please refer to Dr. Choudhry's review for details.

Dose/Dose Response

A dose response for semaglutide 2.4 mg versus semaglutide 1 mg was only formally tested for percent change in weight. As noted above, the difference in weight between the 2.4 mg and 1 mg doses was statistically significant, with an ETD of -2.65% (95% CI -3.66, -1.64).

Other evaluations of dose response are descriptive, as they were not formally tested to control for type 1 error. The results of these analyses are presented in different sections in this review; below is a summary of changes of these various endpoints from baseline at week 68 for semaglutide 2.4 mg – semaglutide 1 mg (with p-values provided for descriptive purposes):

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

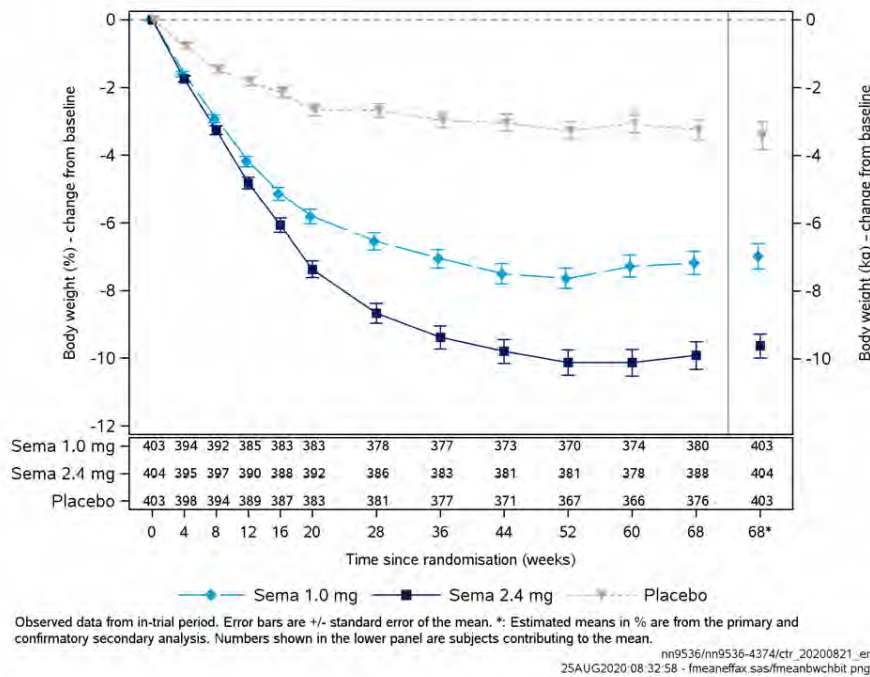
- Waist circumference: -2.69 cm (-3.72, -1.65), p<0.0001
- HbA1c: -0.15% (-0.34, +0.04), p=0.1218
- SBP: -1.04 mmHg (-3.33, +1.24), p=0.3713
- SF-36 physical functioning: +0.12 (-0.95, +1.20), p=0.8235
- IWQOL-Lite physical function score: +1.41 (-1.50, +4.31), p=0.3423

Reviewer comment: In summary, there is a dose-response for body weight change (and likewise, waist circumference), but other parameters showed similar results for the 2 doses. The study was not designed to detect a dose-response for these other parameters.

Durability of Response

Figure 9 presents percent weight change by week. Separation of the weight curves (both semaglutide arms versus placebo) is apparent by week 4. Dosing for the 2 semaglutide arms diverged after week 8; separation of these curves is apparent by week 20. Plateau in the curves in the semaglutide arms occurs around week 52, whereas the placebo group exhibits most weight loss before week 20 and then trends down slowly thereafter until approximately week 52.

Figure 19: Percent Body Weight Change from Baseline by Week, Trial 4374



Source: Study 4374 CSR, Figure 14.2.8

Persistence of Effect

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Persistence of effect was not tested in this trial.

Additional Analyses Conducted on the Individual Trial

DBP and Lipids

The differences in changes in DBP were nominally significantly significant for semaglutide 2.4 mg versus placebo (favoring semaglutide), and not different between the 2 semaglutide doses (Table 22).

Table 22: Diastolic Blood Pressure, Trial 4374

	Sema 2.4 mg		Sema 1 mg		Placebo		Sema 2.4 minus Placebo (95% CI ^a)	Sema 2.4 minus Sema 1 (95% CI ^a)
	Baseline	Change from Baseline	Baseline	Change from Baseline	Baseline	Change from Baseline		
DBP (mmHg)	80	-1.55	80	-0.64	80	-0.88	-0.67 (-1.95, +0.61)	-0.91 (-2.20, +0.38)

Sema=semaglutide
 a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error

Source: Study 4374 CSR, Tables 14.2.95, 14.2.98

The percent differences in HDL-C and triglycerides were nominally significantly significant for semaglutide 2.4 mg versus placebo (favoring semaglutide), and not different for total cholesterol or LDL-C.

Table 23: Lipids, Trial 4374

	Semaglutide 2.4 mg		Placebo		Relative Difference of Semaglutide 2.4 mg to Placebo (95% CI ^a)
	Baseline	% Change from Baseline	Baseline	% Change from Baseline	
Total-C (mg/dL)	170.8	-1.36	170.8	-0.50	-0.86 (-3.60, +1.95)
LDL-C (mg/dL)	90.10	+0.48	90.07	+0.12	+0.36 (-4.00, +4.92)
HDL-C (mg/dL)	44.7	+6.86	43.8	+4.07	+2.69 (+0.34, +5.09)
Triglycerides (mg/dL)	154.90	-22.01	159.48	-9.44	-13.88 (-19.04, -8.39)

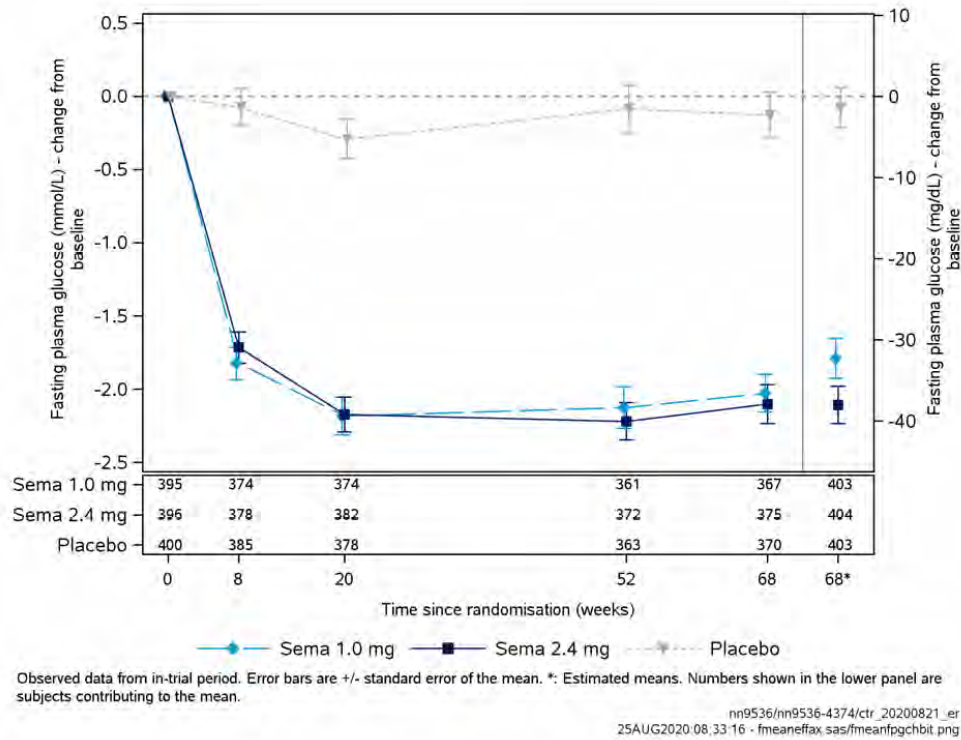
a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error

Source: Study 4374 CSR, Table 14.2.99; ISE, Tables 6.3.127, 6.3.128, 6.3.129, 6.3.132

Glycemic Endpoints

At baseline, fasting plasma glucose was 155.4 mg/dL. At week 68, mean change from baseline was similar for semaglutide 2.4 mg and 1 mg (-37.9 mg/dL and -36.5 mg/dL, respectively) and was decreased to a greater extent than placebo (-2.3 mg/dL).

Figure 20: Fasting Plasma Glucose Change from Baseline by Week, Trial 4374

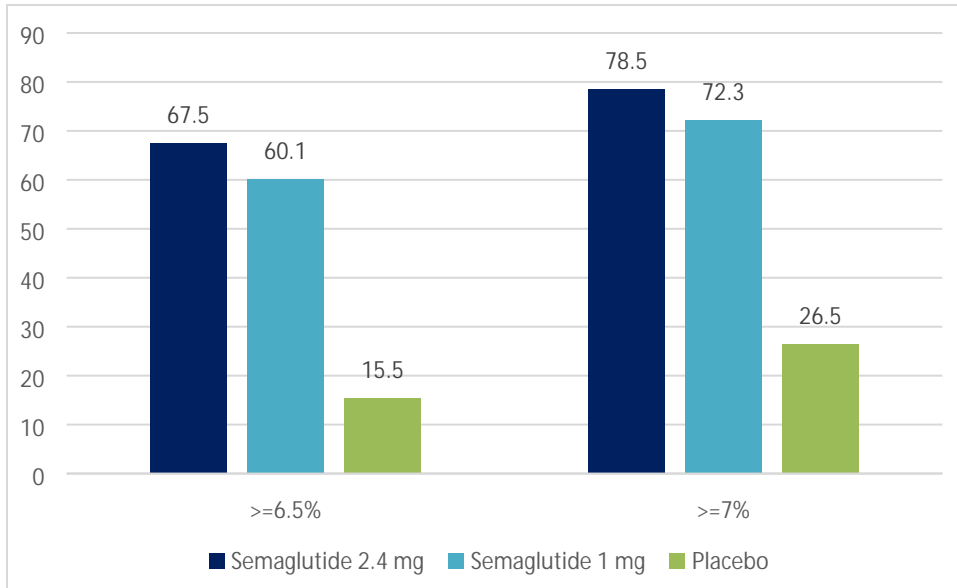


Source: Study 4374 CSR, Figure 14.2.82

At baseline, mean fasting serum insulin was 13.5 mIU/mL. There was no treatment difference observed among any of the comparisons (semaglutide 2.4 mg vs. placebo or semaglutide 1 mg) for fasting insulin.

Other clinically relevant endpoints include the proportions of subjects achieving HbA1c of 6.5% or 7% or lower; a greater proportion of both semaglutide groups met these responder cutoffs versus placebo (Figure 21).

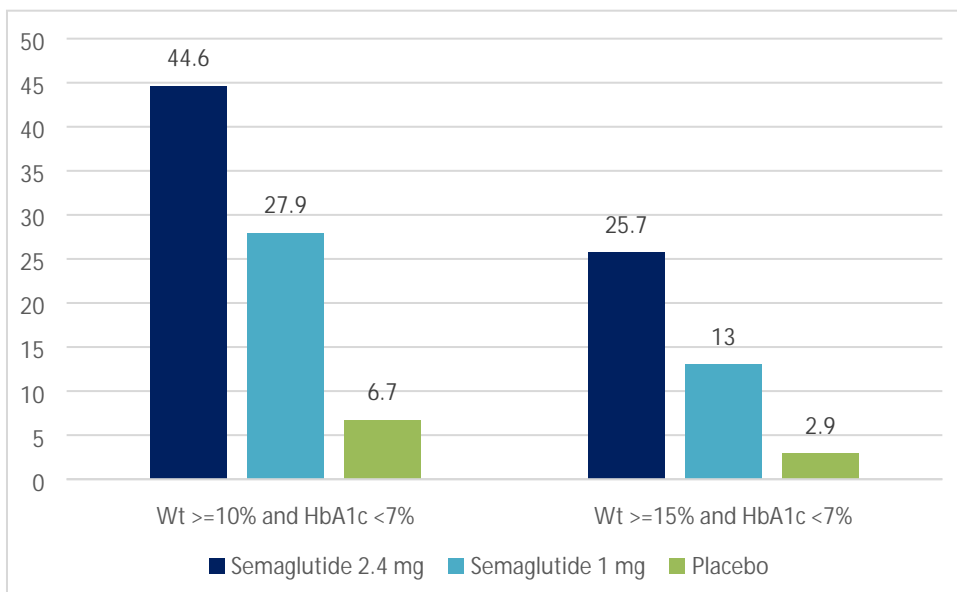
Figure 21: Proportion of Subjects Achieving $\leq 6.5\%$ or $\leq 7\%$ HbA1c at Week 68, Trial 4374



Source: Study 4374 CSR, Figure 14.2.73

A composite endpoint evaluating both weight loss and glycemic control suggest favorable results in a dose-dependent fashion (suggesting that achieving weight loss with semaglutide 2.4 mg is not occurring at the expense of achieving glycemic control, Figure 22 and Figure 12).

Figure 22: Proportion of Subjects Achieving Both Weight Loss and HbA1c Reduction, Trial 4374

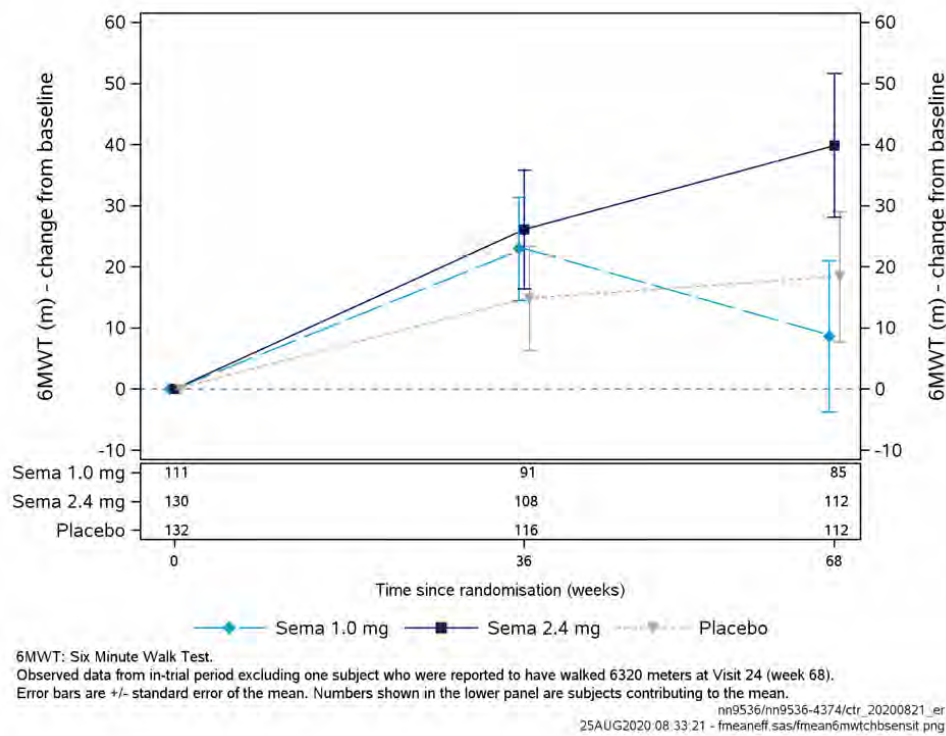


Source: Study 4374 CSR, Figure 14.2.76

6-Minute Walk Test

Subjects with BMI ≥ 35 kg/m² were eligible to take part in an exploratory 6-minute walk test evaluation at weeks 0, 36, and 68. Baseline walk test distance was 380.0 m in the semaglutide 2.4 mg group, 393.7 m in the semaglutide 1 mg group, and 407.6 m in the placebo group. Excluding 1 subject in the semaglutide 2.4 mg group who walked an unrealistically long distance (6320 m) at week 68, the mean distance increased by 39.9 m in the semaglutide 2.4 mg group, 8.6 m in the semaglutide 1 mg group, and 18.4 m in the placebo group. Results are shown in Figure 23.

Figure 23: Change from Baseline in 6-Minute Walk Test, Trial 4374, Sensitivity Analysis



Source: Study 4374 CSR, Figure 14.2.146

Albuminuria

Most subjects in the trial did not have albuminuria at baseline (urine albumin:creatinine ratio (UACR) > 30 mg/g). The shift table below suggests that there is improvement (or less worsening) of UACR over the trial period with semaglutide versus placebo (not dose-dependent), but in some shifts the numbers are too small to draw conclusions.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 24: Albuminuria Shift Table, Trial 4374

			Normal at Baseline			Microalbuminuria at Baseline			Macroalbuminuria at Baseline		
			Normal	Micro	Macro	Normal	Micro	Macro	Normal	Micro	Macro
Week 20	Sema 2.4	N=381	291 (95.7)	13 (4.3)	0	24 (40.7)	24 (57.6)	1 (1.7)	1 (8.3)	4 (33.3)	7 (58.3)
	Sema 1	N=370	270 (96.8)	9 (3.2)	0	34 (50.0)	32 (47.1)	2 (2.9)	1 (6.7)	7 (46.7)	7 (46.7)
	Placebo	N=373	267 (91.4)	25 (8.6)	0	22 (33.3)	36 (54.5)	8 (12.1)	0	3 (27.3)	8 (72.7)
Week 68	Sema 2.4	N=378	287 (95.3)	14 (4.7)	0	30 (50.0)	27 (45.0)	3 (5.0)	2 (20.0)	5 (50.0)	3 (30.0)
	Sema 1	N=367	263 (93.9)	13 (4.6)	4 (1.4)	34 (54.0)	26 (41.3)	3 (4.8)	1 (6.7)	9 (60.0)	5 (33.3)
	Placebo	N=368	246 (86.6)	36 (12.7)	2 (0.7)	21 (30.9)	40 (58.8)	7 (10.3)	0	4 (36.4)	7 (63.6)

Normal: UACR: < 30 mg/g
Microalbuminuria: UACR 30 to <300 mg/g
Macroalbuminuria: UACR ≥ 300 mg/g

Source: Study 4374 CSR, Table 14.2.149

6.3. NN9536-4375 (STEP 3): Effect and safety of semaglutide 2.4 mg once-weekly as adjunct to intensive behavioral therapy in subjects with overweight or obesity

6.3.1. Study Design

Overview and Objective

Trial 4375 was designed to demonstrate that semaglutide 2.4 mg, as an adjunct to intensive behavioral therapy (IBT), is effective and safe for the treatment of subjects with overweight or obesity. Secondary objectives were to assess the effect of semaglutide 2.4 mg as an adjunct to IBT on cardiovascular risk factors, clinical outcome assessments, and glucose metabolism.

Trial Design

This was a 68-week randomized (2:1), double-blind, placebo-controlled, multicenter trial, conducted in the U.S., which compared semaglutide 2.4 mg to placebo as an adjunct to IBT in subjects with overweight or obesity.

Semaglutide was dose-escalated over 16 weeks to the 2.4 mg once-weekly maintenance dose for GI tolerability (i.e., the following doses were given once-weekly for 4 weeks each: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg).

In the first 8 weeks after randomization, subjects were prescribed a 1000-1200 kcal/day low calorie diet (LCD),²³ after which the subjects were gradually transferred to a less strict hypocaloric diet.²⁴ Behavioral counseling was conducted from week 0 to week 68.

Subjects used an activity tracker²⁵ and were asked to record their food intake in order to assist their lifestyle intervention. The activity tracker, food diary/app, and content of the subject handout from the IBT guide were used for counseling purposes by the dietitian or a similarly qualified healthcare professional at all visits.

²³ At the discretion of the investigator, the diet consisted of meal replacements (e.g., liquid shakes and solid bars) and portion-controlled meals

²⁴ The following algorithm was used:

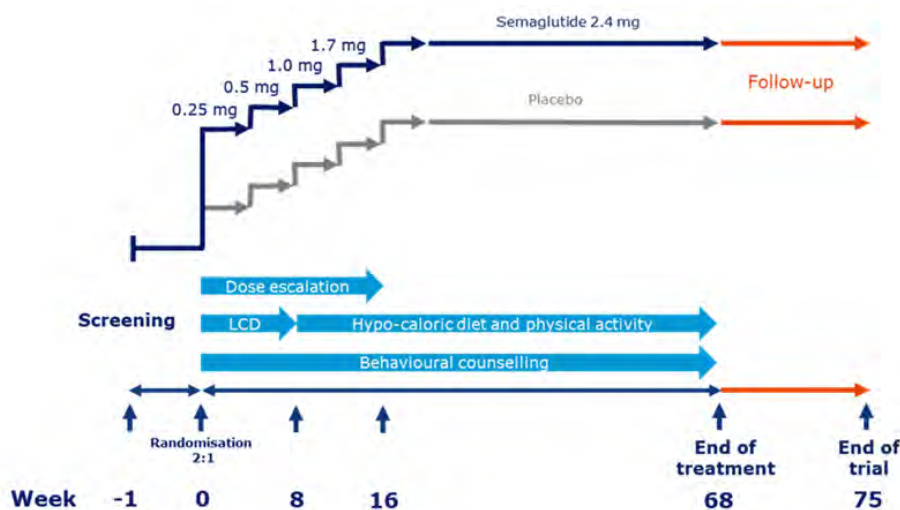
- Subjects weighing less than 200 lbs (90.7 kg): 1200 kcal/day
- Subjects weighing between 200 lbs and 300 lbs: $\text{body weight (lb)} \times 6 \text{ (kcal/lb)} = \text{daily caloric target (kcal)}$
- Subjects weighing more than 300 lbs (136.1 kg): 1800 kcal/day

The calculated caloric target was kept for the remainder of the trial except if a subject achieved a BMI $\leq 22.5 \text{ kg/m}^2$ in which case the recommended energy intake was re-calculated with no caloric deficit for the remainder of the trial.

²⁵ Data collected from the activity trackers were not reported in the CSR

A follow-up visit was scheduled 7 weeks after end-of-treatment to account for the long half-life.

Figure 24: Trial 4375 Design



Source: Study 4375 CSR, Figure 9-1

Subjects in the trial were at least 18 years of age, with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with the presence of at least 1 of the following weight-related co-morbidities (treated or untreated): hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Subjects were excluded with type 1 or type 2 diabetes, HbA1c $\geq 6.5\%$, or body weight change > 5 kg within 90 days before screening. In order to be randomized, subjects must have had a PHQ-9 score < 15 and no suicidal behavior or ideation between screening and randomization.

Study Endpoints

The 2 co-primary endpoints were:

- Percent change in body weight from baseline to week 68
- Proportion of subjects achieving a weight loss of $\geq 5\%$ from baseline to week 68

Confirmatory secondary endpoints were:

- Proportion of subjects achieving a weight loss of $\geq 10\%$ from baseline to week 68
- Proportion of subjects achieving a weight loss of $\geq 15\%$ from baseline to week 68
- Waist circumference change from baseline to week 68
- Systolic blood pressure change from baseline to week 68
- SF-36 Physical Functioning score change from baseline to week 68

Statistical Analysis Plan

The primary estimand quantified the treatment effect of semaglutide as an adjunct to IBT in all randomized subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies.

Given an anticipated number of 600 subjects in the trial, power calculations were as follows:

Table 25: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 600 Subjects, Trial 4375

Order	Endpoint	Assumed mean ($\pm$ SD) or proportion for completers		Expected mean ($\pm$ SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight loss #	17 (10)	7 (10)	15.6 (11)	8.6 %-points	> 99	> 99
2	5% responders	88%	58%	85%	1.5	> 99	> 99
3	10% responders	76%	38%	71%	1.9	> 99	> 99
4	15% responders	58%	21%	53%	2.5	> 99	> 99
5	WC change (cm) #	17 (11)	8 (11)	15.7 (12)	7.7 cm	> 99	> 99
6	sBP change (mmHg) #	9.1 (13)	4.5 (13)	8.5 (14)	4 mmHg	91	91
7	SF-36 PF score change	6 ($\pm$ 10)	2 ($\pm$ 10)	5.4 ($\pm$ 11)	3.4 score-points	95	86

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; # shown as a positive number

All tests in the hierarchy are based on the primary estimand

Source: Study 4375 SAP, Table 2-2

Protocol Amendments

There were 2 global amendments:

- Amendment 1, dated 17 Dec 2018:
 - Removed criteria for discontinuation of trial treatment for subjects included in the trial in violation of eligibility criteria if considered safe to continue
 - Risks associated with semaglutide was removed from the protocol and instead referred to the IB
- Amendment 2, dated 07 Jun 2018:
 - To fulfill the regulatory requirements for clinical trial testing of the intended to-be-marketed drug product (semaglutide B 3.2 mg/mL PDS290), subjects were to switch from semaglutide B 3.0 mg/mL PDS290/semaglutide placebo to semaglutide B 3.2 mg/mL PDS290/semaglutide placebo at week 60 (visit 29)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- Confirmatory, supportive secondary and exploratory endpoints related to WRSSM were updated. Based on new data from recently reported trials, the WRSSM was shown to have substantial ceiling effects and low responsiveness within the target population. The measure was therefore considered unlikely to be able to detect a treatment benefit.

6.3.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and FDA 21 CFR 312.120. The FDA 21 CFR, parts 312, 50, and 56 were followed.

Financial Disclosure

See Section 13.2.

Subject Disposition

All subjects randomized in the trial were exposed to treatment (407 semaglutide-treated subjects and 204 placebo-treated subjects), and therefore were included in the full analysis set (FAS) and the safety analysis set.

Disposition is as follows:

Table 26: Subject Disposition, Trial 4375

	Semaglutide N=407	Placebo N=204
Treatment Completion		
On-treatment at week 68 (treatment completers)	339 (83.3)	166 (81.4)
After at least 1 temporary interruption	46 (11.3)	23 (11.3)
Trial product permanently discontinued	68 (16.7)	38 (18.6)
Adverse event	26 (6.4)	6 (2.9)
Protocol violation	0	1 (0.5)
Pregnancy	1 (0.2)	2 (1.0)
Lack of efficacy	0	1 (0.5)
Investigator discretion	1 (0.2)	0
Safety concern as judged by the investigator	1 (0.2)	2 (1.0)
Withdrawal of consent	4 (1.0)	3 (1.5)
Lost to follow-up	18 (4.4)	7 (3.4)
Other	17 (4.2)	16 (7.8)
Trial Completion		
Attended end-of-trial visit (trial completion)	376 (92.4)	191 (93.6)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	335 (82.3)	165 (80.9)
Withdrawn from trial	31 (7.6)	13 (6.4)
Withdrawal by subject	7 (1.7)	3 (1.5)
Lost to follow-up	24 (5.9)	10 (4.9)
Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68). Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).		

Source: Study 4375 CSR, Table 10-1

Protocol Violations/Deviations

There was 1 important trial-level PD, related to a delay in the dispensing of the activity tracker to subjects randomized between 1 Aug 2018 and 14 Sep 2018.

There were 2 important country-level PDs in the trial (U.S.): 2 safety reports were submitted 1 day and 2 days late.

The 27 important site-level PDs and 195 important subject-level PDs are summarized in Table 27.

Table 27: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4375

Protocol deviation category	Site-level PDs (n)	Subject-level PDs (n)			Total subject-level PDs (n)	Total site and subject-level PDs (n)
		Screening failures (n)	Semaglutide 2.4 mg (n)	Placebo (n)		
Total	27	1	127	67	195	222
Informed consent	0	1	1	3	5	5
Inclusion/exclusion criteria ^a	0	0	0	2	2	2
Treatment administration	0	0	4	0	4	4
Trial procedures/assessments	27	0	80	44	124	151
Concomitant medication	0	0	0	0	0	0
Subject visit schedule	0	0	41	17	58	58
SAE notification/safety procedures	0	0	1	0	1	1
Privacy and data protection	0	0	0	1	1	1

^a also includes randomisation criteria

Source: Study 4375 CSR, Table 10-4

Reviewer comment: I reviewed the protocol deviations and do not believe they significantly impacted the safety of the trial subjects or the interpretation of the study results. The applicant appropriately addressed important deviations when found. See the discussion of protocol deviations for trial 4373 for additional information.

Regarding the impact of the COVID-19 pandemic, almost all subjects had completed their end-of-treatment visits at the time of the pandemic. The main trial procedures affected by COVID-19 were as follows:

- Source data verification was abolished for the last part of the trial (as of 23 March 2020). According to the applicant, all data were still entered into the electronic data capture system and checked for completeness, as well as data cleaning and casebook sign-off were ensured.
- A total of approximately 137 subjects had their follow-up visits (week 75) converted to phone visits and 2 subjects had missing assessments at the end-of-treatment visit (week 68) due to COVID-19. AE reporting and safety follow-up information were ensured for these subjects.
- One subject (semaglutide 2.4 mg) had a COVID-19 related AE (PT: 'Coronavirus test positive'), that was non-serious and of mild severity.

- No subjects discontinued treatment due to COVID-19. One subject (Subject ID: (b) (6); semaglutide 2.4 mg) was reported as withdrawn from the trial during the follow-up period due to COVID-19

Demographic Characteristics

Demographic characteristics were well-balanced among groups, except for sex. Female subjects comprised 77.4% of the semaglutide 2.4 mg group and 88.2% of the placebo group. Overall, mean age was 46 years. The trial was conducted solely in the U.S. A total of 76.1% were White, 19.0% were Black or African American, and 19.8% were Hispanic or Latino.

Table 28: Demographic Characteristics of the Primary Efficacy Analysis

	Semaglutide N=407	Placebo N=204
Sex		
Male	92 (22.6)	24 (11.8)
Female		
Age		
Mean years (SD)	46 (13)	46 (13)
Median (years)	46	46
Min, max (years)	18, 75	19, 75
Age Group		
18 - < 65 years	379 (93.1)	186 (91.2)
65 - < 75 years	27 (6.6)	16 (7.8)
75 - < 85 years	1 (0.2)	2 (1.0)
≥ 85 years	0	0
Race		
White	307 (75.4)	158 (77.5)
Black or African American	80 (19.7)	36 (17.6)
Asian	5 (1.2)	6 (2.9)
American Indian or Alaska Native	1 (0.2)	0
Native Hawaiian or Other Pacific Islander	3 (0.7)	0
Other	11 (2.7)	4 (2.0)
Ethnicity		
Hispanic or Latino	75 (18.4)	46 (22.5)
Not Hispanic or Latino	332 (81.6)	158 (77.5)

Source: Study 4375 CSR, Tables 10-2 and 10-3

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, mean body weight was 105.8 kg, mean BMI was 38.0 kg/m², mean waist circumference

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

was 113.0 cm, and mean HbA1c was 5.7%. Baseline characteristics were well-balanced among groups.

Table 29: Baseline Characteristics

	Semaglutide N=407	Placebo N=204
Body weight		
Mean kg (SD)	106.9 (22.8)	103.7 (22.9)
Median (kg)	102.6	99.0
Min, max (kg)	68.6, 216.8	66.9, 182.7
BMI		
Mean kg/m ² (SD)	38.1 (6.7)	37.8 (6.9)
Median (kg/m ²)	36.7	36.4
Min, max (kg/m ²)	27.1, 65.7	27.0, 69.0
Waist circumference		
Mean cm (SD)	113.6 (15.1)	111.8 (16.2)
Median (cm)	111.0	109.9
Min, max (cm)	84.0, 164.0	77.7, 175.0
HbA1c		
Mean % (SD)	5.7 (0.3)	5.8 (0.3)
Median (%)	5.7	5.8
Min, max (%)	4.8, 7.0	4.6, 6.5
Fasting plasma glucose		
Mean mg/dL (SD)	93.9 (9.4)	94.0 (9.8)
Median (mg/dL)	93.3	93.3
Min, max (mg/dL)	60.4, 141.5	71.5, 122.5

Source: Study 4373, Table 10-3

Table 11 presents a summary of past and concomitant illness of subjects at screening.

Table 30: Medical History and Concomitant Illness, Selected Events

	Semaglutide N=407	Placebo N=204
Anemias nonhemolytic and marrow depression	39 (9.6)	22 (10.8)
Cardiac arrhythmias	24 (5.9)	16 (7.8)
Coronary artery disorders	6 (1.5)	5 (2.5)
Thyroid gland disorders	80 (19.7)	41 (20.1)

	Semaglutide N=407	Placebo N=204
Gastrointestinal motility and defecation conditions	120 (29.5)	56 (27.5)
Benign neoplasms gastrointestinal	27 (6.6)	14 (6.9)
Gastrointestinal inflammatory conditions	9 (2.2)	3 (1.5)
Pancreatitis acute	2 (0.5)	0
Nonalcoholic fatty liver disease	12 (2.9)	6 (2.9)
Nonalcoholic steatohepatitis	2 (0.5)	1 (0.5)
Gallbladder disorders	46 (11.3)	18 (8.8)
Lipid metabolism disorders	132 (32.4)	67 (32.8)
Glucose metabolism disorders	97 (23.8)	56 (27.5)
Glycosylated hemoglobin increased	30 (7.4)	19 (9.3)
Neoplasms benign, malignant and unspecified	74 (18.2)	33 (16.2)
Psychiatric disorders	173 (42.5)	91 (44.6)
Sleep apnea syndrome	60 (14.7)	19 (9.3)

Source: Study 4375 CSR, Table 14.1.10

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

If subjects did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose of 1.7 mg. Of the treatment completers, 82.0% of subjects randomized to semaglutide were reported to be on the maintenance dose of 2.4 mg at the last dosing, 7.4% reported to be on the 1.7 mg dose, and 10.6% reported to be on doses lower than 1.7 mg (which deviated from the protocol). A total of 95.8% of subjects randomized to placebo reported to be on an equivalent volume to the 2.4 mg dose.

Some common medications ongoing at the time of randomization included: anti-inflammatories (28.2%), agents acting on the renin-angiotensin system (21.1%), sex hormones, including estrogens and progestins (20.3%), antacids (17.3%), thyroid hormones (15.7%), diuretics (14.2%), statins (12.6%), and SSRIs (12.1%).²⁶

During the trial, certain classes of drugs were initiated more in the semaglutide group:²⁷

²⁶ Source: Study 4375 CSR, Table 14.1.18

²⁷ Source: Study 4375 CSR, Table 14.1.19

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- Antacids: semaglutide 23.6%, placebo 10.3%
- Antiemetics: semaglutide 19.7%, placebo 6.4%
- Drugs for constipation: semaglutide 14.7%, placebo 7.4%
- Antidiarrheals: semaglutide 8.6%, placebo 4.9%
- Drugs for functional gastrointestinal disorders: semaglutide 7.1%, placebo 4.9%
- Antithrombotic agents: semaglutide 6.4%, placebo 3.4%

The proportions of subjects who received antihypertensive medication from week 0 to week 68 were 31.9% in the semaglutide group and 31.4% in the placebo group.

The proportions of subjects who received lipid-lowering medication from week 0 to week 68 were 17.4% in the semaglutide group and 18.1% in the placebo group.

Table 31: Subjects Receiving Antihypertensive or Lipid-Lowering Medication During the Trial

	Semaglutide 2.4 mg N=373	Placebo N=188
Antihypertensive medication continuing at week 68	95 (25.5)	55 (29.3)
Decreased	19 (5.1)	4 (2.1)
No change	68 (18.2)	41 (21.8)
Increased	8 (2.1)	10 (5.3)
Stopped by week 68	24 (6.4)	4 (2.1)
Lipid-lowering medication continuing at week 68	59 (15.8)	32 (17.0)
Decreased	3 (0.8)	1 (0.5)
No change	49 (13.1)	26 (13.8)
Increased	7 (1.9)	5 (2.7)
Stopped by week 68	6 (1.6)	2 (1.1)

Source: Study 4375 CSR, Table 14.2.116

Efficacy Results – Primary Endpoint

Superiority of the co-primary endpoints – percent change in body weight from baseline to week 68 and proportion of subjects achieving a weight loss of $\geq 5\%$ – was confirmed.

Table 32: Primary Endpoint: Percent Body Weight Change from Baseline at Week 68

Treatment	N	Baseline Mean (SD)	Week 68 Mean (SD) In-trial	% Change from Baseline ANCOVA RD-MI
Semaglutide	407	106.9 (22.8)	88.4 (21.5)	-15.97
Placebo	204	103.7 (22.9)	98.3 (23.6)	-5.70
Semaglutide vs. Placebo		Between treatment difference (95% CI)		p value
		-10.27 (-11.97, -8.57)		<0.0001

Source: Study 4375 CSR, Tables 14.2.2 and 14.2.9

The proportions of subjects on semaglutide 2.4 mg and placebo achieving 5% body weight loss were 86.6% and 47.6%, respectively, $p < 0.0001$.

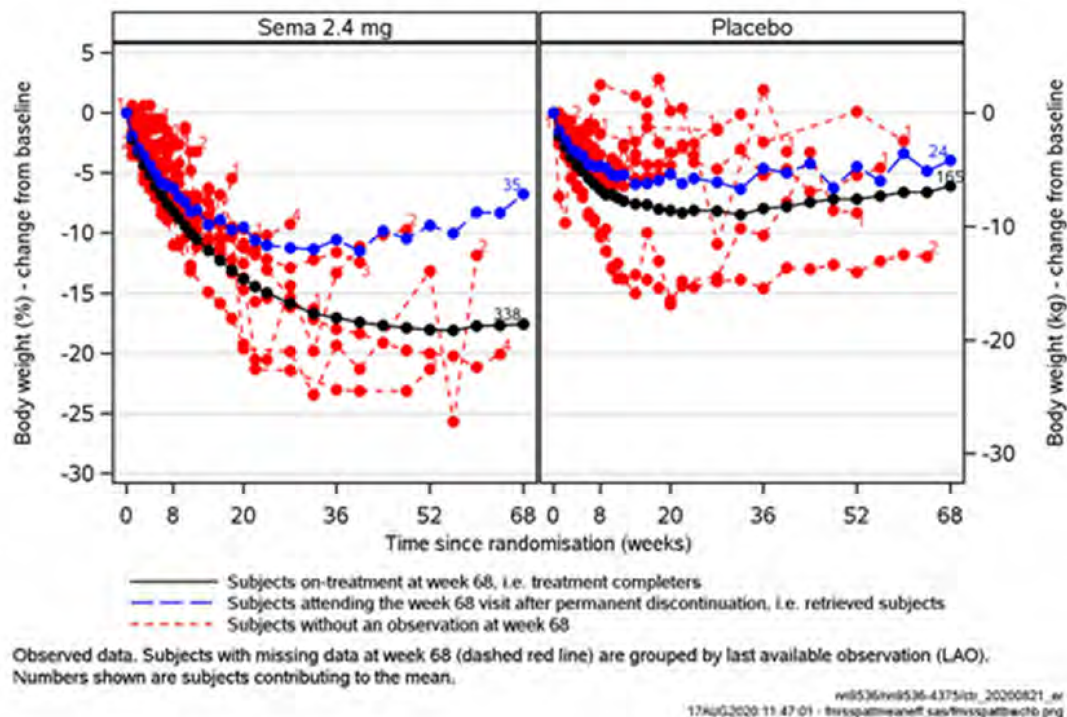
All sensitivity analyses were consistent with the co-primary analyses.

Data Quality and Integrity

Data quality and integrity in this trial are very good. Subjects were encouraged to remain in the trial for data collection, even if trial product was permanently discontinued. A total of 92.8% of the randomized subjects completed the trial; 92.4% semaglutide and 93.6% placebo.

Missing data were evaluated graphically to detect patterns relevant for the interpretation of the primary analysis (Figure 25). Retrieved dropouts; i.e., subjects who discontinued treatment but returned for a week 68 assessment (blue lines), illustrate the differential in weight change as compared to those who remained on-treatment (black line), particularly in the semaglutide group.

Figure 25: Mean Percent Body Weight Change from Baseline by Week, Missing Data Pattern, Trial 4375



Source: Study 4375 CSR, Figure 11-4

Reviewer comment: Given that the overall number of subjects with missing data that contributed to the primary analysis was relatively low, missing data are not likely to substantially impact the interpretation of the primary analysis.

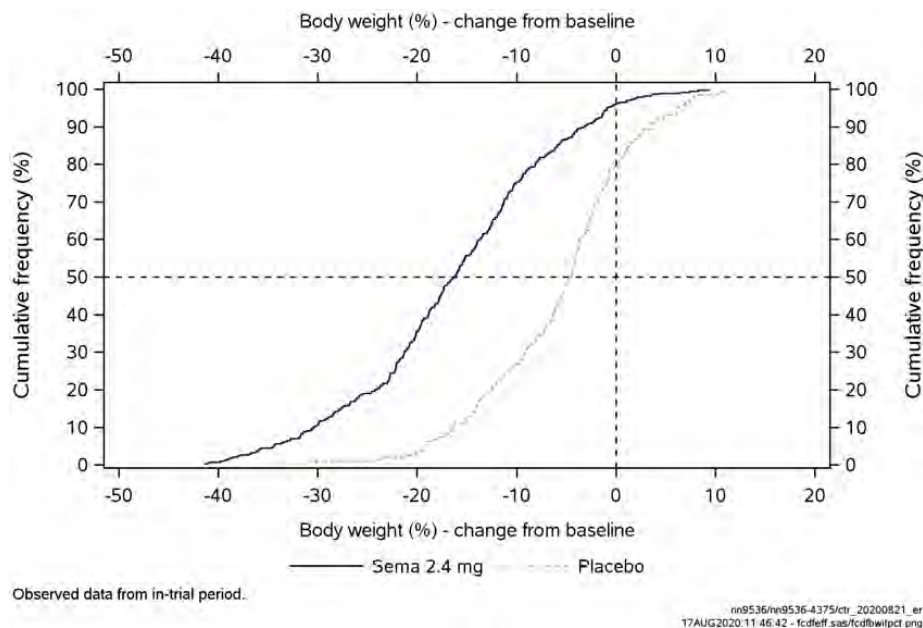
Efficacy Results – Secondary and other relevant endpoints

Superiority of semaglutide versus placebo was confirmed for all secondary confirmatory endpoints in the hierarchical testing procedure, except for the SF-36 physical functioning score.

- The proportions of subjects on semaglutide 2.4 mg and placebo achieving 10% body weight loss were 75.3% and 27.0%, respectively, and those achieving 15% weight loss, 55.8% and 13.2%, respectively; all $p < 0.0001$. In addition (not in the hierarchy), those achieving 20% weight loss were 35.7% and 3.7%, respectively.

Figure 4 presents the cumulative distribution for percent body weight change, which shows a left shift for semaglutide for all proportions of weight change from baseline.

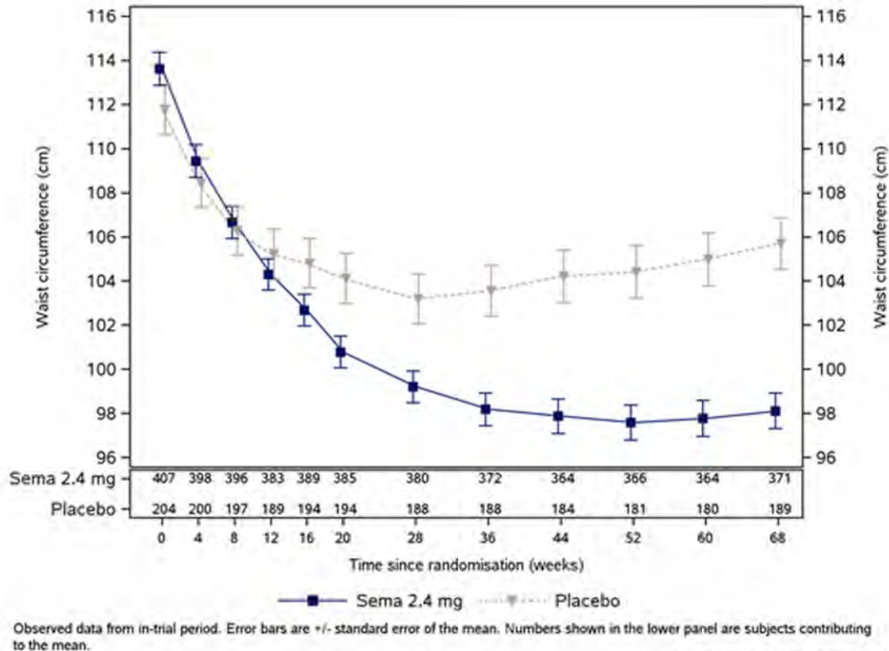
Figure 26: Percent Body Weight Change from Baseline to Week 68, Cumulative Distribution Plot, Trial 4375, In-Trial



Source: Study 4375 CSR, Figure 14.2.5

- At baseline, mean waist circumference was 113.0 cm. Mean changes in waist circumference from baseline at week 68 were -14.61 cm for semaglutide 2.4 mg and -6.27 cm for placebo, for an ETD of -8.34 cm (95% CI -10.08, -6.59), $p < 0.0001$.

Figure 27: Mean Waist Circumference by Week, Trial 4375

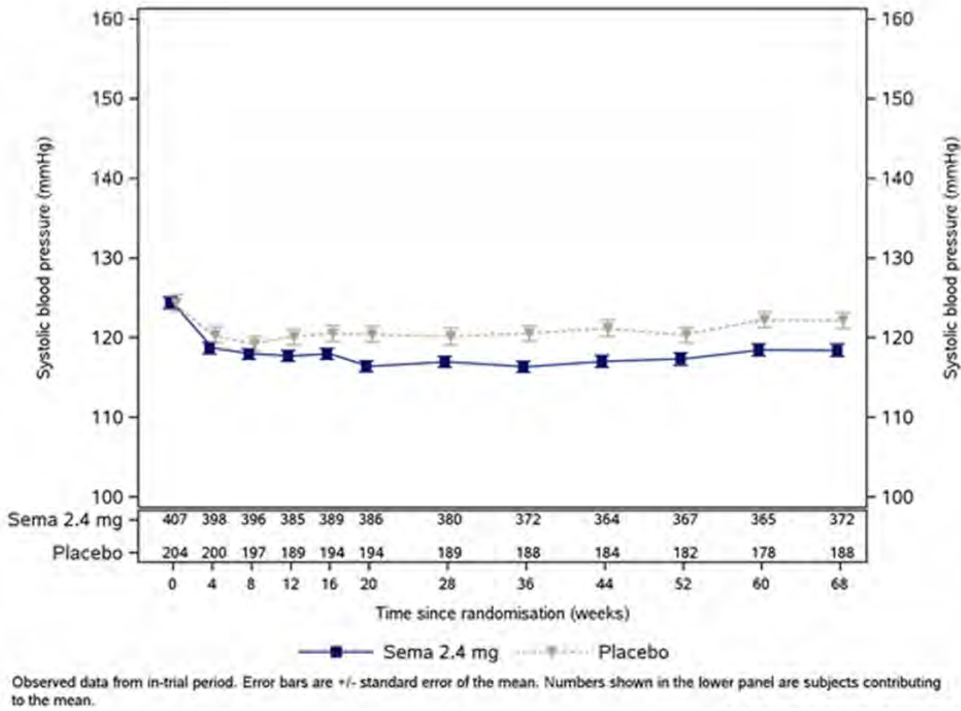


Source: Study 4375 CSR, Figure 11-10

- At baseline, mean systolic blood pressure was 124 mmHg. Mean changes in systolic blood pressure were -5.55 mmHg for semaglutide 2.4 mg and -1.62 mmHg for placebo, for an ETD of -3.94 mmHg (95% CI -6.36, -1.52), p=0.0014.

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

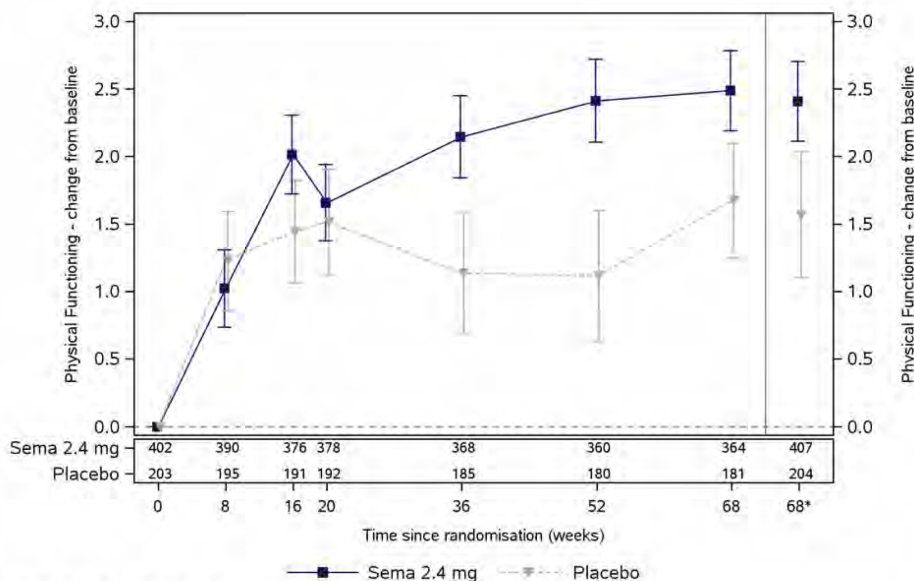
Figure 28: Mean Systolic Blood Pressure by Week, Trial 4375



Source: Study 4375 CSR, Figure 11-13

- At baseline, mean SF-36 physical functioning score was 51.9. Mean changes in SF-36 physical functioning scores were +2.41 for semaglutide 2.4 mg and +1.57 for placebo, for an ETD of +0.84 (95% CI -0.23, +1.92), p=0.1249.

Figure 29: Mean Change in SF-36 Physical Functioning from Baseline by Week, Trial 4375



SF-36: Short Form 36 v2.0 acute.
 Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the confirmatory secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.
 SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Source: Study 4375 CSR, Figure 14.2.99

Reviewer comment: The lack of statistical significance is noted here and could be due to the increased physical activity implemented in both study groups as part of the intensive lifestyle program.

Dose/Dose Response

There was only 1 dose tested in this trial (2.4 mg/week). See the discussion under treatment compliance for information regarding dosing during the trial.

Durability of Response

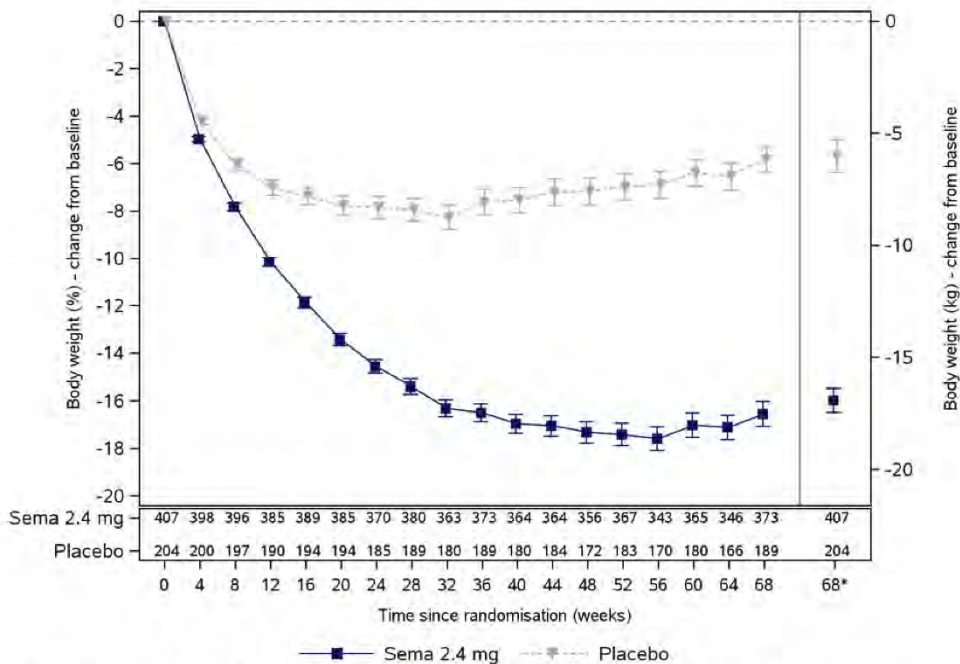
Figure 9 presents percent weight change by week; separation of the weight curves is apparent by week 8. Plateau in the curve in the semaglutide arm occurs around week 56, with a slight increase in weight change after that time. Plateau occurs in the placebo group around week 32.

As noted under discussion of the protocol amendments, the to-be-marketed concentration (3.2 mg/mL) and volume (0.75 mL) was administered for the last 8 weeks of the trial, rather than the concentration (3.0 mg/mL) and volume (0.80 mL) used in the first 46 weeks of the maintenance period of this trial (and the maintenance period of the other phase 3 trials).

Reviewer comment: Any conclusion about difference in the semaglutide weight loss over this

trial period due to change in formulation would be speculative. There is a slight increase in mean weight in the same period in the placebo group.

Figure 30: Percent Body Weight Change from Baseline by Week, Trial 4375



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4375 CSR, Figure 14.2.8

Persistence of Effect

Persistence of effect was not tested in this trial.

Additional Analyses Conducted on the Individual Trial

An evaluation of percent body weight change from baseline to week 8 (the end of the LCD period) was conducted as a supportive analysis. Weight change from baseline to week 8 was -7.78% in the semaglutide 2.4 mg group and -6.05% in the placebo group, for an ETD of -1.73% (95% CI -2.29, -1.16).

The differences (or percent differences) in changes in DBP, HbA1c, Total-C, LDL-C, and triglycerides were nominally significantly different for semaglutide versus placebo (favoring semaglutide).

Table 33: Selected Supportive Secondary Endpoints, Trial 4375

	Semaglutide		Placebo		Semaglutide minus Placebo (95% CI ^a)
	Baseline	Change from Baseline	Baseline	Change from Baseline	
DBP (mmHg)	80	-3.01	81	-0.77	-2.24 (-3.90, -0.58)
HbA1c (%)	5.7	-0.51	5.8	-0.27	-0.24 (-0.29, -0.19)
	Baseline	% Change from Baseline	Baseline	% Change from Baseline	Relative Difference of Semaglutide to Placebo (95% CI ^a)
Total-C (mg/dL)	185.4	-3.85	188.7	+2.12	-5.85 (-8.45, -3.17)
LDL-C (mg/dL)	107.74	-4.73	111.79	+2.59	-7.14 (-10.93, -3.18)
HDL-C (mg/dL)	51.6	+6.53	50.9	+4.99	+1.46 (-1.84, +4.88)
Triglycerides (mg/dL)	107.91	-22.46	110.90	-6.54	-17.03 (-22.83, -10.79)

^a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error

Source: Study 4375 CSR, Tables 14.2.64, 14.2.67, 14.2.83, 14.2.86, 14.2.87, ISE Tables 6.3.127, 6.3.128, 6.3.129, 6.3.132

6.4. NN9536-4376 (STEP 4): Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during run-in period

6.4.1. Study Design

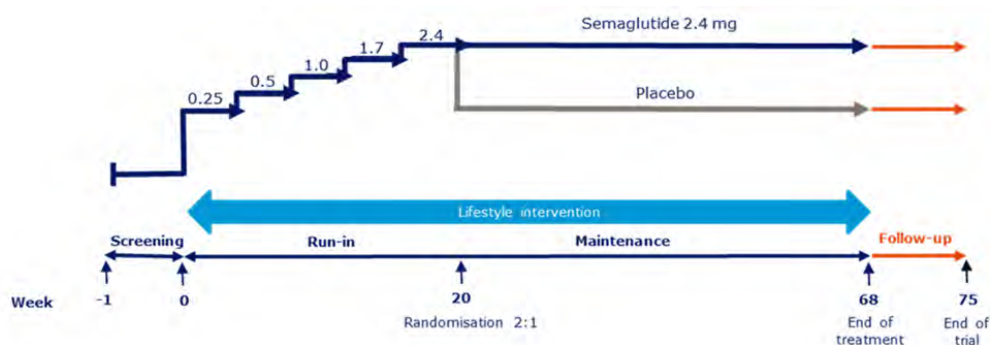
Overview and Objective

Trial 4376 was designed to compare the effect of semaglutide 2.4 mg versus placebo as an adjunct to a reduced calorie diet and increased physical activity on body weight in subjects with overweight or obesity who have reached a target dose of semaglutide in a 20-week run-in period (i.e., to evaluate weight change from weeks 20 to 68). Secondary objectives were to assess the effect of semaglutide 2.4 mg versus placebo on cardiovascular risk factors, clinical outcome assessments, and glucose metabolism. An additional efficacy-related secondary objective was to investigate weight change in semaglutide versus placebo over the 68 week-period (i.e., weight change from weeks 0 to 68).

Trial Design

This was a multinational, two-armed, multi-center, randomized, double-blind, placebo-controlled, multiple-dose withdrawal trial consisting of a screening period of approximately 1 week, a 20-week run-in period (including 16 weeks of dose escalation), a 48-week period on maintenance dose, and a 7-week off-drug follow-up period. Subjects were randomized after the run-in period at week 20.

Figure 31: Trial 4376 Design



Source: Study 4376 CSR, Figure 9-1

Subjects in the trial were at least 18 years of age, with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with the presence of at least 1 of the following weight-related co-morbidities: hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease. Subjects were excluded with type 1 or type 2 diabetes, HbA1c $\geq 6.5\%$, or body weight change > 5 kg within 90 days before

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

screening. In order to enter the run-in period, subjects must have had a PHQ-9 score < 15 and no suicidal behavior or ideation between screening and randomization.

In order to be randomized, subjects must have attended the week 20 randomization visit, escalated to the target dose after 16 weeks +/- 3 days since week 0, and achieved the target dose at the week 20 randomization visit. Subjects not fulfilling all randomization criteria were considered run-in failures and were to attend the end-of-trial visit 7 weeks +/- 5 days after their scheduled week 20 visit.

Study Endpoints

The primary endpoint was:

- Percent change in body weight from baseline (week 20) to week 68

Confirmatory secondary endpoints were:

- Waist circumference change from baseline (week 20) to week 68
- Systolic blood pressure change from baseline (week 20) to week 68
- SF-36 Physical Functioning score change from baseline (week 20) to week 68

Statistical Analysis Plan

The primary estimand quantified the treatment effect of semaglutide in all randomized subjects regardless of adherence to treatment and regardless of initiation of other anti-obesity therapies. One set of estimands were defined for endpoints addressing effects from baseline (week 20) to week 68 and another set of estimands for endpoints addressing effects from the start of the run-in period (week 0) to week 68.

A total of 900 subjects were planned for entry into the run-in period to achieve approximately 750 randomized subjects. Given the anticipated number of 750 randomized subjects (500 to semaglutide and 250 to placebo), the power calculations were as follows:

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 34: Assumptions, Marginal Power, and Effective Power for Each Endpoint in the Hierarchical Testing Procedure Given an Anticipated Number of 600 Subjects, Trial 4376

Order	Endpoint	Assumed mean ($\pm$ SD) for completers		Expected mean ($\pm$ SD) Semaglutide 2.4 mg	Expected difference	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight change	-4 ($\pm$ 10)	+5 ($\pm$ 10)	-3.7 ($\pm$ 11)	8.7 %-points	> 99	> 99
2	WC change (cm)	-3 ($\pm$ 10)	+3 ($\pm$ 10)	-2.8 ($\pm$ 11)	5.8 cm	> 99	> 99
3	sBP change (mmHg)	-3.1 ($\pm$ 13)	+1 ($\pm$ 13)	-3 ($\pm$ 14)	4 mmHg	95	95
4	SF-36 PF score change	+6 ($\pm$ 10)	+2 ($\pm$ 10)	+5.9 ($\pm$ 11)	3.9 score-points	> 99	95

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning

All tests in the hierarchy are based on the primary estimand

Source: Study 4376 SAP, Table 2-2

Protocol Amendments

There were 2 global amendments:

- Amendment 2, dated 21 Dec 2017:
 - Removed criteria for discontinuation of trial treatment for subjects included in the trial in violation of eligibility criteria if considered safe to continue
 - Risks associated with semaglutide was removed from the protocol and instead referred to the IB
- Amendment 3, dated 06 Jun 2018:
 - Confirmatory, supportive secondary and exploratory endpoints related to WRSSM were updated. Based on new data from recently reported trials, the WRSSM was shown to have substantial ceiling effects and low responsiveness within the target population. The measure was therefore considered unlikely to be able to detect a treatment benefit.

6.4.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice, and FDA 21 CFR 312.120. The FDA 21 CFR, parts 312, 50, and 56 were followed.

Financial Disclosure

See Section 13.2.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Subject Disposition

A total of 902 subjects were enrolled in the run-in period. Of these, 99 (11%) were withdrawn before randomization. During the randomized period, 535 subjects received semaglutide 2.4 mg and 268 received placebo. A full description of disposition is as follows:

Table 35: Subject Disposition, Study 4376

	Semaglutide 2.4 mg	Placebo
Run-in	N=902	
Trial product permanently discontinued before randomization	99 (11.0)	
Adverse event	48 (5.3)	
Protocol violation (intention of becoming pregnant)	1 (0.1)	
Pregnancy	1 (0.1)	
Run-in failure	19 (2.1)	
Safety concern as judged by investigator	2 (0.2)	
Withdrawal of consent	11 (1.2)	
Lost to follow-up	8 (0.9)	
Other	9 (1.0)	

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

	Semaglutide 2.4 mg	Placebo
Randomization	N=535	N=268
Exposed after randomization	534 (99.8)	268 (100)
On-treatment at week 68 (treatment completion)	504 (94.2)	237 (88.4)
After at least 1 temporary interruption	31 (5.8)	15 (5.6)
Trial product permanently discontinued	31 (5.8)	31 (11.6)
Adverse event	13 (2.4)	6 (2.2)
Protocol violation (intention of becoming pregnant)	1 (0.2)	0
Pregnancy	2 (0.4)	0
Withdrawal of consent	1 (0.2)	1 (0.4)
Lost to follow-up	2 (0.4)	1 (0.4)
Other	12 (2.2)	23 (8.6)
Attended end-of-trial visit (trial completion)	527 (98.5)	260 (97.0)
Attended end-of-trial visit and end-of-treatment visit without permanent discontinuation of trial product	503 (94.0)	237 (88.4)
Withdrawn from trial	8 (1.5)	8 (3.0)
Withdrawal by subject	2 (0.4)	4 (1.5)
Lost to follow-up	5 (0.9)	3 (1.1)
Death	1 (0.2)	1 (0.4)
Permanent discontinuation is when a subject stopped taking trial product and did not resume treatment and is therefore not considered as 'on-treatment' at end of treatment period (week 68).		
Temporary interruption is when a subject missed at least 2 consecutive doses of trial product and resumed treatment before end of treatment period (week 68).		

Source: Study 4376 CSR, Tables 10-1 and 10-2

Protocol Violations/Deviations

There were no important trial-level PDs.

There was 1 important country-level PD (South Africa): The “Barriers and Motivations” questionnaire at screening had not been completed according to the protocol requirement. When the PD was discovered, the affected subjects subsequently completed the questionnaire and no concerns were noted by the investigators.

The 25 important site-level PDs and 208 important subject-level PDs are summarized in the table below.

Table 36: Summary of Important Site- and Subject-Level Protocol Deviations, Trial 4376

Protocol deviation category	Site-level PDs (n)	Subject-level PDs (n)			Total subject-level PDs (n)	Total site and subject-level PDs (n)
		Run-in failures (n)	Semaglutide 2.4 mg (n)	Placebo (n)		
Total	25	24	115	69	208	233
Informed consent	1	2	2	2	6	7
Inclusion/exclusion criteria ^a	0	6	6	7	19	19
Treatment administration	2	0	6	2	8	10
Trial procedures/assessments	19	16	64	36	116	135
Concomitant medication	0	0	0	0	0	0
Subject visit schedule	1	0	30	19	49	50
SAE notification/safety procedures	2	0	6	3	9	11
Privacy and data protection	0	0	1	0	1	1

n: number of PDs; PD: protocol deviation

^aalso includes run-in criteria and randomisation criteria

Source: Study 4376 CSR, Table 10-5

Reviewer comment: I reviewed the protocol deviations and do not believe they significantly impacted the safety of the trial subjects or the interpretation of the study results. The applicant appropriately addressed important deviations when found. See the discussion of protocol deviations for trial 4373 for additional information.

Regarding the impact of the COVID-19 pandemic, almost all subjects had completed their last visits at the time of the pandemic. The main trial procedures affected by COVID-19 were as follows:

- Source data verification was abolished for the last part of the trial (as of 23 March 2020). According to the applicant, all data were still entered into the electronic data capture system and checked for completeness, as well as data cleaning and casebook sign-off was ensured.
- 13 subjects had their follow-up visits (week 75) converted to phone visits.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Demographic Characteristics

At the start of the run-in period, the mean age was 46 years and 79.5% of subjects were female.

Table 37: Demographic Characteristics at Start of Run-In (Week 0), Trial 4376

	Semaglutide 2.4 mg run-in N=902
Sex	
Male	185 (20.5)
Female	717 (79.5)
Age	
Mean years (SD)	46 (12)
Median (years)	46
Min, max (years)	18, 79
Age Group	
18-<65	844 (93.6)
65-<75	52 (5.8)
75-<85	6 (0.7)
≥85	0
Race	
White	751 (83.3)
Black or African American	123 (13.6)
Asian	19 (2.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)
American Indian or Alaska Native	0
Other	8 (0.9)
Ethnic origin	
Not Hispanic or Latino	832 (92.2)
Hispanic or Latino	70 (7.8)
Country	
United States	381 (42.2)
Rest of World	521 (57.8)

Source: Study 4376 CSR, Tables 14.1.4 and 14.1.6

A total of 803 subjects were randomized. Of these, 79.0% were female, and mean age was 46 years. A total of 83.7% were White, 13.0% were Black or African American, 7.8% were Hispanic or Latino, and 38.9% resided in the U.S.

Table 38: Demographic Characteristics of the Primary Efficacy Analysis (Randomized Population), Trial 4376

	Semaglutide N=535	Placebo N=268
Sex		
Male	106 (19.8)	63 (23.5)
Female	429 (80.2)	205 (76.5)
Age		
Mean years (SD)	47 (12)	46 (12)
Median (years)	46	46
Min, max (years)	18, 77	20, 78
Age Group		
18 - < 65 years	503 (94.0)	252 (94.0)
65 - < 75 years	29 (5.4)	15 (5.6)
75 - < 85 years	3 (0.6)	1 (0.4)
≥ 85 years		
Race		
White	446 (83.4)	226 (84.3)
Black or African American	69 (12.9)	35 (13.1)
Asian	15 (2.8)	4 (1.5)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	5 (0.9)	3 (1.1)
Ethnicity		
Hispanic or Latino	42 (7.9)	21 (7.8)
Not Hispanic or Latino	493 (92.1)	247 (92.2)

Source: Study 4376 CSR, Tables 10-3 and 10-4

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

At the start of the run-in period, mean BMI was 38.3 kg/m², mean body weight was 106.8 kg, and mean waist circumference was 115.1 cm.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 39: Baseline Characteristics, Run-In Period, Trial 4376

	Semaglutide 2.4 mg run-in N=902
Body weight	
Mean kg (SD)	106.8 (23.1)
Median (kg)	102.1
Min, max (kg)	63.1, 252.1
BMI	
Mean kg/m ² (SD)	38.3 (7.0)
Median (kg/m ²)	36.7
Min, max (kg/m ²)	27.4, 75.9
Waist circumference	
Mean cm (SD)	115.1 (15.6)
Median (cm)	112.5
Min, max (cm)	79.0, 195.0
HbA1c	
Mean % (SD)	5.7 (0.3)
Median (%)	5.7
Min, max (%)	4.5, 7.1
Fasting plasma glucose	
Mean mg/dL (SD)	96.8 (11.2)
Median (mg/dL)	95.7
Min, max (mg/dL)	62.9, 163.8

Source: Study 4376 CSR, Table 14.1.6

At randomization, mean body weight was 96.1 kg, mean BMI was 34.4 kg/m², mean waist circumference was 105.3 cm, and mean HbA1c was 5.4%.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 40: Baseline Characteristics, Randomized Period, Trial 4376

	Semaglutide N=535	Placebo N=268
Body weight		
Mean kg (SD)	96.5 (22.5)	95.4 (22.7)
Median (kg)	92.7	91.0
Min, max (kg)	57.6, 200.1	51.9, 193.7
BMI		
Mean kg/m ² (SD)	34.5 (6.9)	34.1 (7.1)
Median (kg/m ²)	33.2	32.4
Min, max (kg/m ²)	22.4, 72.6	22.7, 67.4
Waist circumference		
Mean cm (SD)	105.5 (15.9)	104.7 (16.9)
Median (cm)	103.0	103.1
Min, max (cm)	73.0, 171.0	71.1, 181.0
HbA1c		
Mean % (SD)	5.4 (0.3)	5.4 (0.3)
Median (%)	5.4	5.4
Min, max (%)	4.5, 6.2	4.5, 6.1
Fasting plasma glucose		
Mean mg/dL (SD)	87.9 (7.7)	86.9 (7.6)
Median (mg/dL)	87.8	86.7
Min, max (mg/dL)	54.1, 119.3	66.3, 130.8

Source: Study 4376, Table 14.1.5

Table 11 presents a summary of past and concomitant illness of subjects at screening by randomized group.

Table 41: Medical History and Concomitant Illness at Screening, Selected Events, Randomized Groups, Trial 4376

	Semaglutide N=535	Placebo N=268
Anemias nonhemolytic and marrow depression	18 (3.4)	8 (3.0)
Cardiac arrhythmias	25 (4.7)	4 (1.5)
Coronary artery disorders	5 (0.9)	1 (0.4)
Thyroid gland disorders	86 (16.1)	37 (13.8)
Gastrointestinal motility and defecation conditions	84 (15.7)	43 (16.0)
Benign neoplasms gastrointestinal	12 (2.2)	7 (2.6)
Gastrointestinal inflammatory conditions	20 (3.7)	9 (3.4)
Nonalcoholic fatty liver disease	17 (3.2)	8 (3.0)
Nonalcoholic steatohepatitis	3 (0.6)	3 (1.1)
Gallbladder disorders	45 (8.4)	16 (6.0)
Lipid metabolism disorders	175 (32.7)	87 (32.5)
Glucose metabolism disorders	82 (15.3)	29 (10.8)
Neoplasms benign, malignant and unspecified	87 (16.3)	39 (14.6)
Psychiatric disorders	163 (30.5)	82 (30.6)
Sleep apnea syndrome	61 (11.4)	33 (12.3)

Source: Study 4376 CSR, Table 14.1.15

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

If subjects did not tolerate the maintenance dose of 2.4 mg, the subject could stay at a lower dose of 1.7 mg. Of the treatment completers, 89.5% of subjects randomized to semaglutide were reported to be on the maintenance dose of 2.4 mg at the last dosing, 4.0% reported to be on the 1.7 mg dose, and 2.8% reported to be on doses lower than 1.7 mg (which deviated from the protocol). A total of 94.5% of subjects randomized to placebo reported to be on an equivalent volume to the 2.4 mg dose.

Some common medications ongoing at the time of screening by the subjects who were ultimately randomized included: sex hormones, including estrogens and progestins (26.0%), agents acting on the renin-angiotensin system (19.9%), anti-inflammatories (15.8%), diuretics

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

(14.2%), antacids (13.1%), antihistamines (12.0%), statins (11.7%), thyroid hormones (10.3%), beta-blocking agents (8.1%), and SSRIs (7.6%).²⁸

Most of these classes were used at similar proportions at the time of randomization, except antacids, which increased (19.3%).²⁹

During the randomized portion of the trial, certain classes of drugs were initiated differentially in the semaglutide versus placebo groups (e.g., gastrointestinal drug classes were more frequently used in the semaglutide group and psychoanaleptics were used more frequently in the placebo group):³⁰

- Psychoanaleptics (including SSRIs and other antidepressants): semaglutide 4.1% vs. placebo 7.8%
- Drugs for functional gastrointestinal disorders: 4.9% vs. 3.7%
- Antidiarrheals: 5.2% vs. 3.0%
- Drugs for constipation: 4.1% vs. 2.2%
- Antiemetics: 3.2% vs. 1.1%

One subject randomized to placebo initiated anti-obesity medication (liraglutide) during the randomized period.

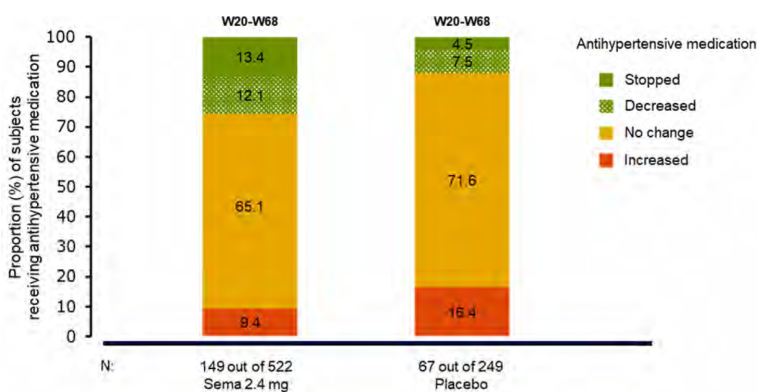
Change in antihypertensive medication during the randomized period of the trial was an exploratory endpoint. Between baseline (week 20) and week 68, 28.5% in the semaglutide group and 26.9% in the placebo group received antihypertensive medication. Changes (decreased or stopped, increased) are visually shown in Figure 32.

²⁸ Source: Study 4376 CSR, Table 14.1.23

²⁹ Source: Study 4376 CSR, Table 14.1.24

³⁰ Source: Study 4376 CSR, Table 14.1.25

Figure 32: Antihypertensive Medication During Randomized Portion of Trial 4376



N: Number of subjects receiving antihypertensive medication between baseline (week 20) and week 68 out of the total treatment group; sema: semaglutide

%: Percentages are based on subjects with an observation at the visit. Observed data from the in-trial period.

Source: Study 4376 CSR, Figure 11-11

Changes in lipid-lowering medication were also evaluated as an exploratory endpoint. Between baseline (week 20) and week 68, 13.4% of semaglutide-treated subjects and 14.5% of placebo-treated subjects received lipid-lowering medication. Those with no change during this period were 84.3% of semaglutide-treated subjects and 75.0% of placebo-treated subjects; those who stopped or decreased medication were 11.4% and 11.1%, respectively; and those who increased medication were 4.3% and 13.9%, respectively.

Efficacy Results – Primary Endpoint

Superiority of the primary endpoint – percent change in body weight from baseline (week 20) to week 68 – was confirmed. At the start of the run-in period, mean body weight for the 803 subjects who were ultimately randomized was 107.2 kg. The observed mean body weight decreased to 96.1 kg in the 20-week run-in period, for a change of -10.6%. Table 42 provides the results of the primary analysis from baseline (week 20) to week 68 in the randomized groups.

Table 42: Primary Endpoint: Percent Body Weight Change from Baseline (Week 20) at Week 68, Trial 4376

Treatment	N	Baseline (Week 20) Mean (SD)	Week 68 Mean (SD) In-trial	% Change from Baseline ANCOVA RD-MI
Semaglutide	535	96.5 (22.5)	89.0 (24.5)	-7.88
Placebo	268	95.4 (22.7)	100.6 (22.7)	+6.87
Semaglutide vs. Placebo		Between treatment difference (95% CI)		p value
		-14.75 (-16.00, -13.50)		<0.0001

Source: Study 4376 CSR, Tables 14.2.2 and 14.2.9

All sensitivity analyses were consistent with the primary analysis.

The sponsor also conducted supportive secondary endpoints related to weight. Given the novel design of this trial, these will be presented here to provide context to the primary endpoint.

Table 43 presents weight changes from the start of the run-in period (week 0) to week 68. Note that this randomized population (N=803) is a subgroup of the population enrolled at the start of the run-in period (N=902) and represents individuals who tolerated the dose-escalation period up to and including the target dose of semaglutide 2.4 mg.

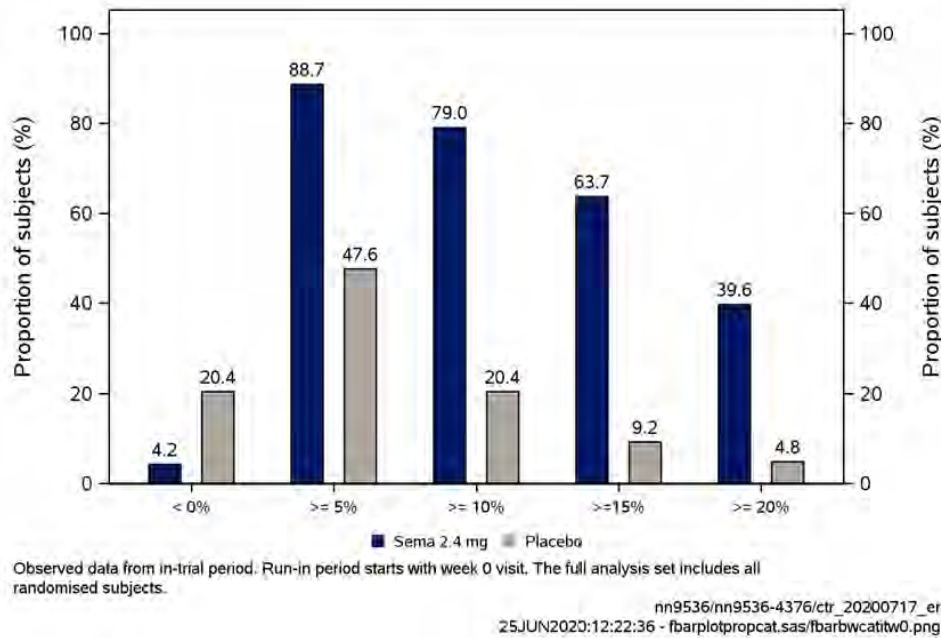
Table 43: Percent Body Weight Change from Start of Semaglutide Run-In (Week 0) to Week 68, Trial 4376

Treatment	N	Week 0 Mean (SD)	Week 68 Mean (SD) In-trial	% Change from Week 0 ANCOVA RD-MI
Semaglutide	535	107.2 (22.7)	89.0 (24.5)	-17.38
Placebo	268		100.6 (22.7)	-5.02
Semaglutide vs. Placebo		Between treatment difference (95% CI)		p value ^a
		-12.36 (-13.71, -11.02)		<0.0001
a p-value provided for descriptive purposes; endpoint not included in testing hierarchy to control for Type I error				

Source: Study 4376 CSR, Tables 14.2.2 and 14.2.15

Figure 33 illustrates the proportions of subjects with weight gain or categorical weight loss by treatment group from the start of run-in (week 0) to week 68; for all cut-offs, the proportions appeared to favor semaglutide (fewer subjects gained weight and more subjects lost weight by categorical cut-off on semaglutide versus placebo).

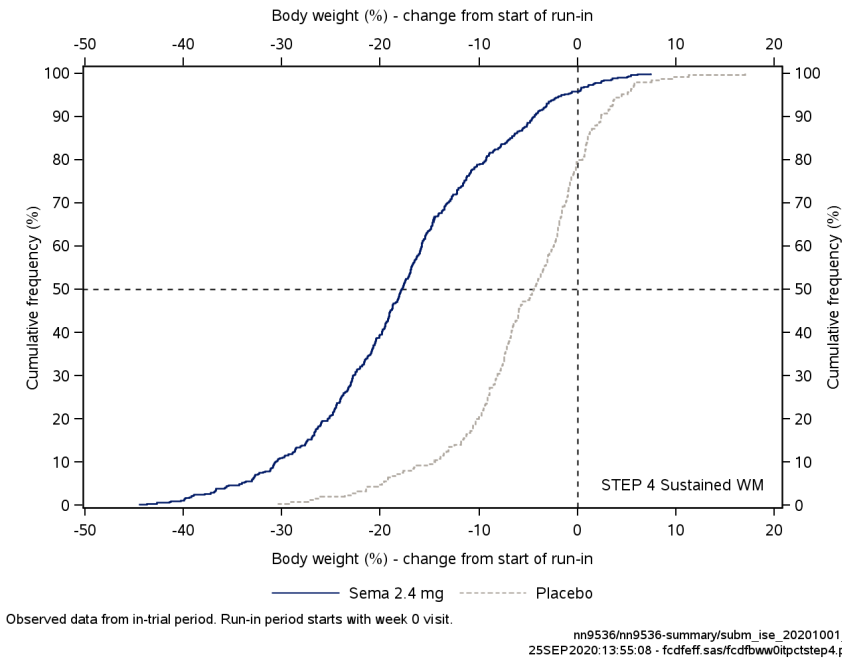
Figure 33: Proportions of Subjects with Weight Gain (<0%) or Categorical Weight Loss ($\geq 5\%$, 10%, 15%, 20%) Since Start of Run-In (Week 0) at Week 68, Trial 4376



Source: Study 4376 CSR, Figure 14.2.30

This is also shown in the cumulative distribution plot of percent body weight change from the start of run-in (week 0) to week 68, demonstrating a robust left-shift in the semaglutide versus placebo curve.

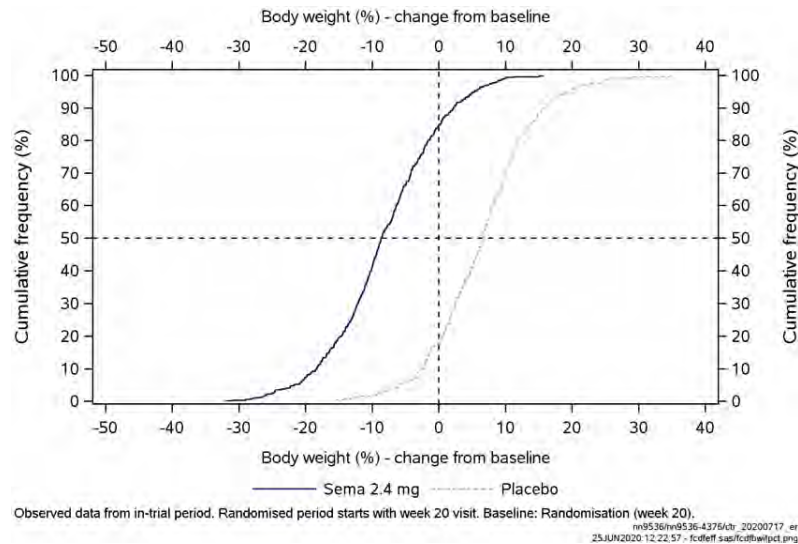
Figure 34: Percent Body Weight Change from Start of Run-In (Week 0) to Week 68, Cumulative Distribution Figure, Trial 4376, In-Trial



Source: ISE, Figure 6.3.143

From baseline (week 20) to week 68, 15.2% of subjects in the semaglutide group gained weight versus 82.4% of subjects in the placebo group, supporting the effectiveness of semaglutide in preventing weight gain after an initial 20-week treatment with semaglutide. The cumulative distribution plot for percent body weight change from baseline (week 20) to week 68 is shown in Figure 35, below.

Figure 35: Percent Body Weight Change from Baseline (Week 20) to Week 68, Cumulative Distribution Plot, Trial 4376, In-Trial



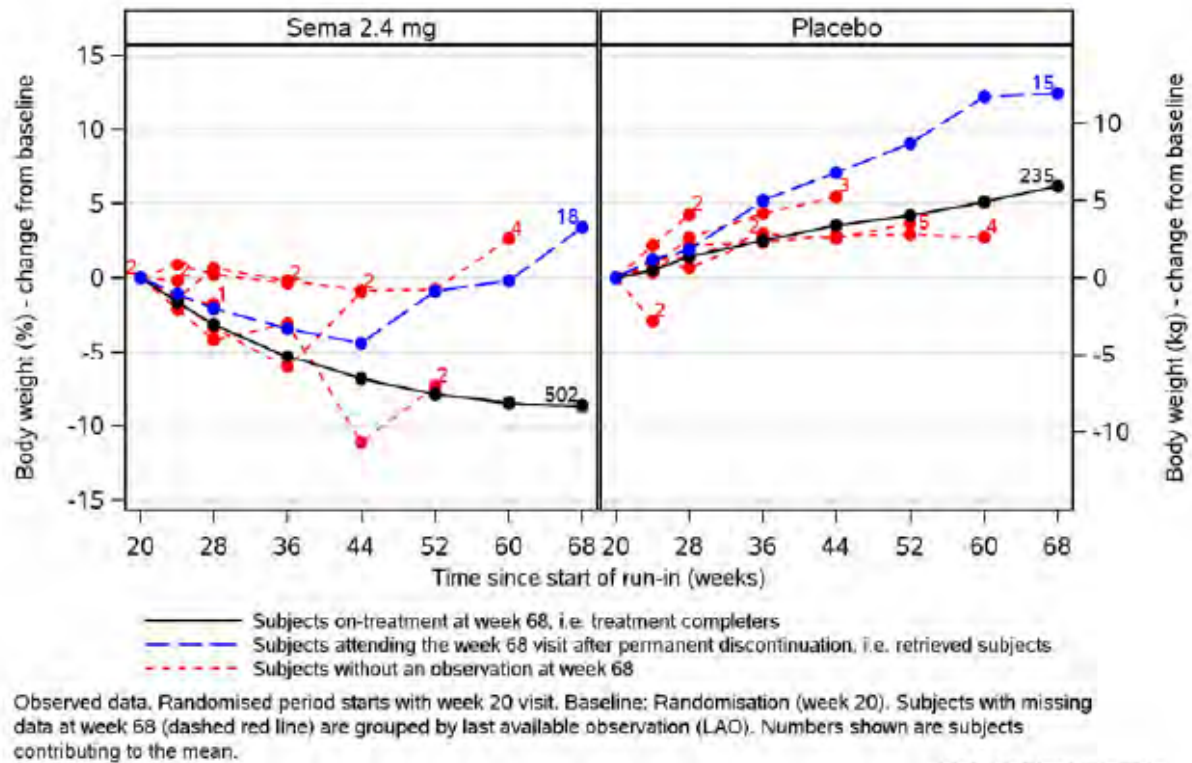
Source: Study 4376 CSR, Figure 14.2.5

Data Quality and Integrity

Data quality and integrity in this trial are very good. Subjects were encouraged to remain in the trial for data collection, even if trial product was permanently discontinued. A total of 98% of the randomized subjects completed the trial; 98.5% semaglutide and 97.0% placebo. As noted above, this was a select group of subjects who were randomized after an initial run-in period (i.e., could tolerate semaglutide 2.4 mg).

Missing data were evaluated graphically to detect patterns relevant for the interpretation of the primary analysis (Figure 36). Retrieved dropouts; i.e., subjects who discontinued treatment but returned for a week 68 assessment (blue lines), illustrate the differential in weight change as compared to those who remained on-treatment (black line), particularly in the semaglutide group.

Figure 36: Mean Body Weight Change from Baseline (Week 20) by Week, Missing Data Pattern, Trial 4376



Source: Study 4376 CSR, Figure 11-4

Reviewer comment: Given that the overall number of subjects with missing data that contributed to the primary analysis was very low, missing data are not likely to substantially impact the interpretation of the primary analysis.

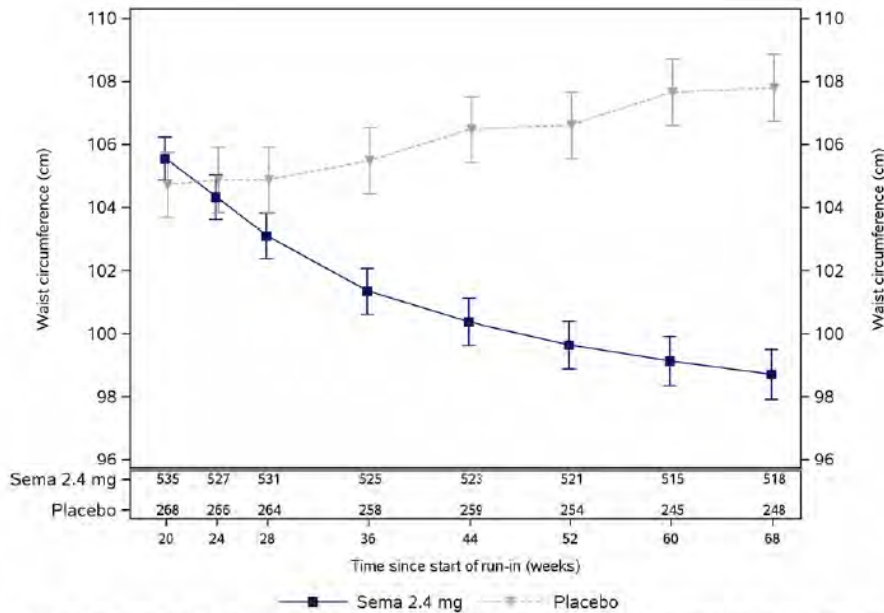
Efficacy Results – Secondary and other relevant endpoints

Superiority of semaglutide versus placebo was confirmed for all secondary confirmatory endpoints in the hierarchical testing procedure.

- At the start of the semaglutide run-in period (week 0), the mean waist circumference for the 803 subjects ultimately randomized was 115.3 cm. At baseline (week 20), mean waist circumference was 105.3 cm. Mean changes in waist circumference from week 20 at week 68 were -6.43 cm for semaglutide 2.4 mg and +3.31 cm for placebo, for an estimated treatment difference (ETD) of -9.74 cm (95% CI -10.94, -8.54), $p < 0.0001$.³¹

³¹ Source: Study 4376 CSR, Table 14.2.43

Figure 37: Mean Waist Circumference by Week, Randomized Period, Trial 4376



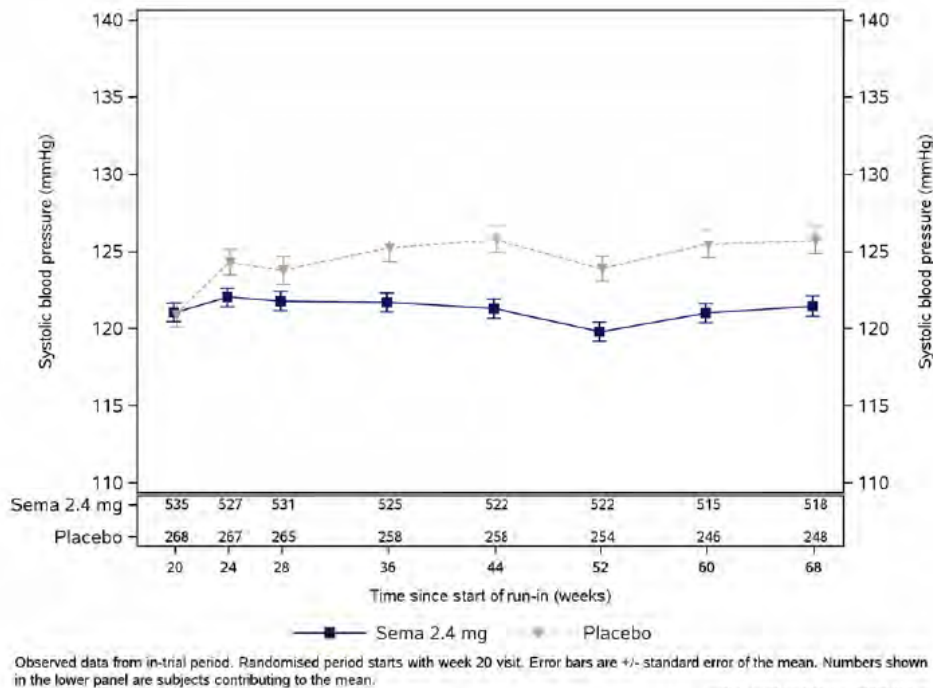
Observed data from in-trial period. Randomised period starts with week 20 visit. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.

Source: Study 4376 CSR, Figure 11-6

- At the start of the semaglutide run-in period (week 0), the mean SBP for the 803 subjects ultimately randomized was 127 mmHg. At baseline (week 20), mean SBP was 121 mmHg. Mean changes in SBP from week 20 at week 68 were +0.49 mmHg for semaglutide 2.4 mg and +4.42 mmHg for placebo, for an ETD of -3.92 mmHg (95% CI -5.82, -2.03), $p < 0.0001$.³²

³² Source: Study 4376 CSR, Table 14.2.67

Figure 38: Mean Systolic Blood Pressure by Week, Randomized Period, Trial 4376

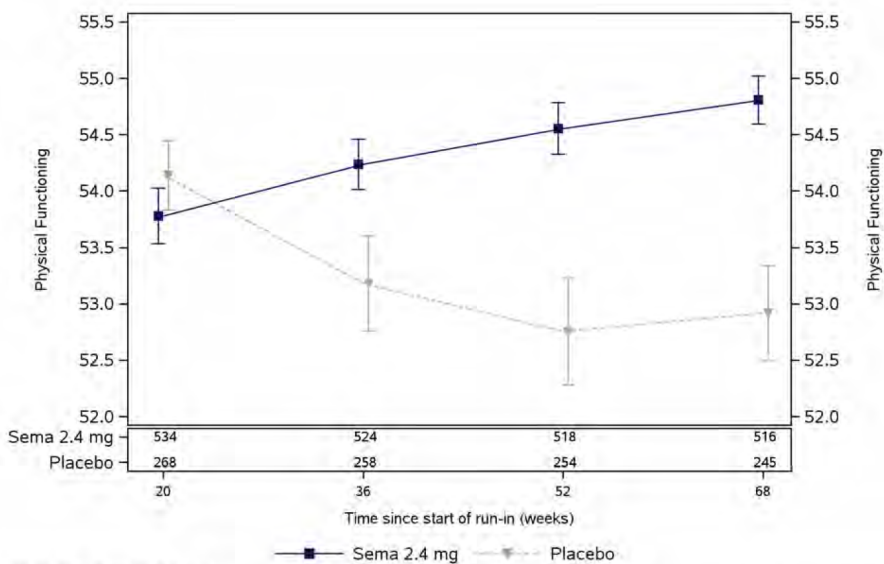


Source: Study 4376 CSR, Figure 11-9

- At the start of the semaglutide run-in period (week 0), the mean SF-36 physical functioning score for the 803 subjects ultimately randomized was 51.7. At baseline (week 20), mean SF-36 physical functioning score was 53.9. Mean changes in SF-36 physical functioning scores from week 20 at week 68 were +0.99 for semaglutide 2.4 mg and -1.46 for placebo, for an ETD of +2.45 (95% CI +1.59, +3.32), $p < 0.0001$.³³

³³ Source: Study 4376 CSR, Table 14.2.83

Figure 39: Mean SF-36 Physical Functioning by Week, Randomized Period, Trial 4376



SF-36: Short Form 36 v2.0 acute.
Observed data from in-trial period. Randomised period starts with week 20 visit. Error bars are +/- standard error of the mean. Numbers shown in the lower panel are subjects contributing to the mean.
SF-36 scores are norm based scores (NBS). NBS are scores transformed to a scale where the 2009 US general population has a mean of 50 and a standard deviation of 10.

Source: Study 4376 CSR, Figure 11-13

Reviewer comment: As discussed in other sections of this review, while the results based on the mean difference between groups were statistically significant for these instruments, the clinical significance of these results is uncertain. The applicant did not request that these results be included in labeling.

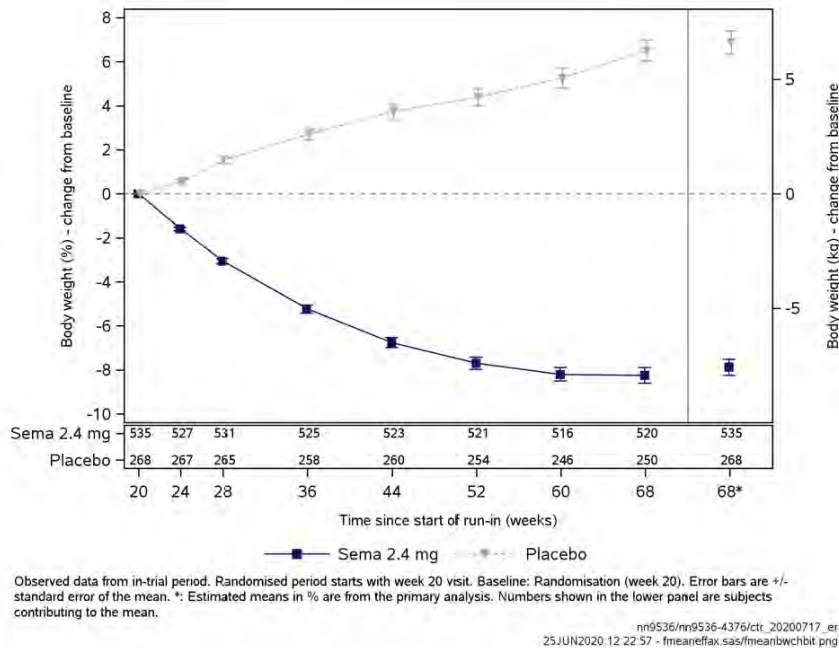
Dose/Dose Response

There was only 1 dose tested in this trial (2.4 mg/week). See the discussion under treatment compliance for information regarding dosing during the trial.

Durability of Response

After randomization, body weight decreased in the semaglutide 2.4 mg group until approximately week 60, after which time it stabilized. In the placebo arm, weight progressively increased from week 20 (Figure 40).

Figure 40: Mean Body Weight Change from Baseline (Week 20) by Week, Trial 4376



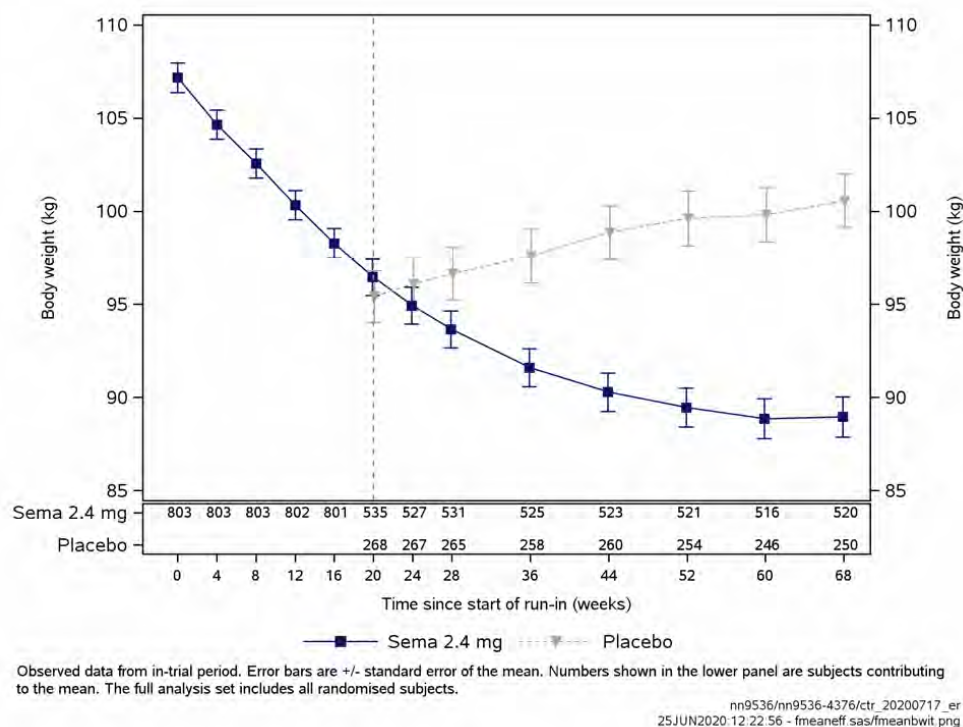
Source: Study 4376 CSR, Figure 14.2.8

Persistence of Effect

This trial, which employed a randomized withdrawal design, supports the assertion that there is *not* a persistence of weight loss effect after drug discontinuation. The odds of gaining any weight from baseline (week 20) at week 68 was 0.20 for the semaglutide group and 5.01 for the placebo group, for an estimated treatment odds ratio (semaglutide / placebo) of 0.04 (95% CI 0.03, 0.06).

Figure 9 presents body weight by week. During the run-in period, body weight decreased from a mean of 107.2 kg to 96.1 kg. After randomization, body weight further decreased in the semaglutide 2.4 mg group. In the placebo arm, weight progressively increased from week 20, and did not appear to have stabilized by the end of the trial.

Figure 41: Percent Body Weight by Week, Trial 4376



Source: Study 4375 CSR, Figure 14.2.3

Additional Analyses Conducted on the Individual Trial

Selected supportive secondary endpoints at week 0 and week 20 (i.e., at the beginning and end of the run-in period) for the randomized population were as follows:

- DBP: week 0 = 81 mmHg, week 20 = 78 mmHg
- HbA1c: week 0 = 5.7%, week 20 = 5.4%
- Total-C: week 0 = 193.1 mg/dL, week 20 = 175.6 mg/dL
- LDL-C: week 0 = 114.78 mg/dL, week 20 = 108.81 mg/dL
- HDL-C: week 0 = 49.6 mg/dL, week 20 = 44.2 mg/dL
- TG: week 0 = 121.47 mg/dL, week 20 = 97.13 mg/dL

Table 44 presents the changes in these secondary endpoints over the randomized period. No differences in change or percent change (semaglutide – placebo) were observed for DBP or HDL-C. The differences in change or percent change in HbA1c, Total-C, LDL-C, and triglycerides were nominally significantly different for semaglutide versus placebo (favoring semaglutide) during the randomized period.

Table 44: Selected Supportive Secondary Endpoints, Trial 4376

	Semaglutide		Placebo		Semaglutide minus Placebo (95% CI ^a)
	Baseline	Change from Baseline	Baseline	Change from Baseline	
DBP (mmHg)	78	+0.32	78	+0.87	-0.55 (-2.01, +0.92)
HbA1c (%)	5.4	-0.15	5.4	+0.09	-0.24 (-0.29, -0.19)
	Baseline	% Change from Baseline	Baseline	% Change from Baseline	Relative Difference of Semaglutide to Placebo (95% CI ^a)
Total-C (mg/dL)	175.9	+4.95	175.1	+11.45	-5.83 (-7.73, -3.90)
LDL-C (mg/dL)	108.68	+1.07	109.07	+7.58	-6.05 (-8.82, -3.20)
HDL-C (mg/dL)	44.5	+18.19	43.6	+17.83	+0.30 (-2.50, +3.18)
Triglycerides (mg/dL)	98.07	-5.60	95.28	+14.81	-17.78 (-24.06, -10.98)

^a 95% CIs are provided for descriptive purposes. The endpoint was not included in the testing procedure to control for Type I error

Source: Study 4375 CSR, Tables 14.2.70, 14.2.73, 14.2.51, 14.2.54, 14.2.74, ISE 6.3.133

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoint(s) in all phase 3 trials relate to percent change in body weight from baseline. This endpoint is accepted for confirming efficacy of weight management drugs, as a weight loss of 5 to 10% in individuals with obesity is associated with improved cardiometabolic health.²

In all trials, treatment with semaglutide 2.4 mg led to statistically and clinically significant weight loss versus placebo. Details of the weight changes in each trial are described fully in Section 6; estimated treatment differences using the primary analytic approach are summarized in Table 45.

Table 45: Percent Body Weight Change Primary Endpoint, Phase 3 Trials

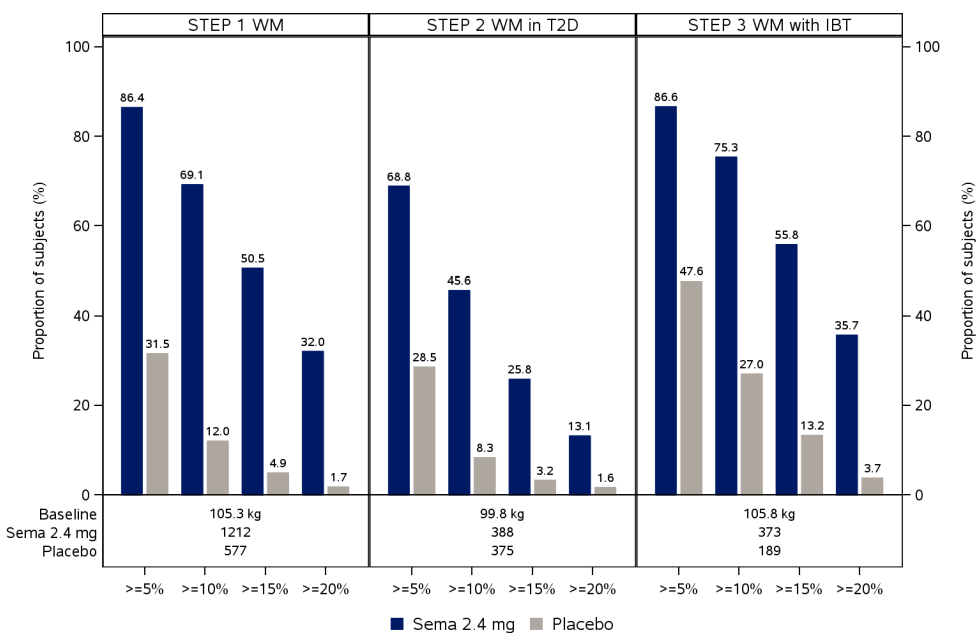
	Trial 4373		Trial 4374		Trial 4375		Trial 4376	
	Sema 2.4 N=1306	Pbo N=655	Sema 2.4 N=404	Pbo N=403	Sema 2.4 N=407	Pbo N=204	Sema 2.4 N=535	Pbo N=268
BL ^a mean weight (kg)	105.4	105.2	99.9	100.5	106.9	103.7	96.5	95.4
% weight change from BL ^a	-14.85	-2.41	-9.64	-3.42	-15.97	-5.70	-7.88	+6.87
Difference from placebo (95% CI)	-12.44* (-13.37, -11.51)		-6.21* (-7.28, -5.15)		-10.27* (-11.97, -8.57)		-14.75* (-16.00, -13.50)	

^a a BL=baseline; defined as week 0 for trials 4373, 4374, and 4375; defined as week 20 for trial 4376
* p<0.0001 compared to placebo

Source: Clinical Review, Table 12, Table 21, Table 32, Table 42; SCE, Figure 3-6

The proportion of subjects who achieved at least 5% weight loss was a co-primary endpoint in trials 4373, 4374, and 4375. In these trials, which differed in patient population and background (lifestyle) therapy, 68.8-86.6% of subjects on semaglutide 2.4 mg versus 28.5-47.6% on placebo achieved at least 5% body weight loss. Superiority was demonstrated, with statistically significant odds ratios (p<0.0001). In addition, secondary and exploratory endpoints of proportions with ≥ 10%, ≥ 15%, and ≥ 20% weight loss were evaluated, demonstrating or suggesting superiority of semaglutide versus placebo (Figure 42).

Figure 42: Proportions of Subjects Achieving Selected Categories of Weight Loss at Week 68, Trials 4373, 4374, and 4375



Observed data from in-trial period. Numbers shown in the lower panel are subjects with an observation at the visit.

nn9536/n9536-summary/summ_ise_20201001_er
25SEP2020.13:53:49 - fbarplotprop.sas/fbarbwcatit.png

Source: ISE, Figure 6.3.50

7.1.2. Secondary and Other Endpoints

Table 46 and Table 47 present the cardiometabolic endpoints typically included in weight management drug labeling (note that not all endpoints were included in the statistical testing hierarchy to control for type I error). Despite some study differences, the treatment differences are generally consistent across trials and support the clinical relevance of the weight loss observed with semaglutide in these clinical trials.

Table 46: Selected Secondary Endpoints, Phase 3 Trials

	Trial 4373		Trial 4374		Trial 4375		Trial 4376	
	Sema N=1306	Pbo N=655	Sema N=404	Pbo N=403	Sema N=407	Pbo N=204	Sema N=535	Pbo N=268
Waist circumference (cm)								
Baseline ^a	114.6	114.8	114.5	115.5	113.6	111.8	105.5	104.7
Change from Baseline ^a	-13.5	-4.1	-9.4	-4.5	-14.6	-6.3	-6.4	+3.3
Sema - Placebo	-9.4		-4.9		-8.3		-9.7	
Systolic blood pressure (mmHg)								
Baseline ^a	126	127	130	130	124	124	121	121
Change from Baseline ^a	-6.2	-1.1	-3.9	-0.5	-5.6	-1.6	+0.5	+4.4
Sema - Placebo	-5.1		-3.4		-3.9		-3.9	
Diastolic blood pressure (mmHg)								
Baseline ^a	80	80	80	80	80	81	78	78
Change from Baseline ^a	-2.8	-0.4	-1.6	-0.9	-3.0	-0.8	+0.3	+0.9
Sema - Placebo	-2.4		-0.7		-2.2		-0.6	
HbA1c (%)								
Baseline ^a	5.7	5.7	8.1	8.1	5.7	5.8	5.4	5.4
Change from Baseline ^a	-0.45	-0.15	-1.60	-0.37	-0.51	-0.27	-0.15	+0.09
Sema - Placebo	-0.29		-1.23		-0.24		-0.24	

^a BL=baseline; defined as week 0 for trials 4373, 4374, and 4375; defined as week 20 for trial 4376

Source: Study 4373 CSR, Tables 14.2.49, 14.2.54, 14.2.82, 14.2.87, 14.2.90, 14.2.93, 14.2.71, 14.2.74; Study 4374 CSR, Tables 14.2.49, 14.2.54, 14.2.87, 14.2.92, 14.2.95, 14.2.98, 14.2.62, 14.2.67; Study 4375 CSR, Tables 14.2.51, 14.2.56, 14.2.75, 14.2.80, 14.2.83, 14.2.86, 14.2.64, 14.2.67; Study 4376 CSR, Tables 14.2.38, 14.2.43, 14.2.62, 14.2.67, 14.2.70, 14.2.73, 14.2.51, 14.2.54

Table 47: Lipids, Phase 3 Trials

	Trial 4373		Trial 4374		Trial 4375		Trial 4376	
	Sema N=1306	Pbo N=655	Sema N=404	Pbo N=403	Sema N=407	Pbo N=204	Sema N=535	Pbo N=268
Total-C (mg/dL)								
Baseline ^a	189.6	192.1	170.8	170.8	185.4	188.7	175.9	175.1
% Change from Baseline ^a	-3.25	+0.06	-1.36	-0.50	-3.85	+2.12	+4.95	+11.45
Sema - Placebo	-3.31		-0.86		-5.85		-5.83	
LDL-C (mg/dL)								
Baseline ^a	110.29	112.45	90.10	90.07	107.74	111.79	108.68	109.07
% Change from Baseline ^a	-2.53	+1.27	+0.48	+0.12	-4.73	+2.59	+1.07	+7.58
Sema - Placebo	-3.76		+0.36		-7.14		-6.05	
HDL-C (mg/dL)								
Baseline ^a	49.4	49.5	44.7	43.8	51.6	50.9	44.5	43.6
% Change from Baseline ^a	+5.24	+1.42	+6.86	+4.07	+6.53	+4.99	+18.19	+17.83
Sema - Placebo	+3.77		+2.69		+1.46		+0.30	
TG (mg/dL)								
Baseline ^a	126.21	127.94	154.90	159.48	107.91	110.90	98.07	95.28
% Change from Baseline ^a	-21.89	-7.26	-22.01	-9.44	-22.46	-6.54	-5.60	+14.81
Sema - Placebo	-15.78		-13.88		-17.03		-17.78	

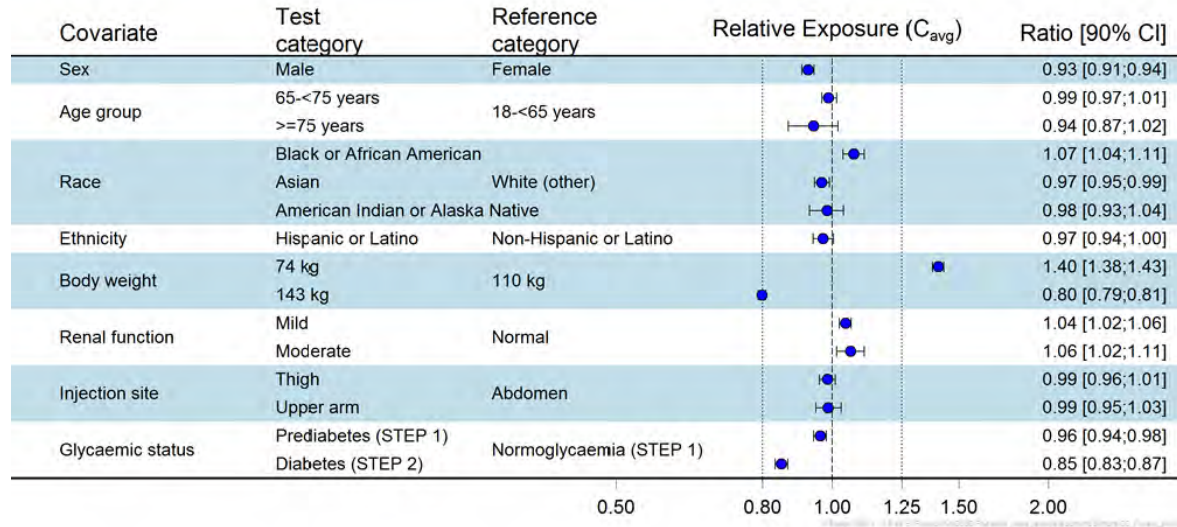
^a a BL=baseline; defined as week 0 for trials 4373, 4374, and 4375; defined as week 20 for trial 4376

Source: Clinical Review, Table 14, Table 23, Table 33, Table 44

7.1.3. Subpopulations

The applicant presented covariate effects for semaglutide exposure (C_{avg}) as evaluated in a population PK analysis from trials 4373 and 4374. Data were steady-state dose-normalized relative to a reference subject profile (non-Hispanic or Latino, normoglycemic (trial 4373), white, female, aged 18-<65 years, body weight 110 kg, normal renal function, and abdominal injection site). As the applicant notes, the most important covariate on semaglutide exposure is body weight, with lower exposures at higher body weights and vice versa. This has been seen with other semaglutide trials as well as liraglutide trials. In addition, lower exposure was observed with T2D versus normoglycemia. The estimated exposure ratio was within the accepted bioequivalence interval, however.

Figure 43: Forest Plot of Covariate Effects for Semaglutide Exposure, Trials 4373 and 4374



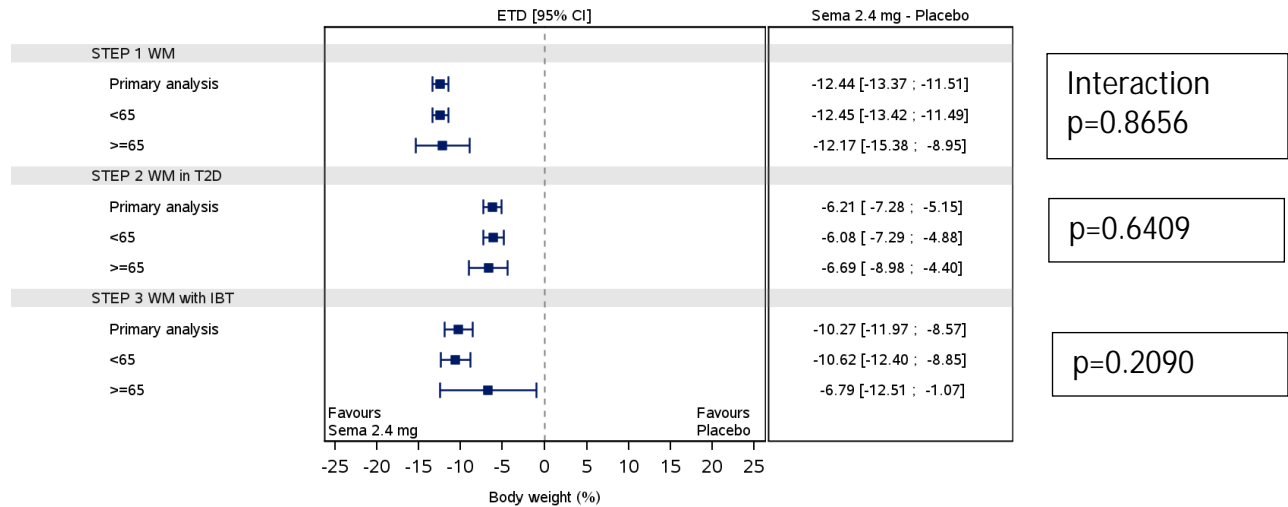
Source: SCE, Figure 3-25

A summary of key subgroups with interaction p-values are presented for the primary endpoint of percent change in body weight.

Age

No subgroup interactions were observed by age group (Figure 44 and Figure 45).

Figure 44: Percent Body Weight Change by Age Group, Trials 4373, 4374, and 4375

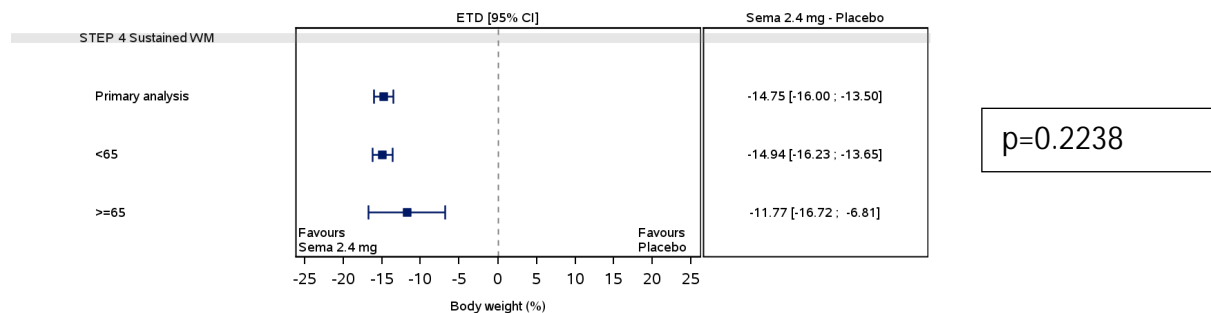


FAS: Full analysis set.
 Analysis of data from in-trial period.

nn9536/mn9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:05 - fforest.sas/forestbwages13.png

STEP 1=trial 4373, STEP 2=trial 4374, STEP 3=trial 4375
 Source: ISE, Figure 6.4.90, Tables 6.4.37, 6.4.38, 6.4.39

Figure 45: Percent Body Weight Change by Age Group, Trial 4376



FAS: Full analysis set.
 Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

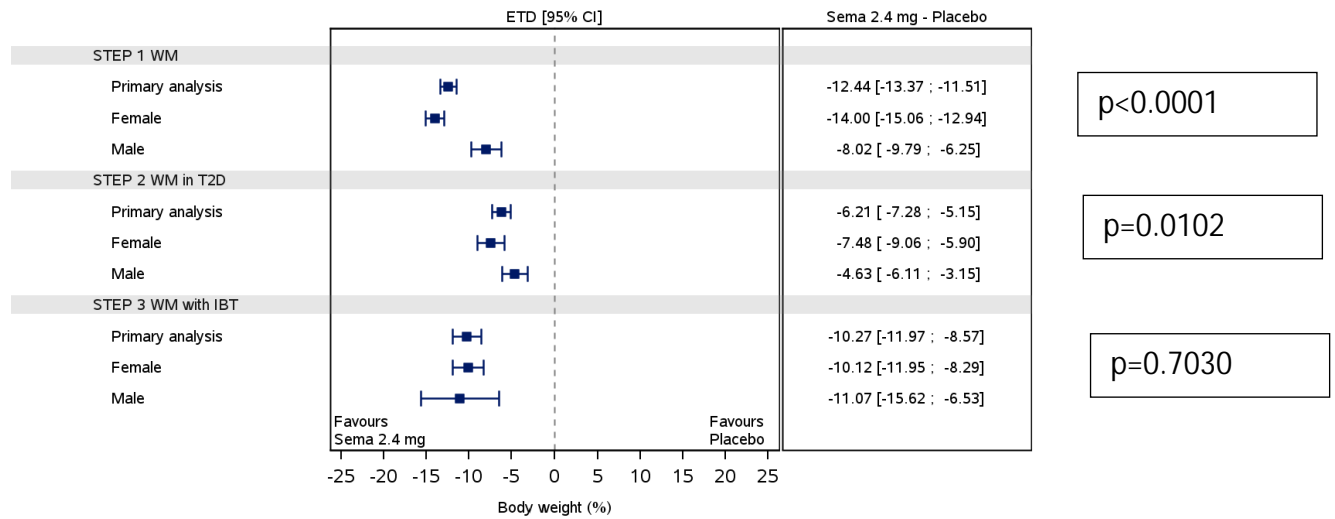
nn9536/mn9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:05 - fforest.sas/forestbwages4.png

STEP 4=trial 4376
 Source: ISE, Figure 6.4.91, Table 6.4.40

Sex

For sex, a differential effect was observed in trial 4373, 4374, and 4376. The differences in treatment effect were driven by greater percent weight loss on semaglutide in females versus males (the sex differences in the placebo groups were not as pronounced). Both sexes had similar treatment effect for percent body weight in trial 4375. This trial employed a more intensive behavioral program.

Figure 46: Percent Body Weight Change by Sex, Trials 4373, 4374, and 4375

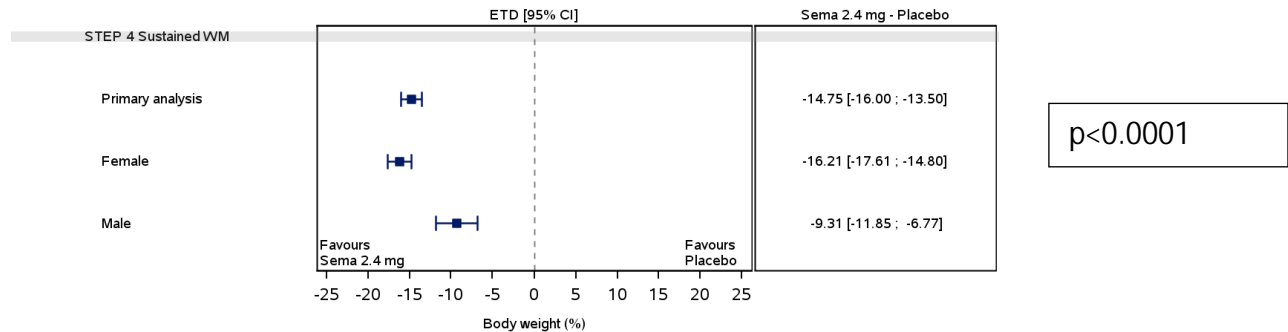


FAS: Full analysis set.
 Analysis of data from in-trial period.

nn9536/nn9536-summary/summ_ise_20201001_er
 25SEP2020:13:53:57 - forest.sas/forestbwsexs13.png

Source: ISE, Figure 6.4.92, Table 6.4.41, 6.4.42, 6.4.43

Figure 47: Percent Weight Change by Sex, Trial 4376



FAS: Full analysis set.
 Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

nn9536/nn9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:03 - forest.sas/forestbwsexs4.png

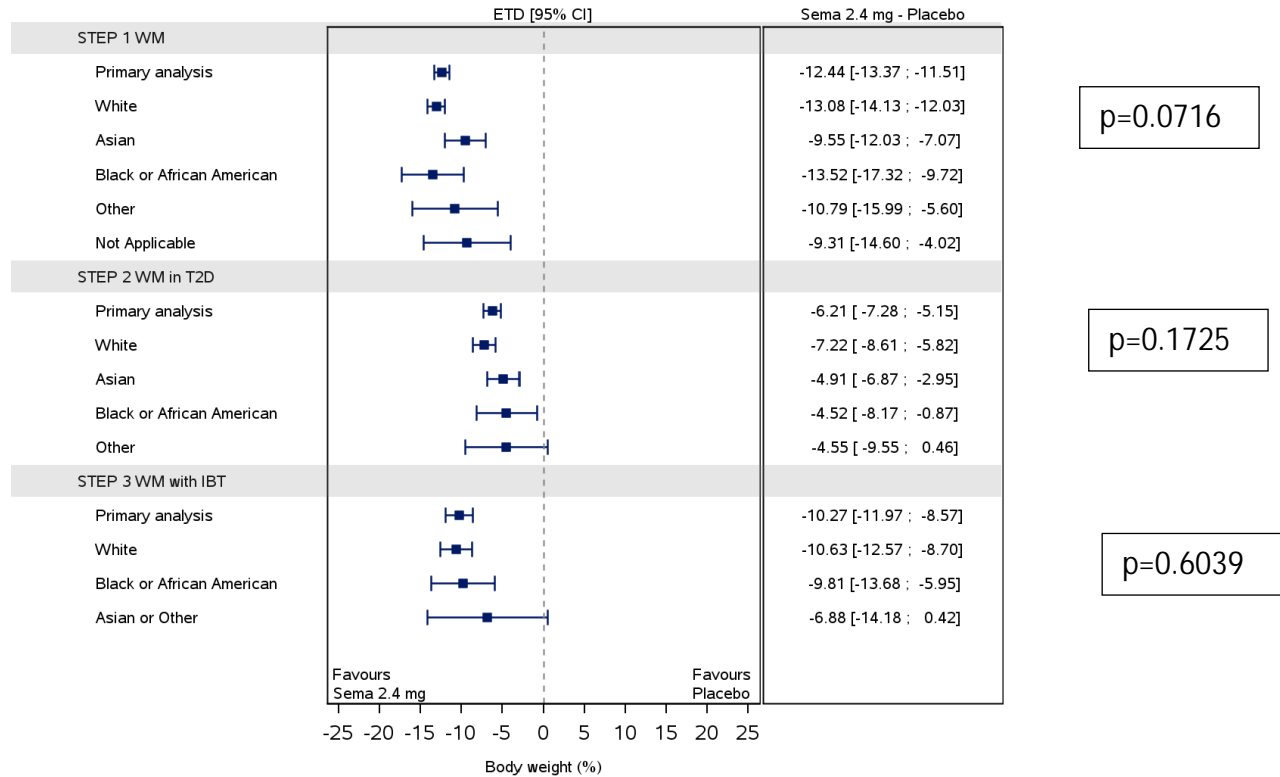
Source: ISE, Figure 6.4.93, Table 6.4.44

Reviewer comment: Although baseline body weight was lower for females than males (which could explain a higher semaglutide exposure), as seen in Figure 43, females had only a slightly higher semaglutide exposure than males in trials 4373 and 4374, and therefore baseline weight seems unlikely to entirely explain the sex dichotomy.

Race

For race, no clinically significant interactions were observed (Figure 48 and Figure 49).

Figure 48: Percent Weight Change by Race, Trials 4373, 4374, and 4375

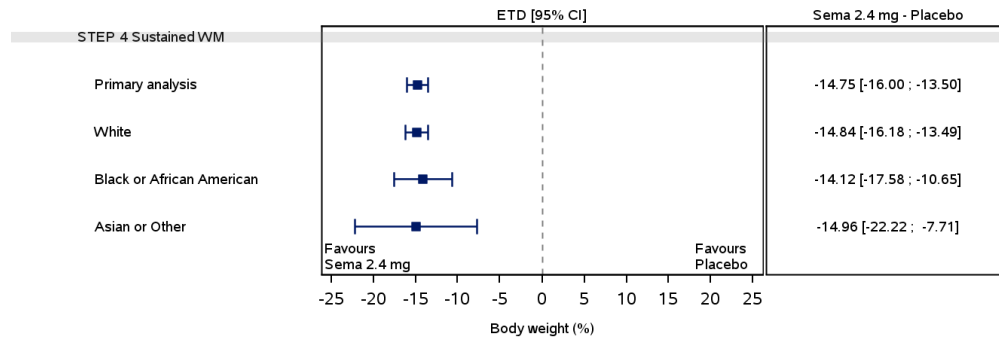


FAS: Full analysis set.
 Analysis of data from in-trial period.

nn9536/mn9536-summary/subm_ise_20201001_er
 25SEP2020:13:54:07 · forest.sas/forestbwaces13.png

Source: ISE, Figure 6.4.98, Tables 6.4.53, 6.4.54, 6.4.55

Figure 49: Percent Weight Change by Race, Trial 4376



p=0.9273

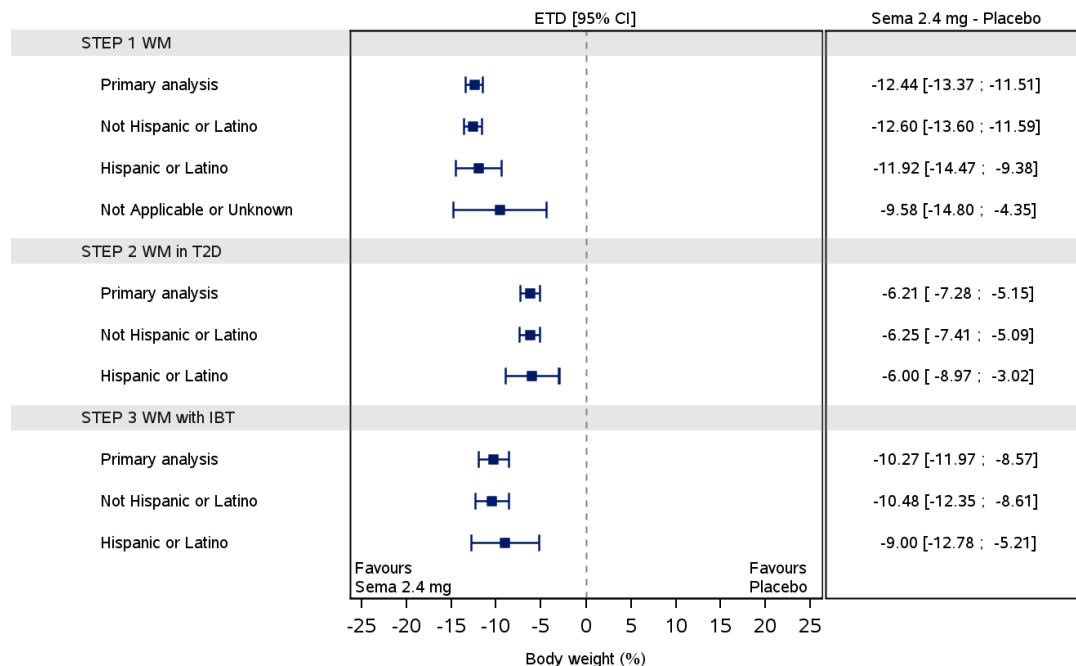
FAS: Full analysis set.
 Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).
 nn9536/nn9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:09 - fforest.sas/forestbwrces4.png

Source: ISE, Figure 6.4.99, Table 6.4.56

Ethnicity

No subgroup interactions were observed by ethnicity (Figure 50 and Figure 51).

Figure 50: Percent Weight Change by Ethnicity, Trials 4373, 4374, and 4375



p=0.4989

p=0.8788

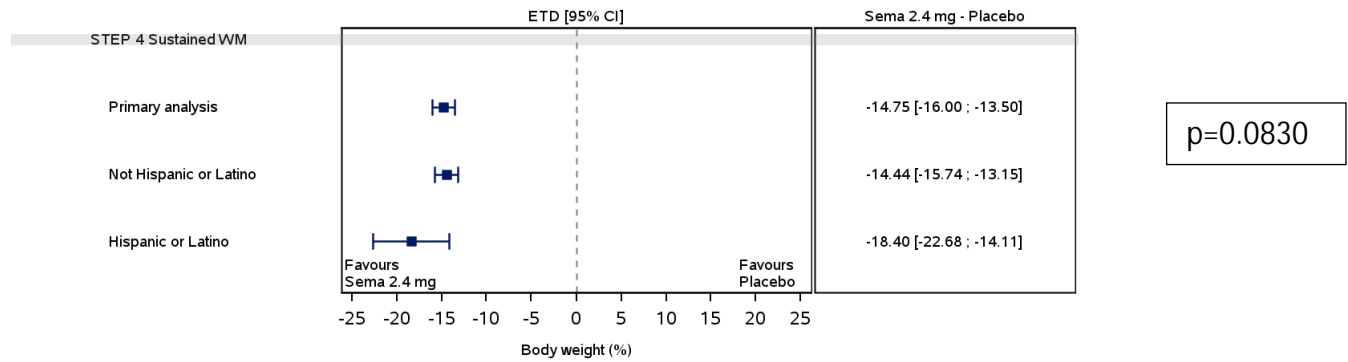
p=0.4874

FAS: Full analysis set.
 Analysis of data from in-trial period.

nn9536/nn9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:10 - fforest.sas/forestbweths13.png

Source: ISE, Figure 6.4.96, Tables 6.4.49, 6.4.50

Figure 51: Percent Weight Change by Ethnicity, Trial 4376



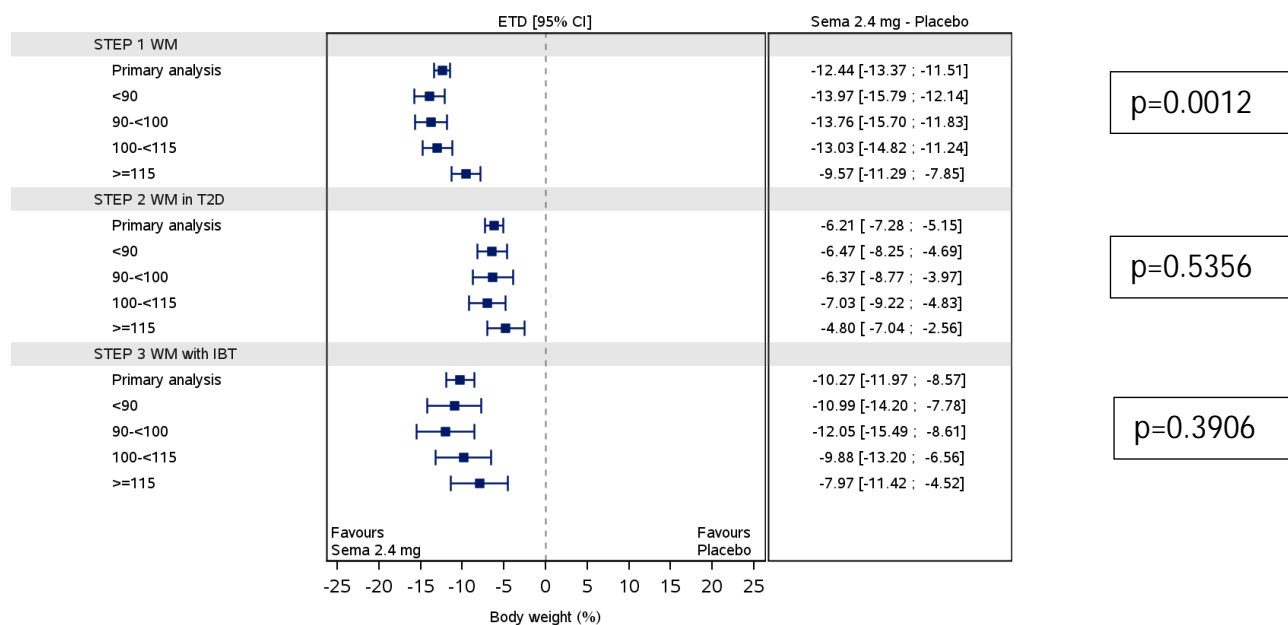
FAS: Full analysis set.
 Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).
nr9536/nr9536-summary/subm_ise_20201001_er
 25SEP2020:13:54:11 - fforest.sas/forestbweths4.png

Source: ISE, Figure 6.4.97

Baseline Body Weight

Regarding the baseline body weight subgroups, significant interactions were observed for trials 4373 and 4376. There is also a suggestion of an attenuated treatment effect at the highest baseline body weight for all trials. As noted above and in Figure 43, body weight is a significant covariate for semaglutide exposure.

Figure 52: Percent Weight Change by Baseline Body Weight, Trials 4373, 4374, and 4375

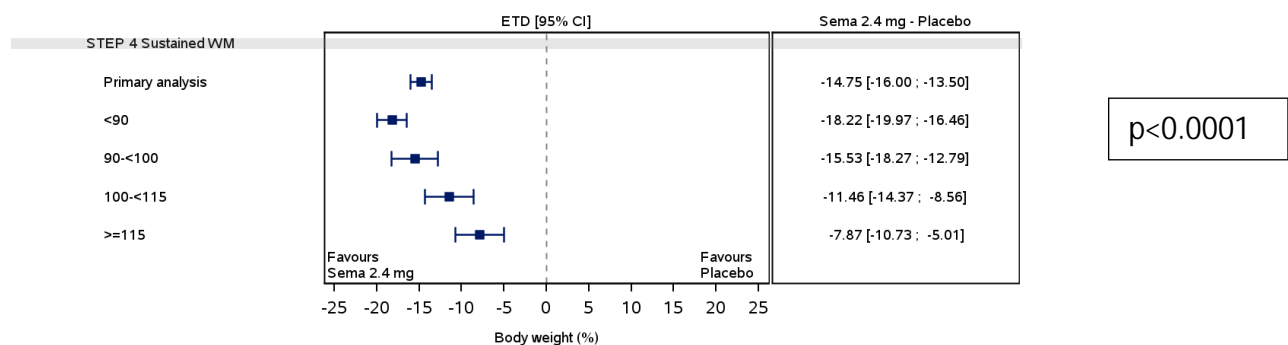


FAS: Full analysis set.
 Analysis of data from in-trial period.

m9536/m9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:15 - fforest.sas/forestbwbbws13.png

Source: SCE, Figure 3-28; ISE, Tables 6.4.57, 6.4.58, 6.4.59

Figure 53: Percent Weight Change by Baseline Body Weight, Trial 4376



FAS: Full analysis set.
 Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

m9536/m9536-summary/summ_ise_20201001_er
 25SEP2020:13:54:16 - fforest.sas/forestbwbbws4.png

Source: SCE, Figure 3-29

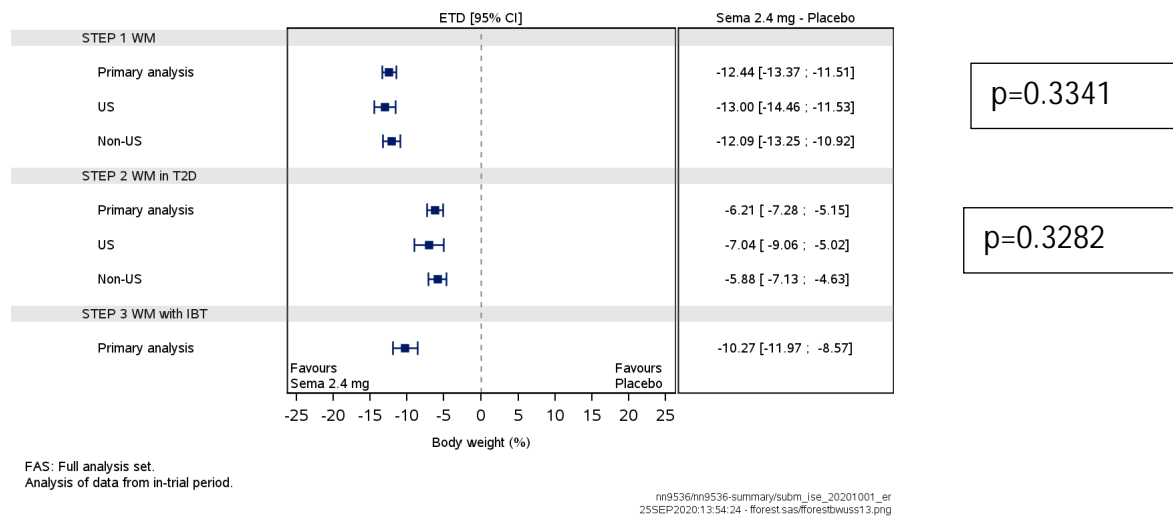
Reviewer comment: It is unsurprising that an interaction (or suggestion of one) for greater weight loss with semaglutide was observed at lower baseline body weights as compared to higher baseline body weights in the phase 3 trials. The significant interaction seen in Figure 53 from trial 4376 could also reflect weight loss during the run-in period; i.e., body weight at randomization to some extent reflects weight lost during the run-in period. Those with the lowest body weight at baseline (randomization) lost more weight with semaglutide and

gained more weight on placebo during the randomized treatment period than those with higher weights at baseline.

U.S. versus non-U.S.

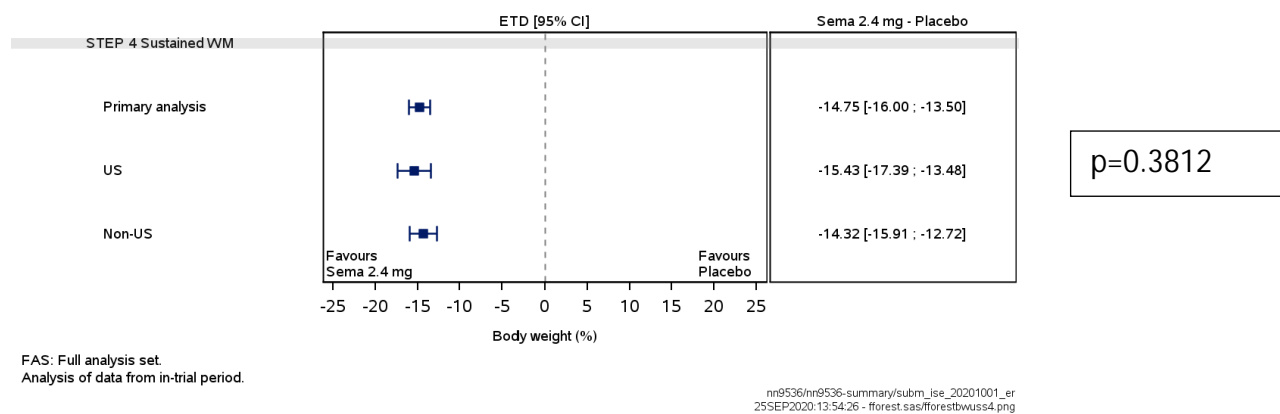
In response to a specific request by the Division, the applicant provided U.S. versus non-U.S. subgroup data. These results do not suggest significant differences in efficacy based on treatment effect and interaction p-values.

Figure 54: Percent Weight Change by Region, Trials 4373, 4374, and 4375



Source: Applicability of non-U.S. data to U.S. population, Figure 1.26, Tables 1.20, 1.21

Figure 55: Percent Change in Weight by Region, Trial 4376



Source: Applicability of non-U.S. data to U.S. population, Figure 1.27, Table 1.23

7.1.4. Dose and Dose-Response

Phase 2 trial 4153³⁴ was a 52-week, randomized, double-blinded, placebo-controlled, 16-arm trial that investigated 5 once-daily doses of semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, and 0.4 mg) with dose escalation every fourth week and 2 additional semaglutide dose regimens to evaluate a faster dose escalation every second week (0.3 mg and 0.4 mg) on body weight in subjects with obesity without diabetes. Placebo and liraglutide were included as comparators. The trial design is summarized as follows:

Figure 56: Trial 4153 Design



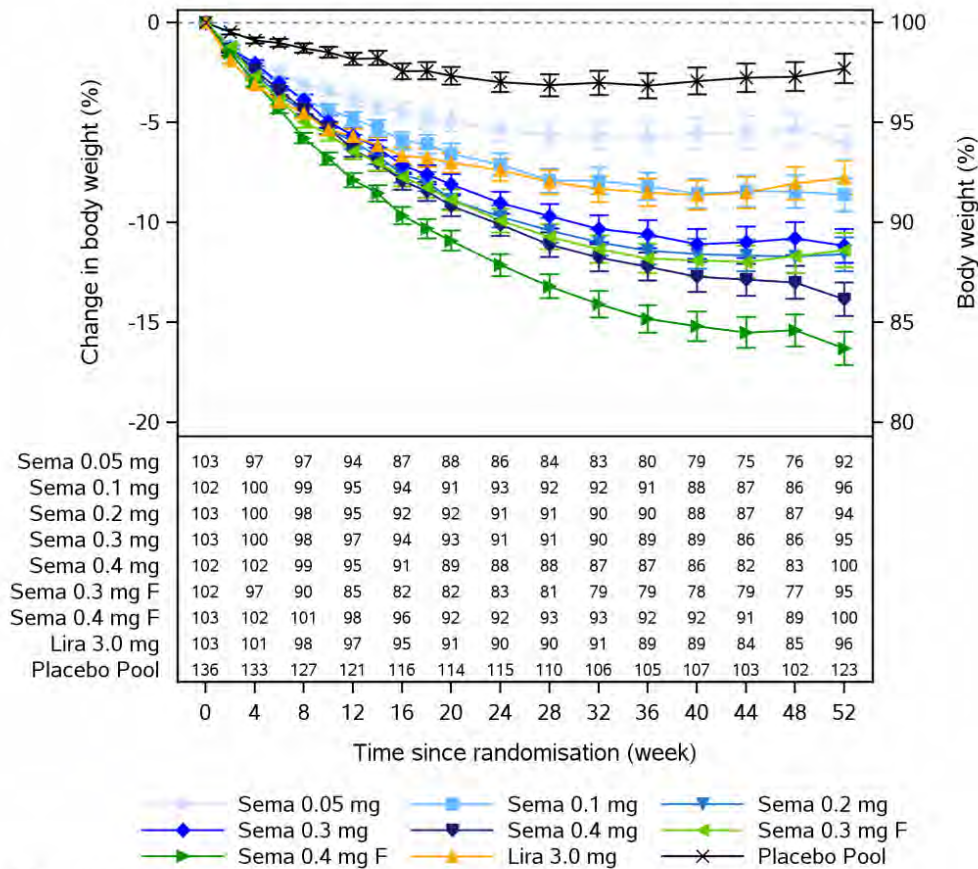
*Each active treatment arm was blinded towards placebo with matching injection volumes, but not towards the other treatment arms. A. The dose-finding part of the trial (part A). B. The dose escalation part of the trial (part B) (see Section 9.7).

Source: Study 4153 CSR, Figure 9-1

The primary endpoint was percent change in body weight from baseline at 52 weeks. Semaglutide was associated with increased percent body weight loss from baseline in a generally dose-dependent manner (semaglutide 0.2 mg and 0.3 mg showed similar point estimates); see Figure 57, Figure 58, and Figure 59.

³⁴ At the time this trial was designed, these regimens were tested with the idea that daily dosing might lead to lower semaglutide C_{max} and reduce gastrointestinal AEs. Subsequently (based on data from trial 4153 and a similar trial in T2D) it was determined that there were no benefits in weight loss or GI tolerability to justify pursuing a daily dose regimen.

Figure 57: Change in Percent Body Weight by Treatment Week, Trial 4153



F: Fast dose escalation.

J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 missing observations were additionally multiply (x1000) imputed from retrieved subjects of the same randomised treatment arm.

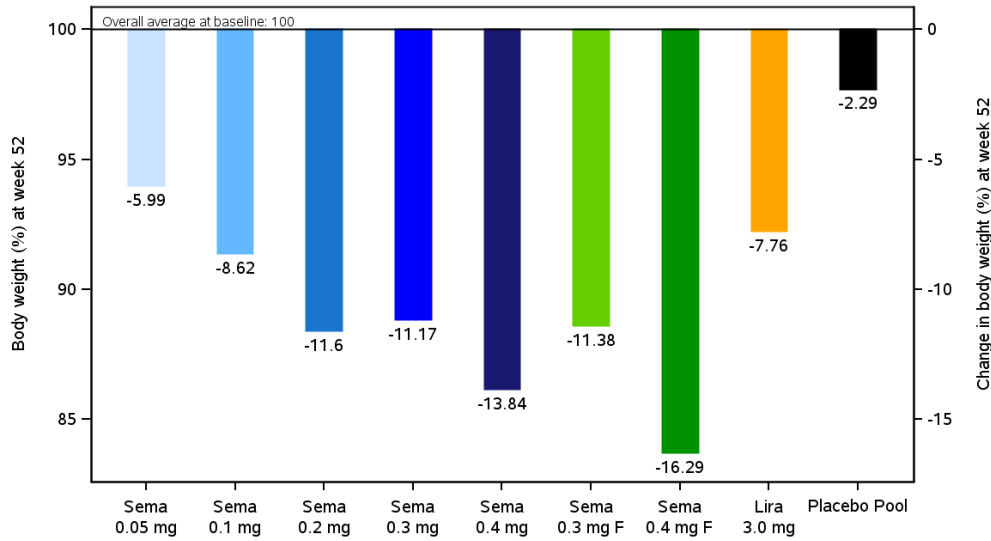
Responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Means show estimated means and error bars show standard errors.

Bottom panel: Number of contributing subjects by treatment arm

nn9536/nn9536-4153/ctr_20170918_er
 19SEP2017:02:32:06 - f_anc_j2r_mi_bw_chb_fas/f_anc_j2r_mi_bw_chb_fas_a.png

Source: Study 4153 CSR, Figure 11-2

Figure 58: Percent Change in Body Weight from Baseline at Week 52, Trial 4153



F: Fast dose escalation.

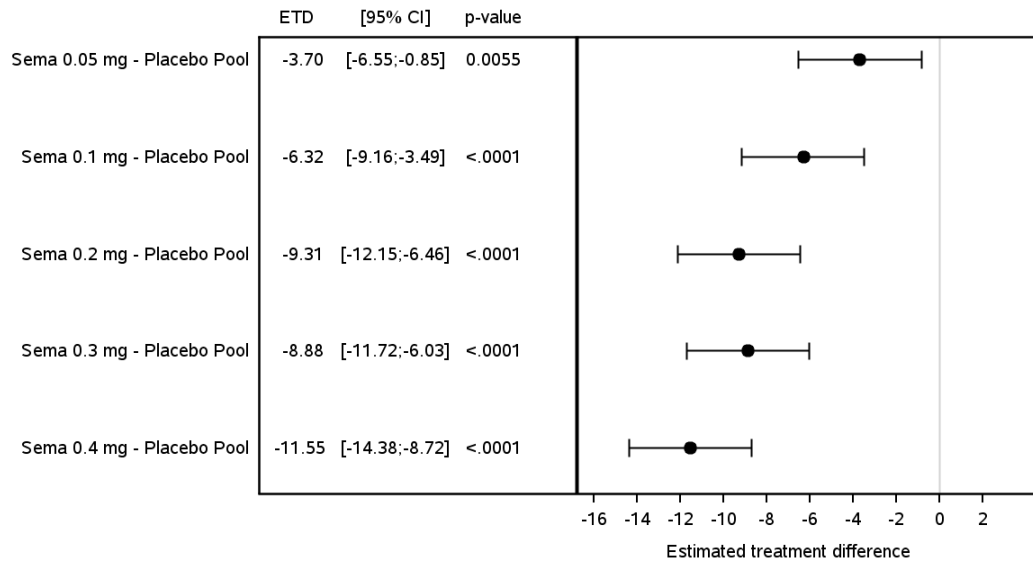
J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Bars show estimated means.

mn9536/mn9536-4153/ctr_20170918_er
 19SEP2017.02:32:41 - f_bar_plot_eff.sas/t_ancova_j2r_mi_w52_bw_chb_a.png

Source: Study 4153 CSR, Figure 11-3

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Figure 59: Percent Change in Body Weight from Baseline at Week 52, Primary Efficacy Analysis, Trial 4153



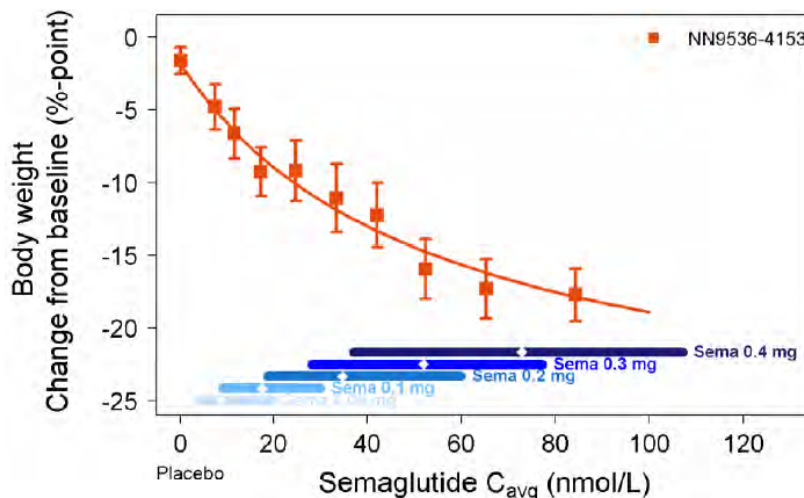
ETD: Estimated treatment difference, CI: Confidence Interval. J2R-MI: Analysis of in-trial data with missing observations imputed from the pooled placebo arms based on a jump to reference multiple (x1000) imputation approach. Week 52 responses were analysed using an analysis of covariance model with treatment, region and sex as factors and baseline body weight as covariate. Dunnett's method was used to adjust for multiple comparisons.

nn9536/mn9536-4153/ctr_20170918_er
 19SEP2017:02:44:41 - f_forest_plot_eff.sas/f_anc_j2r_mi_f_prim_bw_w52_chb_a.png

Source: Study 4153 CSR, Figure 11-4

Furthermore, the exposure-response relationship for percent weight change from baseline until the end of treatment showed a consistent increase in effect with increasing exposure.

Figure 60: Percent Body Weight Change from Baseline Versus Exposure of Semaglutide, Trial 4153



Data are mean body weight changes with 95% CI obtained after 52 weeks versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). The lines through data represent covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds along the x-axes represent median and 95% exposure ranges. Data from trial 4153 excluding treatment with fast dose escalation.

Source: SCE, Figure 4-5

Data from trial 4153 were used to support the 2.4 mg once-weekly phase 3 dosage³⁵:

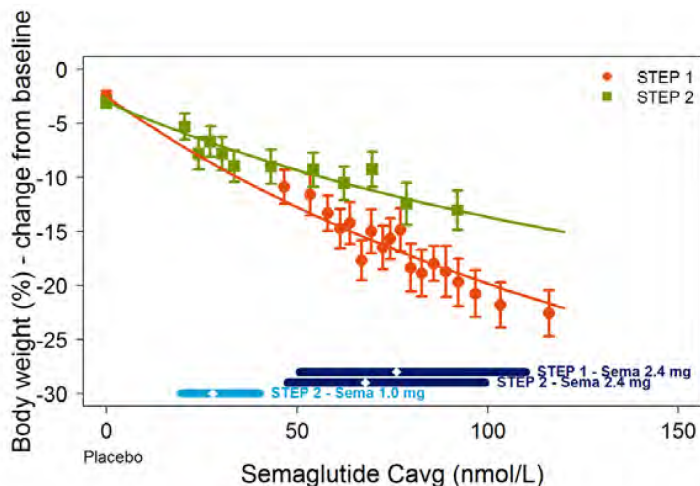
- Simulated 2.4 mg once weekly semaglutide concentrations did not exceed the concentration range for 0.4 mg once daily (which was considered important for GI tolerability, as GI symptoms are dose-related, see Section 8.5.10). The proportions of subjects with GI AEs and the proportions discontinuing treatment were expected to be similar or slightly lower for semaglutide 2.4 mg once weekly compared to 0.4 mg once daily (approximately 2 percentage points lower).
- Semaglutide 2.4 mg once weekly was expected to provide approximately 1 percentage point smaller body weight loss compared to 0.4 mg once daily, primarily due to a slightly lower weekly dose (2.4 mg vs. 2.8 mg).

The phase 3 trial 4374 in subjects with T2D, which evaluated 2 semaglutide doses (1 mg and 2.4 mg) provides additional evidence that weight (and to a lesser extent, glycemic efficacy) is dose-dependent. See more information in Section 6.2.2.

³⁵ The Division did not object to the applicant's proposal for the phase 3 dose regimen at the time of the end-of-phase 2 meeting, although because the 2.4 mg weekly dosage was not evaluated in a phase 2 dose-ranging trial, the company was reminded that there was some risk in dose selection.

The population PK analysis supports a dose-proportional exposure for semaglutide up to 2.4 mg, as weight loss increased in an exposure-dependent manner (and a dichotomous finding by diagnosis: with or without T2D).

Figure 61: Percent Body Weight Change from Baseline Versus Exposure, Trials 4373 and 4374



03-sep-2020 10:53:41 E:\Project\N8536\Phase3a_meta_analysis\current\Scripts\05_ER_BW.F

Data points with error bars are mean body weight changes with 95% CI obtained after 68 weeks of treatment versus exposure expressed as quantiles of C_{avg} (plus placebo at C_{avg} of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds represent the median and 95% exposure range. Missing data at week 68 were predicted using a mixed model for repeated measures, using treatment as factor and baseline BW as covariate all nested within visit. Data from trials STEP 1 and STEP 2.

STEP 1=trial 4373; STEP 2=trial 4374

Source: SCE, Figure 4-7

Reviewer comment: The 2.4 mg once-weekly dosage has been demonstrated to be effective. Dosing recommendations mimicking those in the phase 3 trials is reasonable; i.e., dose escalating every 4 weeks to a maximum target dose of semaglutide 2.4 mg once weekly. The review of the individual trials suggests that most, although not all, subjects reached the 2.4 mg once weekly dose (for example, see Table 13 in Section 6.1.2).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

As described in Section 6, which discussed the efficacy of the individual trials, missing data were kept to a minimum, allowing for confidence in the estimates at the week 68 endpoint.

In trials 4373 and 4374, separation of the weight curves between semaglutide 2.4 mg and placebo was apparent by week 4. In trial 4375, which employed a more intensive background therapy of diet and exercise (including low calorie diet until week 8), separation of the weight

curves was observed around week 8. In the randomized withdrawal trial 4376, weight diverged in the first 4 weeks after randomization, such that mean body weight continued to decrease in the semaglutide group and started to increase in the placebo group.

Plateau in mean weight loss was seen in the semaglutide 2.4 mg arm around weeks 52 to 60 depending on trial. Plateau in mean weight loss was seen in the placebo arm around weeks 20 to 32.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Weight loss with semaglutide and related salutary effects in the postmarket setting will depend on a number of factors, including compliance with adjunct diet and exercise recommendations and compliance with the drug long-term.

Although more subjects discontinued semaglutide due to gastrointestinal adverse events (AEs) as compared to placebo (Section 8.4.3), weight loss was similar in those who did and did not report any GI AE, and nausea, vomiting, and diarrhea, specifically (the most commonly reported GI AEs).³⁶

With respect to the general impact of discontinuation of semaglutide on weight loss (of note, high frequency of discontinuation has been observed with other weight management drug treatments in the postmarket setting³⁷), trial 4376 informs the expected trajectory of weight regain with drug discontinuation and supports semaglutide as a chronic therapy. Other chronic weight management labels (Qsymia, Contrave, and Saxenda) include a “stopping rule” to discontinue treatment if a certain amount of weight is not achieved at a certain time in order to ensure a favorable benefit-risk for an individual patient. None of these labeled instructions with other weight management drugs were based on trials designed to evaluate the recommendation and were therefore derived *post hoc*.³⁸

The applicant conducted analyses to assess the appropriateness of a stopping rule, by predicting clinically relevant weight loss at week 68 by week 20 weight loss in trial 4376. Trial 4376 evaluated drug discontinuation after randomization, therefore allowing the stopping rule to be considered in a more formalized fashion than with previous products. The applicant notes that an appropriately selected criterion should ideally have both a high positive predictive

³⁶ Source: ISE, Tables 6.4.108 to 6.4.113

³⁷ Internal FDA estimates based on outpatient retail data

³⁸ See, for example, McEvoy B. Statistical Review Addendum, NDA 206321 (Saxenda); dated in DARRTS 16 Oct 2014

value (% week 68 responders out of week 20 responders) and a high negative predictive value (% week 68 non-responders out of week 20 non-responders). If an early weight loss criterion fulfilling these requirements was applied, responders would remain on the treatment, whereas unnecessary treatment of non-responders would be avoided.

In trial 4376, most subjects (719 of 803 subjects, 89.5%) had achieved a weight loss $\geq 5\%$ at week 20. The change in percent body weight from the start of the run-in period in trial 4376 by week 20 weight loss shows that the estimated change in percent body weight for both treatment groups, as well as the estimated treatment difference, was lower for week 20 non-responders compared to week 20 responders (Table 48).

Table 48: Percent Weight Change from Start of Run-in (Week 0) to Week 68 by Start of Randomization (Week 20) Weight Loss, Trial 4376

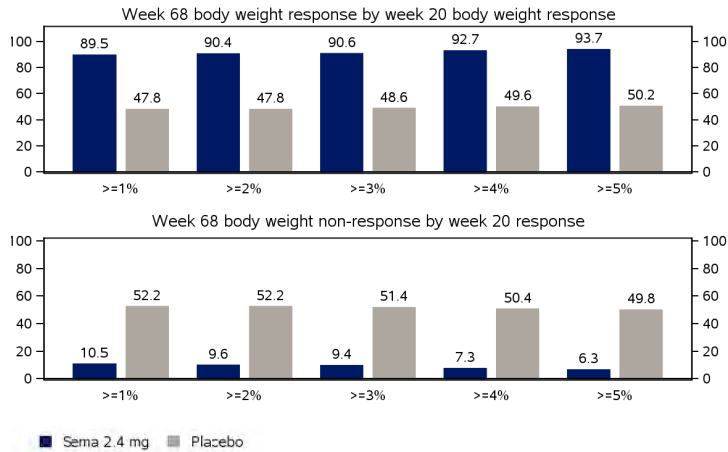
	Number of subjects		Estimated change in body weight (%) at week 68		Estimated treatment difference (%) [95% CI]
	Sema 2.4 mg	Placebo	Sema 2.4 mg	Placebo	
Week 20 responders			Change from week 0		
$\geq 1\%$	515	249	-17.54	-5.07	-12.47 [-13.81; -11.13]
$\geq 2\%$	509	249	-17.76	-5.11	-12.65 [-13.97; -11.33]
$\geq 3\%$	500	245	-17.93	-5.14	-12.79 [-14.11; -11.46]
$\geq 4\%$	480	240	-18.46	-5.27	-13.19 [-14.50; -11.88]
$\geq 5\%$	458	233	-18.91	-5.43	-13.48 [-14.79; -12.18]
Week 20 non-responders			Change from week 0		
$\geq 1\%$	5	1	-0.28	2.19	-2.47 [-17.25; 12.31]
$\geq 2\%$	11	1	0.57	2.49	-1.92 [-13.73; 9.89]
$\geq 3\%$	20	5	-3.30	-0.68	-2.61 [-10.33; 5.10]
$\geq 4\%$	40	10	-4.33	0.17	-4.51 [-10.06; 1.05]
$\geq 5\%$	62	17	-6.07	-0.08	-5.99 [-10.26; -1.72]

All subjects were treated with semaglutide from week 0–20 (run-in). Baseline (randomisation) was at week 20. Subjects in the placebo group were treated with placebo from week 20–68.

Source: SCE, Table 5-1

Positive predictive values were high with semaglutide 2.4 mg (top panel), meaning that few subjects would be continued on treatment without achieving clinically relevant weight loss (bottom panel).

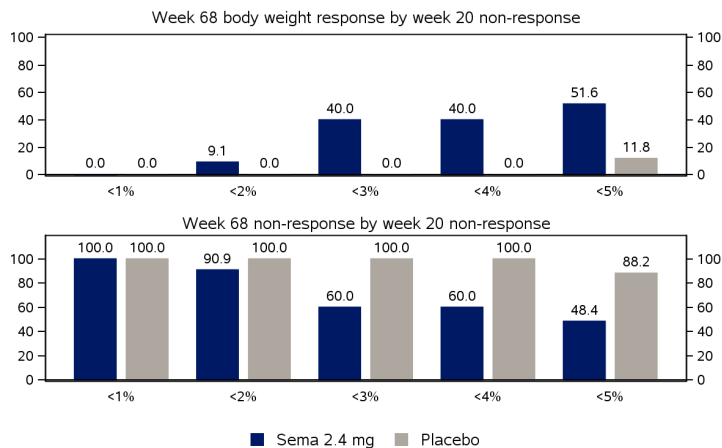
Figure 62: Week 68 5% Weight Response / Non-Response by Week 20 Weight Response



Source: ISE, Figure 6.5.5

Negative predictive values decreased with increasing week 20 weight loss criteria (bottom panel), meaning that an increasing number of subjects would be discontinued from treatment who eventually would have achieved clinically relevant weight loss (top panel).

Figure 63: Week 68 5% Weight Response / Non-Response by Week 20 Non-Response



Source: ISE, Figure 6.5.5

Reviewer comment: A stopping criterion based on prediction of week 68 weight from week 20 weight loss seems unlikely to be informative, as there were so few subjects in these categories [Table 48]. This is, however, contingent on subjects being on the 2.4 mg dose as was designed in trial 4376. Furthermore, as there were few subjects at lower doses in the other phase 3 trials (see for example Table 13 from trial 4373), efficacy cannot be inferred for doses lower than semaglutide 2.4 mg.

7.2.2. Other Relevant Benefits

Unlike the other injectable weight management drug currently marketed, Saxenda (liraglutide), semaglutide offers the unique benefit of being administered weekly, rather than daily. It is unknown whether a reduced injection frequency will confer efficacy benefit, but one could speculate that a weekly injection is preferable to patients over a daily injection. Dosing regimens that improve convenience, compliance, or decreased risk for drug error in theory could contribute to the weight loss benefit of semaglutide. Whether any of that is true with the once-weekly regimen is speculative.

7.3. Integrated Assessment of Effectiveness

As detailed in the assessments of the phase 3 trials 4373, 4374, 4375, and 4376 in Section 6 of this review, semaglutide 2.4 mg is effective for weight management in patients with obesity and overweight with co-morbidities. Weight loss was achieved at the maintenance dose of 2.4 mg and continued for up to a year for an estimated placebo-subtracted weight loss from baseline of 10.3-12.4% in a non-diabetic population and 6.2% in a population with T2D. The majority (68.8-86.6%) of subjects on semaglutide 2.4 mg achieved at least 5% body weight loss at 68 weeks, and this was 2 to 3 times the proportions of subjects randomized to placebo. The statistically significant treatment effects observed with semaglutide in this program are larger in magnitude than has been seen with any currently approved drug for chronic weight management and are clinically meaningful. Weight loss with semaglutide was associated with improvements in glycemia, blood pressure, lipids, and physical functioning in most trials. Patients who were withdrawn from treatment in a randomized fashion were observed to regain weight, supporting the chronic use of semaglutide treatment.^{39,40,41}

8. Review of Safety

8.1. Safety Review Approach

The development program to support the use of semaglutide 2.4 mg SC weekly dosing for weight management includes 8 clinical trials: 3 phase 1 clinical pharmacology trials, 1 phase 2

³⁹ This phenomenon has been observed with other weight management products studied with a randomized withdrawal design; see ref. 40 and 41

⁴⁰ Davidson MH, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat. JAMA 1999; 281: 235-42.

⁴¹ Smith SR, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010; 363: 245-56.

dose-finding trial, and 4 phase 3 safety and efficacy trials. In addition, safety data from the off-drug extension phase of 4373 and from 5 blinded, phase 3 clinical trials with semaglutide 2.4 mg that were ongoing as of the safety cut-off date (1 Sept 2020) were included in the NDA Summary of Clinical Safety with limited data.

The 4 phase 3 trials comprise the main substance of the safety review. As the applicant notes, these trials investigated the proposed indicated population, had the same treatment duration (68 weeks with a 7-week follow-up period), investigated once-weekly dosing of semaglutide 2.4 mg with a 16-week dose-escalation, and contributed to the majority of the total exposure to semaglutide 2.4 mg.

- Trial 4373 evaluated weight management with semaglutide 2.4 mg as an adjunct to a reduced calorie diet and increased physical activity in subjects with obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) or subjects with overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$) and at least 1 weight-related comorbidity.
- Trial 4374 evaluated subjects with obesity or overweight ($\text{BMI} \geq 27 \text{ kg/m}^2$) and T2DM (HbA1c of 7–10%), and included 2 weekly semaglutide doses: 2.4 mg and 1 mg. The 1 mg dose is approved for use in treatment of T2DM (Ozempic).
- Trial 4375 studied subjects with $\text{BMI} \geq 30 \text{ kg/m}^2$ or subjects with $\text{BMI} \geq 27 \text{ kg/m}^2$ and at least 1 weight-related comorbidity, and included an 8-week low-calorie meal-replacement diet as well as intensive behavioral treatment.
- Trial 4376 included a 20-week run-in period with semaglutide 2.4 mg treatment, followed by randomization of subjects to either continue treatment with semaglutide 2.4 mg or switch to placebo.

In addition to the safety evaluation of the individual trials, the phase 3 trials were pooled such that specific safety topics could be evaluated in prespecified groupings:

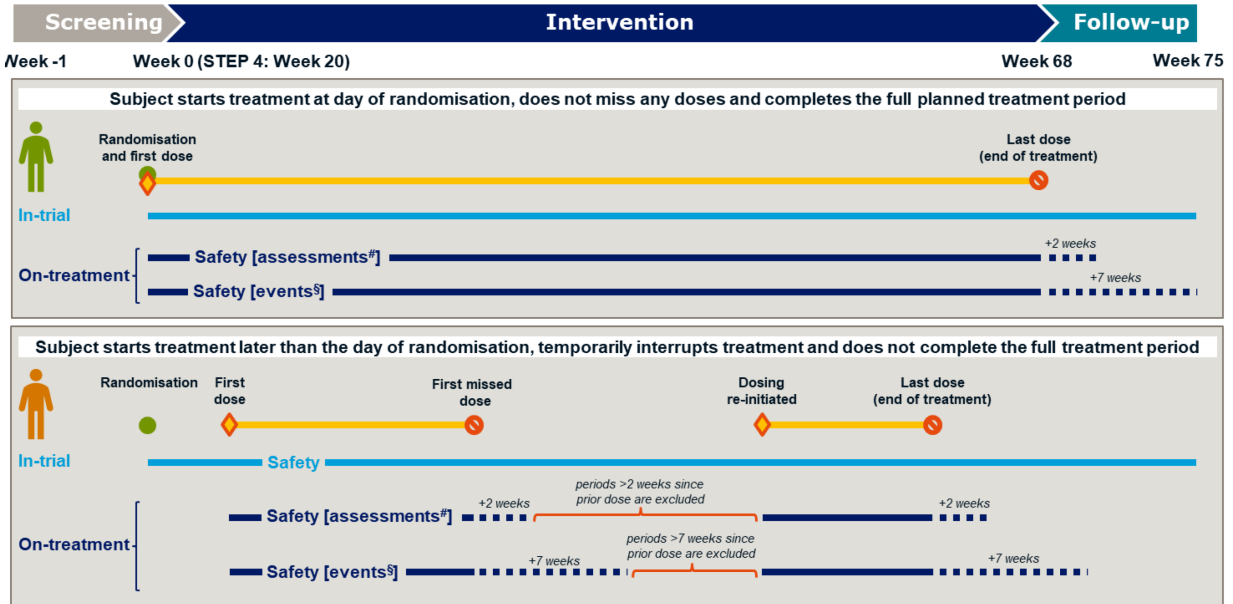
- Phase 3 pool: This pool includes trials 4373, 4374, 4375, and 4376 to compare semaglutide 2.4 mg to placebo during the randomized, controlled trial period. The non-randomized 20-week run-in period of trial 4376 is omitted since this period was not placebo-controlled. The semaglutide 1 mg group in trial 4374 is omitted as the pool is evaluating the 2.4 mg dose. To minimize the potential risk of confounding by trial (Simpson's Paradox) caused by any differences in trial population or unequal randomization ratios, adjustments were made for the proportion of subjects with events and the event rate for the phase 3 pool (Cochran-Mantel-Haenzel weights, CMH). Subgroups of the phase 3 pool were also evaluated as follows:

- Phase 3 dose-escalation group: This group includes trials 4373, 4374, and 4375 to compare semaglutide 2.4 mg to placebo where the randomized controlled trial period included a dose-escalation period. This grouping allows for evaluation of safety issues that are known or suspected to show a higher prevalence during the dose escalation period (e.g., gastrointestinal events).
- Phase 3 with T2DM group: This group is comprised solely of trial 4374 to evaluate specific safety issues of semaglutide 2.4 mg in a population with T2DM, such as hypoglycemia, retinal disorders, and certain renal assessments.
- Phase 3 without T2DM group: This group includes trials 4373, 4375, and 4376 to evaluate safety issues of semaglutide 2.4 mg in a population with overweight or obesity without T2DM, such as hypoglycemia.
- Dose-response evaluation: The evaluation of potential dose-response effects of semaglutide on safety parameters is based on data from trial 4374, which included semaglutide 2.4 mg and 1 mg once-weekly, and the phase 2 dose finding trial 4153, which included semaglutide 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, and 0.4 mg once-daily for 52 weeks.

The safety analysis set, defined as all randomized subjects exposed to at least 1 dose of trial product, was used for the safety evaluation of all trials and the phase 3 pool. Two observation periods were defined:

- The in-trial period was the uninterrupted time interval from date of randomization to date of last contact. This period was used to evaluate deaths and events with potential long latency to diagnosis (e.g., malignancies); this period defines the patient-years of observation (PYO).
- The on-treatment period was the interval from first to last date of trial product administration plus a follow-up period after last dose and excluding any period of temporary treatment interruption; this period defines the patient-years of exposure (PYE). The length of the periods for follow-up after last dose and temporary treatment interruption were:
 - 2 weeks for the following assessments: ECG, laboratory assessments, physical examination, and heart rate (HR)
 - 7 weeks for the following assessments: AEs, adjudicated events, and hypoglycemic episodes

Figure 64: Observation Periods for Safety Evaluations Across the Phase 3 Trials



ECG, laboratory assessments, physical examination and pulse; § AEs, adjudicated events and hypoglycaemic episodes.

Source: SCS, Figure 1-5

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 49 enumerates the numbers of subjects exposed to semaglutide and comparators throughout the weight management program.

Table 49: Safety Database

Safety Database for the Study Drug Individuals exposed to any treatment in this development program for the indication under review N=5846 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Semaglutide ¹ (n=4346)	Active Control (n=103)	Placebo (n=1397)
Healthy volunteers (with overweight/obesity)	208	0	0
Controlled trials conducted for this indication	3236	103	1397
All other trials conducted for this indication	902 ²	0	0
Controlled trials conducted for other indications	Not applicable: semaglutide already approved for treatment of T2DM		
¹ All studied semaglutide doses ² Subjects exposed to semaglutide in the run-in period in trial 4376; the subjects randomized after 20 weeks (535 semaglutide, 268 placebo) are <u>not</u> double counted in this table			

Source: Study reports from trials listed in Table 1

Table 50 enumerates the duration of exposure of subjects to semaglutide by dose in the phase 3 trials.

Table 50: Duration of Exposure in Phase 3 Trials

Dosage	Number of subjects exposed to the study drug:				
	>= 1 dose	>=6 months	>=12 months	>=15 months	>=18 months
2.4 mg QW	N=2650	N=2499	N=2370	N=1809	N=2
1 mg QW	N=402	N=370	N=356	N=344	N=0
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days Only includes randomized subjects during controlled portions of the trials					

Source: SCS Tables 1-6 and 1-10, Study 4374 CSR Table 14.1.30

Table 51 enumerates the subjects and exposure duration in patient-years in various pools/groups and the individual trials. These values are used as denominators throughout the safety evaluation.

Table 51: Exposure in Pools and Individual Trials

	Semaglutide 2.4 mg		Semaglutide 1 mg		Placebo	
	N	PYE	N	PYE	N	PYE
Phase 3 pool	2650	3309			1529	1885
Phase 3 without T2D group	2247	2776			1127	1357
Phase 3 dose-escalation group	2116	2765			1261	1619
Trial 4373	1306	1706			655	830
Trial 4374	403	533	402	530	402	528
Trial 4375	407	526			204	261
Trial 4376	534	544			268	266

Source: ISS, Table 7.1.3

8.2.2. Relevant characteristics of the safety population:

Demographics and baseline characteristics of the phase 3 pool is shown in Table 52. The average age at baseline was 48 years, with a mean BMI of 36.8 kg/m². Most subjects (71.6%) were female, and 73.8% were White, 9.6% were Black or African American, 12.2% were Asian, and 12.3% were Hispanic or Latino. A total of 46.2% were from the United States (U.S.).

Table 52: Selected Baseline Characteristics of the Phase 3 Pool

	Semaglutide N=2650	Placebo N=1529
Age, yrs		
Mean (SD)	48 (13)	49 (12)
Min, Max	18, 86	18, 82
≥ 65, n (%)	256 (9.7)	167 (10.9)
Sex		
F	1920 (72.5)	1073 (70.2)
M	730 (27.5)	456 (29.8)
United States, n (%)	1247 (47.1)	682 (44.6)
Race		
White	1962 (74.0)	1124 (73.5)
Asian	313 (11.8)	198 (12.9)
Black or African American	255 (9.6)	147 (9.6)
Other	57 (2.2)	28 (1.8)
Not Applicable	38 (1.4)	17 (1.1)
Ethnicity		
Not Hispanic or Latino	2298 (86.7)	1309 (85.6)
Hispanic or Latino	314 (11.8)	202 (13.2)
Not Applicable	38 (1.4)	17 (1.1)
Unknown	0	1 (<0.1)
BMI, kg/m ²		
Mean (SD)	36.9 (6.8)	36.7 (6.8)
Min, Max	22.4, 83.0	22.7, 69.0
≥ 40, n (%)	690 (26.0)	393 (25.7)

Source: ISS, Appendix 7.1, Tables 7.1.8 and 7.1.9

8.2.3. Adequacy of the Safety Database

The size and duration of the safety database is consistent with the FDA draft weight management guidance² (i.e., approximately 3000 subjects randomized to semaglutide, with the majority of subjects randomized to the highest dose) and is therefore considered adequate for this NDA review. Sex and age generally reflect those who might seek weight management care in a primary care office; the trial with T2D included more males and older subjects. The trials were somewhat under-representative of the Black or African American and Hispanic or Latino populations in the U.S. (13.4% and 18.5%, respectively).¹⁶

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In general, the submission and data quality were very good. All clinical items requested in meetings with FDA leading up to submission were provided and easy to locate. This reviewer was able to confirm key safety outputs in clinical trial reports and safety summaries with the provided analysis datasets.

8.3.2. Categorization of Adverse Events

In order to assess the appropriateness of AE categorization, this reviewer compared SAE verbatim terms and PTs, and identified 7 events that did not match the intent of the verbatim term (in this reviewer's opinion). In addition, to evaluate neoplasms specifically (serious and non-serious), this reviewer searched verbatim terms for "CANCER" and "CARCINOMA," and found 2 additional cases (both non-serious basal cell carcinoma).⁴² Table 53 outlines the result of the search. Although some of these cases were missed in pre-defined MedDRA searches, most notably the papillary thyroid cancer (PT: 'Thyroidectomy'), the number of cases were limited and do not impact the overall assessment of safety.

⁴² Upon FDA request, the applicant conducted a separate search of verbatim terms in the phase 3 pool using the in-trial period with the following search terms: Biops, Cancer, Carcino, Dissection, Ectomy, Exci, Exeresis, Operat, Procedure, Remov, Scop, Surgery, and Wound. No additional malignant neoplasms not otherwise captured were identified.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 53: Selected Miscategorized AEs (as Identified by Reviewer), Phase 3 Program

USUBJID	TRTA	AETERM	AEDECOD
PT did not capture important neoplasm in verbatim term (and was not reported separately)			
NN9536-4374/ (b) (6)	Semaglutide 2.4 mg	SURGERY FOR EXCISION OF PAPILLARY CARCINOMA OF LEFT LOBE OF THYROID	Thyroidectomy
NN9536-4374/ (b) (6)	Placebo	ACUTE BLOOD LOSS ANEMIA FOLLOWING COLONOSCOPIC POLYPECTOMY	Anaemia postoperative
NN9536-4373/ (b) (6)	Semaglutide 2.4 mg	EXCISED BASAL CELL CARCINOMA UPPER BACK	Skin neoplasm excision
NN9536-4373/ (b) (6)	Semaglutide 2.4 mg	SURGICAL WOUND ON LEFT CHEEK SECONDARY TO BASAL CELL CARCINOMA EXCISION	Wound
Although PT did not capture important neoplasm in verbatim term, the neoplasm event was separately reported and captured			
NN9536-4373 (b) (6)	Semaglutide 2.4 mg	ACUTE GI BLEED STATUS POST COLONOSCOPY SHOWING CECAL POLYPECTOMY SITE BLEED.	Post procedural haemorrhage
	Semaglutide 2.4 mg	LARGE CECAL POLYP	Large intestine polyp
PT captured procedure, but not diagnosis			
NN9536-4374 (b) (6)	Placebo	LEFT MICROSCOPIC TESTICULAR SPERM EXTRACTION, HISTOPATHOLOGY SERTOLI CELL-ONLY SYNDROME	Sperm aspiration
PT did not capture proper or full meaning of verbatim term			
NN9536-4374 (b) (6)	Semaglutide 1 mg	CONSTITUTIONAL SYNDROME	Cachexia
NN9536-4373 (b) (6)	Placebo	LAPAROSCOPIC SLEEVE GASTRIC RESECTION	Gastrectomy

Source: Reviewer created from ISS dataset ADAE.XPT

As this was a search to specifically compare verbatim terms and PTs using SAEs, non-serious AEs are not captured in the table above. Other AEs that were not appropriately coded were incidentally found during the safety review. For example:

- Trial 4373, semaglutide 2.4 mg: A verbatim term (JUNCTIONAL RHYTHM W ACUTE ST CHANGES, ASYMPTOMATIC) was not fully captured by the PT (Nodal rhythm).

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

- Trial 4376, semaglutide run-in period: A non-serious event was identified that may have been misclassification due to a verbatim term spelling error (cholelithiasis misspelled and PT reported 'Cholestasis'). This is also mentioned in Table 126 in Section 8.5.5, Hepatic Disorders.

For completeness, an additional review of non-serious *severe* AEs comparing verbatim to PTs was conducted. This review did not alert this reviewer to a systemic AE categorization problem.

8.3.3. Routine Clinical Tests

Routine clinical testing was appropriate for the size and scope of the clinical program.

In the phase 3 trials, the same central laboratories and methods and sampling frequency were used. A summary of parameters collected in routine clinical laboratory testing is listed below:

Table 54: Clinical Laboratory Testing in the Phase 3 Trials

Biochemistry (measured in serum)	Haematology (measured in whole blood)
Amylase and lipase	Haemoglobin
ALT, AST, ALP, TBL	Haematocrit
CK	Leucocytes
Creatinine	Thrombocytes
Albumin	Differential cell count (eosinophils, neutrophils, basophils, monocytes and lymphocytes)
Urea	
Albumin corrected calcium	
Potassium	Urine analysis
Sodium	UACR ^a
Bicarbonate ^a	
GGT ^b	Other tests
Calcitonin	eGFR (CKD-EPI)
TSH	Tryptase, in case of severe hypersensitivity

^a only collected in STEP 2; ^b only collected in STEP 1 and 2.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; CK: creatine kinase; eGFR (CKD-EPI): estimated glomerular filtration rate (eGFR) as per the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI); GGT: gamma glutamyl transferase; TBL: total bilirubin; TSH: thyroid stimulating hormone; UACR: urinary albumin to creatinine ratio.

Source: SCS, Table 1-3

Heart rate and blood pressure were measured every 4 to 8 weeks. Physical examinations were conducted at week 0 and week 68 (and week 20/randomization in trial 4376). ECGs were obtained at weeks 0, 20, and 68.

8.4. Safety Results

8.4.1. Deaths

Total deaths were too few to identify any trends, but reported causes of death were generally consistent with expected morbidity in the trial population. There was no clear imbalance in total deaths between the semaglutide and placebo arms.

The following table provides a summary of the 8 deaths that were reported in the phase 2 and 3 trials conducted for the semaglutide for weight management program. No deaths were reported in any of the 3 phase 1 studies in the weight management program. Furthermore, no additional deaths from the completed trials were reported in the 120-day safety update.

All deaths in the phase 2 and 3 program were adjudicated as cardiovascular (CV) or non-CV death by an independent external adjudication committee (EAC). (Deaths considered “undetermined” by the EAC were adjudicated as CV death in the MACE analysis; see Section 8.5.3.) All CV/undetermined deaths in this program were in semaglutide-treated subjects. There are too few events to draw a conclusion at this time. Section 8.5.3 discusses CV events overall in the weight management program.

Table 55: Listing of Deaths in Weight Management Program, In-Trial

Study	Subject ID	Age / Sex / BMI	Randomized Treatment	Study Drug Exposure (Days)	Study Day of Death	Primary Cause of Death	EAC determination
4153	(b) (6)	40/F/36.7	Sema 0.4 mg F	85	120	Metastatic ovarian carcinoma	Non-CV death
4373	(b) (6)	40/M/83.0	Sema 2.4 mg	198	311	Sudden death	CV death
4373	(b) (6)	63/F/35.7	Placebo	92	145	Glioblastoma	Non-CV death
4374	(b) (6)	67/F/28.1	Sema 1 mg	43	395	Cardiorespiratory arrest	Undetermined
4374	(b) (6)	62/M/46.2	Sema 2.4 mg	148	154	Myocardial infarction	CV death
4374	(b) (6)	65/M/29.4	Placebo	106	161	Metastatic hepatocellular carcinoma	Non-CV death
4376	(b) (6)	66/F/37.8	Sema 2.4 mg	307	307	Found dead in home	Undetermined
4376	(b) (6)	62/F/42.5	Sema/Placebo*	274	458	Metastatic lung cancer	Non-CV death

* Randomized to placebo after 20-week semaglutide 2.4 mg run-in as per study design; death occurred during placebo period
Sema=semaglutide

Source: Reviewer created from study reports and SCS, Table 2-3

Brief narratives are provided for subjects treated with semaglutide below, including the subject in trial 4374 who was treated with semaglutide 1 mg and the subject in trial 4376 who was

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

treated with semaglutide during the run-in period and then was subsequently randomized to placebo.

Phase 2:

- Study 4153: 1 death (semaglutide 0.4 mg F)

Subject (b) (6) was a 40-year-old female who experienced the adverse events of metastatic ovarian carcinoma (study day 96) and pneumonia (study day 105), which ultimately led to her death on study day 120. Medical history included obesity, mild depression, dyslipidemia, "euthyroidism," chronic low back pain, hyperinsulinemia, deafness, bilateral retinitis pigmentosa, gastroesophageal reflux, irregular menstrual cycle, hypovitaminosis D, microcytic anemia, rhonchi, and bronchitis. She had no smoking history and no known family history of neoplasm.

Approximately 2 months prior to diagnosis, the subject presented with pain in the right iliac fossa (reported as a non-serious AE). The subject went to see her general practitioner, who attributed this abdominal pain to the intake of trial medication (there was no idea of cancer at this time).

Two weeks later, the subject started to experience diffuse abdominal pain.

On approximately study day 94, a gynecologic ultrasound was performed showing adhesion in the vaginal vault and the subject was hospitalized.

On the same date the gynecologic ultrasound was repeated due to a necrotic uterine mass oozing, and compared to emergency ultrasound it revealed development of a suspicious mass in gynecological level and effusion ascites paraneoplastic, superinfection mass; malignant neoplasm in the ovary.

Computed tomography showed: metastatic peritoneal carcinomatosis table with wide reaching omental and multiple formations ganglion para-aortic and pelvic metastatic appearance and on study day 98, laparoscopy revealed detection of peritoneal carcinomatosis.

On study day 105, the subject was diagnosed with pneumonia and she died 15 days later.

Reviewer comment: Given the stage of disease at diagnosis, it seems likely that the ovarian cancer was present prior to the start of the trial. The history of obesity, irregular menstrual periods, and hyperinsulinemia is suggestive of polycystic ovarian syndrome, which has been reported as a risk factor for ovarian cancer. The age of 40 is young for an ovarian cancer diagnosis, however, which could suggest a genetic contribution as well. There were no other

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

cases of ovarian cancer in the semaglutide for weight management phase 3 development program.

Of note, there is a suggestion that potential early symptoms of the ovarian cancer (abdominal pain) was attributed to semaglutide and therefore could have been overlooked.

Phase 3:

- Study 4373: 2 deaths (1 semaglutide 2.4 mg, 1 placebo)

Subject (b) (6) (semaglutide 2.4 mg) was a 40-year-old male with a BMI of 83 kg/m² and a history of hypertension and untreated obstructive sleep apnea. He was a previous smoker. The subject had a number of AEs during the dose-escalation period, including abdominal pain, nausea, vomiting, and diarrhea. He was also noted to be bedridden. The subject discontinued treatment on day 198 due to an AE of asthenia (reported on day 141) and later reported 3 separate SAEs of 'Loss of consciousness' (days 282-303). The first SAE was described as dizziness then loss of consciousness for 30 seconds; no CT scan was done because of the subject's weight and he was kept in the hospital for 24-hour neurologic observation. The second SAE was reported as the subject lost consciousness with uncontrolled urination in his bed. No CT scan was done because of the subject's weight. It was reported that bloodwork and cervical spine x-ray were normal. Cardiac evaluations and an MRI were reportedly scheduled. The third SAE again reported that the subject lost consciousness with uncontrolled urination in his bed. No additional information was available. Approximately 8 days later (day 311), the subject was found dead in his bed in the morning. No autopsy was performed, and the cause of death was unknown, but presumed cardiac by the adjudication committee.

Reviewer comment: Not enough information was available to adequately assess causality. A drug contribution cannot be completely dismissed due to temporal relationship to early symptoms, although notably he had been off of drug for almost 6 months at the time of his death. The subject's extreme obesity (BMI 83 kg/m²) was likely a contributing factor and also might have limited the evaluation of the loss of consciousness events.

- Study 4374: 3 deaths (1 semaglutide 1 mg, 1 semaglutide 2.4 mg, 1 placebo)

Subject (b) (6) (semaglutide 1 mg) was a 68-year-old female with a history of type 2 diabetes, dyslipidemia, coronary artery disease (triple vessel), hypertension, diabetic nephropathy, dilated cardiomyopathy, and left ventricular ejection fraction 20%. She was a non-smoker. The subject was treated in the trial for 43 days and then discontinued because of a protocol deviation (randomized in violation of randomization criteria). Approximately 1 year after stopping study drug (but still in-trial), the subject was admitted to the hospital with hypoglycemia (BG 65 mg/dL), breathlessness, cough with expectoration for 1 week, chest pain

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

for 3 days, palpitation, and drowsiness in the last 3-4 days. She was diagnosed with lower respiratory tract infection with multiple organ dysfunction and shock. On the second hospital day, she went into sudden cardiorespiratory arrest and died. An autopsy was not performed.

Reviewer comment: An acute infection in the setting of a complicated medical history was likely the precipitating factor. As the subject had not been on study drug for almost 1 year, this event is unlikely related to semaglutide.

Subject (b) (6) (semaglutide 2.4 mg) was a 62-year-old male subject with a BMI of 46 kg/m², type 2 diabetes, hypertension, nonalcoholic fatty liver disease, nephropathy, albuminuria, and inversion of T wave (V4-V6). He was a previous smoker. On day 154 of the study, the subject had a myocardial infarction. Resuscitation including defibrillation 3 times was unsuccessful and the subject died. An autopsy was performed, which confirmed myocardial infarction (by oral report).

Reviewer comment: The subject had multiple risk factors for myocardial infarction.

- Study 4375: 0 deaths
- Study 4376: 2 deaths (1 semaglutide 2.4 mg, 1 placebo [semaglutide during run-in])

Subject (b) (6) (semaglutide 2.4 mg) was a 67-year-old female with a medical history of hypertension, cervical carcinoma in situ, lower leg edema, knee and hip arthroses, cholecystitis, and chronic obstructive pulmonary disease. The subject was a previous smoker. The subject had several mild AEs reported during the trial, including decreased appetite, gastroesophageal reflux, insomnia, and left shoulder arthrosis. On day 307 the subject was found dead in her home by police. No autopsy was performed; according to the death certificate, her obstructive lung disease was considered an “underlying disease.” No further information was available.

Reviewer comment: Not enough information is available to assess causality. Given the temporal relationship to study drug, a contribution cannot be completely dismissed. It is unknown if the symptoms she had been reporting (reflux, insomnia, left shoulder arthrosis) were in fact undetected cardiac issues.

Subject (b) (6) (semaglutide run-in, randomized to placebo) was a 63-year-old female with a history of hypertension, hyperlipidemia, pre-diabetes, and diverticulitis. She never smoked. Approximately 3 months into the run-in period of the trial she was diagnosed with endometrial cancer. Approximately 5 months into the placebo randomized portion of the trial, the subject was admitted for an SAE of bowel obstruction, for which she had a CT scan that revealed a 1 cm pulmonary nodule. (The bowel obstruction was thought due to scarring, not cancer.) Further work-up included a PET scan: 2 lung lesions and positive pelvic lymph nodes; lung nodule

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

biopsy: poorly differentiated carcinoma with associated necrosis and scattered mitotic figures, immunostains positive for pancytokeratin, CK5/6(patch) and CK7(rare). On update, the pelvic lymph nodes were thought to be metastatic, although unclear whether the source was lung or endometrium. Follow-up PET/CT had shown doubling of right middle lobe nodule and lymph nodes in mediastinum and neck. At an unknown date the subject was diagnosed with a brain tumor, thought to be metastatic from lung. She was treated with radiation and chemotherapy, but ultimately died from pulmonary metastases and pericardial effusion. No autopsy was performed.

Reviewer comment: This is a complicated case, and although temporarily related to treatment, given the metastatic disease, the subject may have developed the cancer prior to treatment. It is notable that the subject had no smoking history.

In summary, the deaths have confounding features that make causality attribution challenging. In addition, there are too few deaths to assess for risk. The ongoing CVOT could help clarify potential benefits or risks of semaglutide on mortality, although CV death was neutral in a CVOT of Ozempic.

Ongoing Trials (Blinded)

As of the data lock date of 01 September 2020, a total of 15,651 subjects were randomized in the ongoing trials:

- Trial 4373 (STEP 1) extension phase
- Trial 4378 (STEP 5): 2-year safety and efficacy
- Trial 4382 (STEP 6): efficacy and safety in East Asian subjects
- Trial 4576 (STEP 8): semaglutide 2.4 mg vs. liraglutide 3 mg
- Trial 4451 (STEP TEENS)
- Trial 4388 (SELECT): CVOT in obesity

This corresponded to 15,277.3 PYO; the majority were from the SELECT CVOT (14,118 subjects, 13577.7 PYO).

A total of 167 AEs with fatal outcome have been reported across the ongoing trials; all occurred in the SELECT CVOT. The most frequent SOC was Cardiac disorders capturing 44/167 of the AEs with fatal outcome. Other fatal AEs are listed below:

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 56: Blinded Fatal AEs, Ongoing Trials, Data Lock 01 September 2020

Study ID	System Organ Class (SOC)	Total
		Total
EX9536-4388	Blood and lymphatic system disorders	2
	Cardiac disorders	44
	Gastrointestinal disorders	2
	General disorders and administration site conditions	31
	Infections and infestations	17
	Injury, poisoning and procedural complications	8
	Investigations	4
	Metabolism and nutrition disorders	1
	Musculoskeletal and connective tissue disorders	1
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15
	Nervous system disorders	19
	Psychiatric disorders	2
	Renal and urinary disorders	4

Study ID	System Organ Class (SOC)	Total
		Total
EX9536-4388	Respiratory, thoracic and mediastinal disorders	11
	Vascular disorders	6
	SubTotal	167
Total		167

Source: ISS, Appendix 7.12

In the 120-day safety update, blinded cases for new cases of death were evaluated from 01 September 2020 until 01 February 2021 from the above ongoing trials. In addition, another phase 3 trial was initiated since the submission of the NDA:

- Trial 4379 (STEP 7): efficacy and safety in Chinese subjects

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Across the 7 ongoing trials, 2 trials (STEP 5 and SELECT) reported new cases of death:

- Trial 4378 (STEP 5): 1 death, 'Acute myocardial infarction'
- Trial 4388 (SELECT): 68 deaths; see Table 57

Table 57: Blinded Fatal AEs from Ongoing SELECT Trial, 01 September 2020 until 01 February 2021

System organ class Preferred term	Total	
	N	E
Number of Subjects	16706	
Events	68	104
Cardiac disorders	24	29
Cardiac arrest	7	7
Acute myocardial infarction	5	5
Myocardial infarction	4	4
Cardio-respiratory arrest	2	2
Acute coronary syndrome	1	1
Arrhythmia	1	1
Arteriosclerosis coronary artery	1	1
Cardiac failure	1	1
Cardiogenic shock	1	1
Cardiomyopathy	1	1
Coronary artery disease	1	1
Left ventricular failure	1	1
Myocardial ischaemia	1	1
Supraventricular tachycardia	1	1
Ventricular arrhythmia	1	1
Infections and infestations	23	25
COVID-19	12	12
COVID-19 pneumonia	6	6
Septic shock	2	2
Lower respiratory tract infection	1	1
Meningitis tuberculous	1	1
Pneumonia	1	1
Pneumonia viral	1	1
Sepsis	1	1
General disorders and administration site conditions	17	17
Death	15	15
Multiple organ dysfunction syndrome	1	1
Sudden death	1	1
Respiratory, thoracic and mediastinal disorders	7	7
Acute respiratory failure	3	3
Respiratory failure	3	3
Pleural effusion	1	1
Nervous system disorders	4	5
Cerebrovascular accident	2	2
Hemiplegia	1	1
Seizure	1	1
Thrombotic stroke	1	1
Gastrointestinal disorders	3	4
Duodenal ulcer perforation	1	1
Gastroesophageal reflux disease	1	1
Ileus paralytic	1	1
Intestinal mass	1	1
Hepatobiliary disorders	2	3
Bile duct stone	1	1
Hepatic failure	1	1
Jaundice cholestatic	1	1

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

System organ class Preferred term	Total	
	N	E
Metabolism and nutrition disorders	2	2
Failure to thrive	1	1
Lactic acidosis	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2
Cholangiocarcinoma	1	1
Pancreatic carcinoma metastatic	1	1
Psychiatric disorders	2	2
Completed suicide	2	2
Renal and urinary disorders	2	2
Acute kidney injury	2	2
Vascular disorders	2	2
Circulatory collapse	1	1
Hypotension	1	1
Blood and lymphatic system disorders	1	1
Anaemia	1	1
Injury, poisoning and procedural complications	1	1
Multiple injuries	1	1
NOT CODED YET SOC	1	1
NOT CODED YET PT	1	1
Skin and subcutaneous tissue disorders	1	1
Decubitus ulcer	1	1

Source: 120-day safety update, Table 7.1.16

Fatal cases of jaundice cholestatic and hepatic failure were of particular interest (see Section 8.5.5, Hepatic Disorders), although still blinded. Additional information about these cases was included in the line listings:

- Subject EX9536-4388 (b) (6): the cholestatic jaundice event was co-reported with a fatal event of pancreatic carcinoma metastatic, choledocholithiasis, and acute kidney injury
- Subject EX9536-4388 (b) (6): the hepatic failure event was reported with fatal events of cholangitis, bile duct stone, acute kidney injury, septic shock, obstructive pancreatitis, lactic acidosis, and gastroesophageal reflux disease

Additional review of blinded hepatic events is in Section 8.5.5.

Blinded fatal suicide events in the CVOT, including from the 120-day safety update, are briefly addressed in Section 8.5.9, Psychiatric Disorders.

Reviewer comment: Blinded cases are very difficult to interpret; event rates will be calculated, and causality assessments will be conducted when the trial is complete. The

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

unblinded safety data from the ongoing CVOT is being monitored by a data monitoring committee (DMC).⁴³

8.4.2. Serious Adverse Events

In the overall development program, a greater proportion subjects treated with semaglutide experienced SAEs compared to patients treated with placebo. The most common SAEs reported by SOC were Infections and infestations (primarily the PT 'Gastroenteritis'), Gastrointestinal disorders, and Hepatobiliary disorders (primarily events of cholelithiasis and cholecystitis).

Clinical Pharmacology Trials

Trial 4455

This was a 20-week trial in 72 subjects randomized 1:1 to semaglutide or placebo. Two SAEs were reported: 1 event (2.8%) with the PT 'Road traffic accident' in the semaglutide 2.4 mg group and 1 event (2.8%) with the PT 'Colonic abscess' in the placebo group.

Trial 4590

This was a 20-week open-label trial in 68 subjects randomized 1:1 to the semaglutide single-dose pen-injector (to-be-marketed) or the multiple-dose PDS290 pen-injector (phase 3 trials). One SAE was reported: a subject treated with the single-dose pen injector had an event of PT 'Arrhythmia supraventricular'. The event in a 47-year-old male subject who had been treated for 20 weeks in the trial. Approximately 1 week after treatment discontinuation, supraventricular arrhythmia was noted incidentally on a study ECG. The subject was asymptomatic and stable. He was hospitalized overnight for monitoring of cardiac arrhythmia with atrial flutter. He had a normal transesophageal echocardiogram and was cardioverted to sinus rhythm. He was also diagnosed with arterial hypertension (non-serious AE).

Trial 4588

This was a 6-week open-label trial in 68 subjects randomized 1:1 to the semaglutide single-dose pen-injector (to-be-marketed) or the multiple-dose PDS290 pen-injector (phase 3 trials). No SAEs were reported.

Phase 2 Trial

⁴³ IND 126360; EX9536-4388 Data Monitoring Committee charter v.2

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial 4153

This was a 52-week trial in 957 subjects randomized in a 6:1 ratio (active:placebo) to the following treatments administered *daily*: semaglutide 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg (dose escalation every fourth week), semaglutide 0.3 mg F, 0.4 mg F (dose escalation every second week), liraglutide 3 mg (dose escalation every week), and placebo to match each active arm. In total, 104 SAEs were reported by 73 subjects.

The most common PTs reported were 6 events of 'Cholelithiasis' in 6 subjects (all with semaglutide) and 4 events of 'Osteoarthritis' in 4 subjects (3 events with semaglutide 0.05 mg and 1 event with semaglutide 0.3 mg). Three events of 'Acute pancreatitis' were reported in 2 subjects in the semaglutide 0.3 mg fast escalation arm. SAEs by SOC and the most frequent ($\geq 1\%$) on-treatment SAEs in the semaglutide groups are presented in the table below, in addition to some additional SAEs of interest (e.g., cholecystitis and pancreatitis).

Table 58: Study 4153, SAEs, On-Treatment

	Semaglutide							Lira N=103	Placebo N=136
	0.05 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
SAEs	13 (12.6)	8 (7.8)	5 (4.9)	6 (5.8)	13 (12.7)	6 (5.9)	7 (6.8)	4 (3.9)	11 (8.1)
Hepatobiliary disorders	1 (1.0)	0	1 (1.0)	1 (1.0)	1 (1.0)	3 (2.9)	1 (1.0)	0	1 (0.7)
<i>Cholelithiasis</i>	0	0	1 (1.0)	0	1 (1.0)	3 (2.9)	1 (1.0)	0	0
<i>Cholecystitis</i>	1 (1.0)	0	0	0	0	0	0	0	0
<i>Cholecystitis acute</i>	0	0	0	1 (1.0)	0	0	0	0	1 (0.7)
Musculoskeletal and connective tissue disorders	4 (3.9)	2 (2.0)	2 (1.9)	2 (1.9)	1 (1.0)	0	1 (1.0)	2 (1.9)	1 (0.7)
<i>Osteoarthritis</i>	3 (2.9)	0	0	1 (1.0)	0	0	0	0	0
<i>Arthralgia</i>	0	2 (2.0)	0	1 (1.0)	0	0	0	0	0
<i>Rhabdomyolysis</i>	0	0	1 (1.0)	0	0	0	0	0	0
Infections and infestations	3 (2.9)	3 (2.9)	0	1 (1.0)	4 (3.9)	0	2 (1.9)	0	1 (0.7)
Gastrointestinal disorders	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)	1 (1.0)	0	1 (0.7)
<i>Pancreatitis</i>	1 (1.0)	0	0	1 (1.0)	0	0	0	0	1 (0.7)
<i>Pancreatitis acute</i>	0	0	0	0	0	2 (2.0)	0	0	0
Renal and urinary disorders	2 (1.9)	0	0	1 (1.0)	1 (1.0)	0	1 (1.0)	0	1 (0.7)
Pregnancy, puerperium and perinatal conditions	1 (1.0)	0	0	0	0	0	0	0	0
Cardiac disorders	0	0	0	0	2 (2.0)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	0	1 (1.0)	0	1 (1.0)	0
Neoplasms benign, malignant and unspecified	1 (1.0)	0	0	0	0	0	1 (1.0)	1 (1.0)	2 (1.5)
Nervous system disorders	1 (1.0)	1 (1.0)	0	0	3 (2.9)	0	0	0	1 (0.7)
Metabolism and nutrition disorders	0	0	0	0	1 (1.0)	0	0	0	2 (1.5)
Reproductive system and breast disorders	1 (1.0)	0	0	0	0	1 (1.0)	0	0	1 (0.7)
Injury, poisoning and procedural complications	0	1 (1.0)	0	1 (1.0)	1 (1.0)	1 (1.0)	0	0	1 (0.7)
Immune system disorders	0	0	0	0	0	0	1 (1.0)	0	0
Surgical and medical procedures	0	0	0	1 (1.0)	1 (1.0)	0	0	0	1 (0.7)
Investigations	1 (1.0)	0	1 (1.0)	0	0	0	0	0	0
Vascular disorders	1 (1.0)	0	0	0	1 (1.0)	0	0	0	1 (0.7)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (1.0)	1 (1.0)	0	1 (0.7)
Congenital, familial and genetic disorders	0	0	1 (1.0)	0	0	0	0	0	0

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

	Semaglutide							Lira N=103	Placebo N=136
	0.05 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
Ear and labyrinth disorders	0	0	1 (1.0)	0	0	0	0	0	0

Lira=liraglutide

Source: Study 4153 CSR, Table 14.3.1.39

Phase 3 Trials

Trial 4373

This was a 68-week trial in 1961 subjects randomized in a 2:1 ratio to semaglutide 2.4 mg or placebo weekly. In the on-treatment period,⁴⁴ 177 SAEs were reported by 108 subjects, with a greater proportion occurring in the semaglutide 2.4 mg group (9.8%) vs. the placebo group (6.4%). The SOCs with the greatest imbalances of SAEs for semaglutide versus placebo were:

- Infections and infestations – primarily the PT ‘Gastroenteritis’
- Gastrointestinal disorders – primarily the PTs ‘Vomiting’ and ‘Abdominal pain’
- Hepatobiliary disorders – primarily the PTs ‘Cholelithiasis,’ ‘Cholecystitis,’ and ‘Cholecystitis acute’

The table below summarizes the SAEs by SOC in this trial. Certain terms that suggest imbalances for semaglutide versus placebo and/or are of specific interest are also presented by either HLT or PT (noted in parentheses).

Table 59: SAEs, Study 4373, On-Treatment

	Semaglutide 2.4 mg N=1306	Placebo N=655
SAEs	128 (9.8)	42 (6.4)
Infections and infestations	27 (2.1)	10 (1.5)
<i>Abdominal and gastrointestinal infections (HLT)</i>	12 (0.9)	1 (0.2)
<i>Upper respiratory tract infections (HLT)</i>	4 (0.3)	0
Gastrointestinal disorders	18 (1.4)	0
<i>Nausea and vomiting symptoms (HLT)</i>	4 (0.3)	0
<i>Colitis (excl infective) (HLT)</i>	3 (0.2)	0
<i>Gastrointestinal and abdominal pains (excl oral and throat) (HLT)</i>	3 (0.2)	0
<i>Pancreatitis acute (PT)</i>	2 (0.2)	0
Hepatobiliary disorders	17 (1.3)	1 (0.2)
<i>Cholecystitis and cholelithiasis (HLT)</i>	15 (1.1)	1 (0.2)
Musculoskeletal and connective tissue disorders	11 (0.8)	5 (0.8)
Neoplasms benign, malignant and unspecified	9 (0.7)	3 (0.3)
<i>Breast and nipple neoplasms malignant (HLT)</i>	3 (0.2)	1 (0.2)
<i>Papillary thyroid cancer (PT)</i>	1 (0.1)	0
Injury, poisoning and procedural complications	8 (0.6)	3 (0.5)
Nervous system disorders	8 (0.6)	3 (0.5)

⁴⁴ On-treatment: if any dose of trial product has been administered within the prior 49 days

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Cardiac disorders	7 (0.5)	7 (1.1)
General disorders and administration site conditions	5 (0.4)	0
Ear and labyrinth disorders	4 (0.3)	0
<i>Vertigo (PT)</i>	3 (0.2)	0
Respiratory, thoracic and mediastinal disorders	4 (0.3)	5 (0.8)
Blood and lymphatic system disorders	3 (0.2)	0
Eye disorders	3 (0.2)	0
Pregnancy, puerperium and perinatal conditions	3 (0.2)	0
Psychiatric disorders	3 (0.2)	1 (0.2)
Reproductive system and breast disorders	3 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	3 (0.2)	0
Surgical and medical procedures	3 (0.2)	5 (0.8)
Metabolism and nutrition disorders	2 (0.2)	0
Renal and urinary disorders	2 (0.2)	0
Investigations	1 (<0.1)	1 (0.2)
Immune system disorders	0	1 (0.2)
Vascular disorders	0	2 (0.3)

Source: Reviewer created from Study 4373 ADAE dataset; checked with Study 4373 CSR, Table 14.3.1.14

Trial 4374

This was a 68-week trial in 1210 subjects with type 2 diabetes randomized in a 1:1:1 ratio to semaglutide 2.4 mg, semaglutide 1 mg, or placebo weekly. In the on-treatment period, 217 SAEs were reported by 170 subjects, with a greater proportion occurring in the semaglutide 2.4 mg group (9.9%) and the placebo group (9.2%) versus the semaglutide 1 mg group (7.7%); the event rates were slightly higher with semaglutide 2.4 mg (13.3 events per 100 PYE) than with semaglutide 1 mg and placebo (10.0 events per 100 PYE). The SOCs with the greatest imbalances of SAEs for semaglutide 2.4 mg versus placebo were:

- Nervous system disorders
- Gastrointestinal disorders

Table 60: SAEs Study 4374, On-Treatment

	Semaglutide 2.4 mg N=403	Semaglutide 1 mg N=402	Placebo N=402
SAEs	40 (9.9)	31 (7.7)	37 (9.2)
Infections and infestations	9 (2.2)	9 (2.2)	9 (2.2)
Nervous system disorders	7 (1.7)	2 (0.5)	3 (0.7)
<i>Hepatic encephalopathy (PT)^a</i>	1 (0.2)	0	0
<i>Hyponatremic encephalopathy (PT)^b</i>	1 (0.2)	0	0
Cardiac disorders	6 (1.5)	7 (1.7)	6 (1.5)
Gastrointestinal disorders	6 (1.5)	3 (0.7)	3 (0.7)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

<i>Nausea and vomiting symptoms (HLT)</i>	2 (0.5)	2 (0.5)	0
Metabolism and nutrition disorders	4 (1.0)	5 (1.2)	4 (1.0)
<i>Dehydration (PT)</i>	1 (0.2)	2 (0.5)	1 (0.2)
<i>Diabetic ketoacidosis (PT)</i>	1 (0.2)	0	0
<i>Hyponatremia (PT)</i>	1 (0.2)	0	0
<i>Ketoacidosis (PT)</i>	1 (0.2)	0	0
<i>Lactic acidosis (PT)</i>	0	1 (0.2)	0
Injury, poisoning and procedural complications	4 (1.0)	3 (0.7)	4 (1.0)
Renal and urinary disorders	3 (0.7)	2 (0.5)	3 (0.7)
<i>Renal failure and impairment (HLT)</i>	1 (0.2)	2 (0.5)	2 (0.5)
Vascular disorders	3 (0.7)	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5)	6 (1.5)	5 (1.2)
Musculoskeletal and connective tissue disorders	2 (0.5)	2 (0.5)	2 (0.5)
Hepatobiliary disorders	2 (0.5)	1 (0.2)	1 (0.2)
<i>Cholecystitis and cholelithiasis (HLT)</i>	1 (0.2)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	1 (0.2)	1 (0.2)
Surgical and medical procedures	1 (0.2)	1 (0.2)	2 (0.5)
Reproductive system and breast disorders	1 (0.2)	0	0
Eye disorders	1 (0.2)	0	1 (0.2)
Immune system disorders	0	1 (0.2)	0
General disorders and administration site conditions	0	0	1 (0.2)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.2)

a This event is discussed further in Section 8.5.5, Hepatic Disorders

b Event of beer potomania and excessive water intake; this event is discussed further in Section 8.4.6, Laboratory Findings

Source: Reviewer created from Study 4374 ADAE dataset; checked with Study 4374 CSR, Table 14.3.1.14

Trial 4375

This was a 68-week trial in 611 subjects randomized 2:1 to semaglutide 2.4 mg or placebo weekly as an adjunct to an intensive lifestyle program. In the on-treatment period, 62 SAEs were reported by 43 subjects, with a greater proportion occurring in the semaglutide 2.4 group (9.1%) versus the placebo group (2.9%). The SOCs with the greatest imbalances of SAEs for semaglutide versus placebo were:

- Hepatobiliary disorders: 13 SAEs in 10 subjects (2.5%) in the semaglutide 2.4 mg group; 7 events of 'Cholelithiasis,' 2 events of 'Cholecystitis,' 3 events of 'Cholecystitis acute,' and 1 event of 'Biliary dyskinesia.' No events were reported in the placebo group.
- Infections and infestations: 12 SAEs in 8 subjects (2.0%) in the semaglutide group; 4 events of 'Appendicitis' and the remaining events comprised single events by PT. No events were reported in the placebo group.
- Musculoskeletal and connective tissue disorders: 8 SAEs in 5 subjects (1.2%) in the semaglutide group; 4 events of 'Osteoarthritis,' 2 events of 'Cervical spinal stenosis,' 1 event of 'Back pain' and 1 event of 'Intervertebral disc protrusion.' No events were reported in the placebo group.

Table 61: SAEs, Study 4375, On-Treatment

	Semaglutide 2.4 mg N=407	Placebo N=204
SAEs	37 (9.1)	6 (2.9)
Hepatobiliary disorders	10 (2.5)	0
<i>Cholecystitis and cholelithiasis (HLT)</i>	9 (2.2)	0
Infections and infestations	8 (2.0)	0
<i>Abdominal and gastrointestinal infections (HLT)</i>	4 (1.0)	0
Musculoskeletal and connective tissue disorders	5 (1.2)	0
<i>Osteoarthropathies (HLT)</i>	3 (0.7)	0
Nervous system disorders	3 (0.7)	0
Injury, poisoning and procedural complications	3 (0.7)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.7)	2 (1.0)
Renal and urinary disorders	2 (0.5)	0
Gastrointestinal disorders	2 (0.5)	2 (1.0)
Blood and lymphatic system disorders	1 (0.2)	0
Ear and labyrinth disorders	1 (0.2)	0
General disorders and administration site conditions	1 (0.2)	0
Psychiatric disorders	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0
Surgical and medical procedures	1 (0.2)	0
Vascular disorders	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	1 (0.5)

Source: Reviewer created from Study 4375 ADAE dataset; checked with Study 4375 CSR, Table 14.3.1.14

Trial 4376

This was a trial that utilized a randomized withdrawal design, such that 902 subjects were treated with semaglutide for 20 weeks; those that completed 20 weeks were randomized 2:1 for 48 weeks to semaglutide or placebo.

In the run-in period, 23 SAEs were reported in 21 subjects (2.3%). The most frequent SAEs during this period were 'Osteoarthritis' (3 subjects), and 'Abdominal pain,' 'Nephrolithiasis,' and 'Acute myocardial infarction' (2 subjects each).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 62: SAEs, Study 4376, On-Treatment, Run-In Period

	Semaglutide N=902
SAEs	21 (2.3)
<i>By PT:</i>	
Osteoarthritis	3 (0.3)
Abdominal pain	2 (0.2)
Acute myocardial infarction	2 (0.2)
Nephrolithiasis	2 (0.2)
Abscess neck	1 (0.1)
Arthropod bite	1 (0.1)
Arthroscopic surgery	1 (0.1)
Biliary cyst	1 (0.1)
Cellulitis	1 (0.1)
Corneal abrasion	1 (0.1)
Dehydration	1 (0.1)
Endometrial cancer stage II	1 (0.1)
Hemiparesthesia	1 (0.1)
Lower limb fracture	1 (0.1)
Ovarian cyst	1 (0.1)
Pulmonary embolism	1 (0.1)
Syncope	1 (0.1)
Vertigo	1 (0.1)

Source: Reviewer created from Study 4376 ADAE dataset

In the randomized period, 51 SAEs were reported in 41 subjects (7.7%) in the semaglutide group and 19 SAEs were reported in 15 subjects (5.6%) in the placebo group. The interpretation of the randomized period safety findings should take into consideration that all subjects were exposed to semaglutide during the trial (even the placebo subjects).

Table 63: SAEs, Study 4376, On-Treatment, Randomized Period

	Semaglutide N=535	Placebo N=268
SAEs	41 (7.7)	15 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1.5)	1 (0.4)
<i>Breast and nipple neoplasms malignant (HLT)</i>	3 (0.6)	0
Hepatobiliary disorders	6 (1.1)	2 (0.7)
<i>Cholecystitis and cholelithiasis (HLT)</i>	6 (1.1)	2 (0.7)
Infections and infestations	6 (1.1)	4 (1.5)
<i>Abdominal and gastrointestinal infections (HLT)</i>	4 (0.7)	1 (0.4)
Nervous system disorders	5 (0.9)	1 (0.4)
<i>Quadriplegia (PT)^a</i>	1 (0.2)	0
Injury, poisoning and procedural complications	5 (0.9)	3 (1.1)
General disorders and administration site conditions	2 (0.4)	0
Renal and urinary disorders	2 (0.4)	0
Vascular disorders	2 (0.4)	0
Cardiac disorders	2 (0.4)	3 (1.1)
Blood and lymphatic system disorders	1 (0.2)	0
Ear and labyrinth disorders	1 (0.2)	0
Endocrine disorders	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.2)	0
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0
Product issues	1 (0.2)	0
Surgical and medical procedures	1 (0.2)	0
Gastrointestinal disorders	1 (0.2)	4 (1.5)
Reproductive system and breast disorders	0	1 (0.4)
a Reported as "partial tetraplegia;" by report, organic causes were ruled out, thought to be stress-related and the subject recovered		

Source: Reviewer created from Study 4376 ADAE dataset

The applicant also provided an assessment of SAEs in a pooled analysis of the phase 3 trials; the table below also includes the event rate.

As with the individual trials, imbalances were particularly noted in SAEs of gastrointestinal infections, cholelithiasis and cholecystitis, and general gastrointestinal disorders such as vomiting and abdominal pain. Specific AEs of interest are discussed in Section 8.5 and include gallbladder disorders and gastrointestinal disorders and their complications. In addition:

- Under the Infections and infestations SOC, in addition to the PT 'Gastroenteritis,' a numerical imbalance was noted for 'Appendicitis' and 'Appendicitis perforated'. All events were recovered. Five events (all semaglutide) led to temporary treatment interruption.
- The imbalance in serious gastrointestinal AEs in Table 64, below, was diluted by using the

phase 3 pool; trial 4376, which only randomized subjects who tolerated semaglutide 2.4 mg, had few GI SAEs and were reported more frequently in the placebo arm (Table 63). In the dose-escalation group, the numbers were: semaglutide 26 (1.2%) versus placebo 4 (0.3%), unadjusted.

A numeric imbalance in nervous system SAEs is noted; however, individual PTs do not suggest clustering. (For example, although there were 3 events of ‘Cerebral infarction’ in the semaglutide group and none in the placebo group, there were 2 events of ‘Ischemic stroke’ in the placebo group and none in the semaglutide group. See Section 8.5.3 for further discussion of cerebrovascular events.)

Small numerical imbalances in the SOCs of ‘Renal and urinary disorders,’ ‘General disorders and administration site conditions,’ and ‘Blood and lymphatic site disorders,’ were also noted, taking into account the 2:1 randomization for semaglutide 2.4 mg and placebo. PTs in these SOCs were reviewed and could be attributed in part to urinary tract stone formation, non-cardiac chest pain, and anemia, respectively. Anemia is discussed further in Section 8.4.6, Laboratory Findings. An imbalance in urolithiasis was not observed overall (serious and non-serious AEs): semaglutide 2.4 mg 0.9%, placebo 1.2%.

Table 64: Phase 3 Pool, SAEs, On-Treatment

	Semaglutide 2.4 mg N=2650 PYE=3309.5		Placebo N=1529 PYE=1885.4	
SAEs	246 (9.3)	341 (10.5)	100 (6.4)	132 (6.8)
Infections and infestations	50 (1.9)	56 (1.7)	23 (1.5)	30 (1.5)
<i>Gastroenteritis</i>	10 (0.4)	10 (0.3)	1 (<0.1)	1 (<0.1)
<i>Appendicitis</i>	10 (0.4)	11 (0.3)	3 (0.2)	3 (0.2)
<i>Appendicitis perforated</i>	1 (<0.1)	1 (<0.1)	0	0
Hepatobiliary disorders	35 (1.3)	43 (1.2)	4 (0.3)	4 (0.2)
<i>Cholelithiasis</i>	25 (0.9)	25 (0.7)	3 (0.2)	3 (0.2)
<i>Cholecystitis</i>	7 (0.2)	7 (0.2)	0	0
<i>Cholecystitis acute</i>	6 (0.2)	6 (0.2)	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	27 (1.1)	37 (1.1)	9 (0.6)	10 (0.6)
<i>Vomiting</i>	7 (0.3)	7 (0.2)	0	0
<i>Abdominal pain</i>	5 (0.2)	5 (0.1)	1 (<0.1)	1 (<0.1)
Nervous system disorders	23 (0.9)	27 (0.9)	7 (0.4)	8 (0.4)
Neoplasms benign, malignant and unspecified	22 (0.8)	22 (0.7)	11 (0.7)	12 (0.6)
Injury, poisoning and procedural complications	20 (0.8)	34 (1.1)	11 (0.7)	11 (0.6)
Musculoskeletal and connective tissue disorders	19 (0.7)	22 (0.6)	7 (0.5)	8 (0.4)
<i>Osteoarthritis</i>	7 (0.3)	8 (0.2)	2 (0.1)	2 (0.1)
Cardiac disorders	15 (0.6)	19 (0.6)	16 (1.0)	16 (0.8)
Renal and urinary disorders	9 (0.4)	11 (0.4)	3 (0.2)	3 (0.1)
Metabolism and nutrition disorders	8 (0.4)	8 (0.3)	5 (0.3)	5 (0.2)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

	Semaglutide 2.4 mg N=2650 PYE=3309.5		Placebo N=1529 PYE=1885.4	
General disorders and administration site conditions	8 (0.3)	8 (0.2)	1 (<0.1)	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	7 (0.3)	8 (0.3)	6 (0.4)	7 (0.4)
Vascular disorders	6 (0.3)	6 (0.2)	3 (0.2)	3 (0.2)
Surgical and medical procedures	6 (0.2)	6 (0.2)	7 (0.5)	7 (0.4)
Ear and labyrinth disorders	6 (0.2)	6 (0.2)	0	0
<i>Vertigo</i>	5 (0.2)	5 (0.1)	0	0
Blood and lymphatic system disorders	5 (0.2)	5 (0.1)	0	0
Eye disorders	4 (0.2)	5 (0.1)	1 (<0.1)	1 (<0.1)
Reproductive system and breast disorders	4 (0.2)	4 (0.1)	2 (0.1)	2 (0.1)
Pregnancy, puerperium and perinatal conditions	4 (0.1)	4 (0.1)	1 (<0.1)	1 (<0.1)
Psychiatric disorders	4 (0.1)	4 (0.1)	1 (<0.1)	1 (<0.1)
Skin and subcutaneous tissue disorders	3 (0.1)	3 (<0.1)	0	0
Endocrine disorders	1 (<0.1)	1 (<0.1)	0	0
Product issues	1 (<0.1)	1 (<0.1)	0	0
Investigations	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Immune system disorders	0	0	1 (<0.1)	1 (<0.1)

Source: ISS, Appendix 7.2, Table 7.2.21

No new SAEs were reported from completed trials in the 120-day safety update. Three post-data lock updates were made to individual SAE terms.^{45,46,47} None of these updates changes the overall SAE assessment, or assessment of individual safety issues.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Overall, a greater proportion of semaglutide-treated patients experienced AEs leading to premature discontinuation compared to placebo-treated patients, most commonly AEs in the Gastrointestinal disorders SOC. Fast dose escalation in the Phase 2 trial 4153 appeared to be

⁴⁵ Subject NN9536-4373 (b) (6) semaglutide): PT changed from 'Musculoskeletal pain' to 'Arthralgia'

⁴⁶ Subject NN9536-4373 (b) (6) (semaglutide): PT 'Anomaly of external ear congenital' severity changed from '-' to 'Mild'

⁴⁷ Subject NN9536-4375 (b) (6) semaglutide): PT 'Benign pancreatic neoplasm' status changed from 'Not recovered' to 'Recovered'; resolution date also provided

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

associated with higher rates of discontinuation.

Clinical Pharmacology Trials

Trial 4455

One AE led to withdrawal from the trial in a placebo subject (colonic abscess).

Trial 4590

No AEs leading to withdrawal from the trial were reported.

Trial 4588

No AEs leading to withdrawal from the trial were reported.

Phase 2 Trial

Trial 4153

A total of 78 subjects had 137 AEs that led to premature discontinuation. The incidence of these AEs increased with increasing semaglutide dose and was greater than placebo; the imbalance was primarily due to gastrointestinal AEs with semaglutide (e.g., nausea, diarrhea, and vomiting). Liraglutide 3 mg had a similar proportion of AE discontinuations compared with semaglutide 0.3 mg and fewer AE discontinuations than semaglutide 0.4 mg. Both of the fast dose escalation arms had more AE discontinuations than liraglutide or placebo, also due to GI AEs.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 65: Adverse Events Leading to Premature Discontinuation of Trial Product

	Semaglutide							Lira N=103	Placebo N=136
	0.05 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
AEs leading to discontinuation	8 (7.8)	8 (7.8)	5 (4.9)	4 (3.9)	15 (14.7)	17 (16.7)	8 (7.8)	9 (8.7)	4 (2.9)
Gastrointestinal disorders	6 (5.8)	5 (4.9)	3 (2.9)	4 (3.9)	13 (12.7)	12 (11.8)	8 (7.8)	4 (3.9)	2 (1.5)
Nervous system disorders	2 (1.9)	0	0	0	1 (1.0)	2 (2.0)	0	0	0
Psychiatric disorders	1 (1.0)	1 (1.0)	0	0	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (0.7)
Metabolism and nutrition disorders	1 (1.0)	0	0	0	0	1 (1.0)	0	0	1 (0.7)
General disorders and administration site conditions	1 (1.0)	0	0	0	0	2 (2.0)	0	2 (1.9)	0
Skin and subcutaneous tissue disorders	1 (1.0)	1 (1.0)	0	0	0	1 (1.0)	0	2 (1.9)	0
Hepatobiliary disorders	1 (1.0)	0	0	0	0	0	0	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (1.0)	0	0	0	0	0	0	0	0
Infections and infestations	1 (1.0)	0	0	0	0	0	0	1 (1.0)	0
Investigations	0	0	1 (1.0)	0	0	2 (2.0)	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	1 (1.0)	0	1 (1.0)	0
Musculoskeletal and connective tissue disorders	0	1 (1.0)	0	0	0	0	0	0	0
Cardiac disorders	0	0	0	0	0	0	0	1 (1.0)	0
Eye disorders	1 (1.0)	0	0	0	0	0	0	0	0
Lira=liraglutide									

Source: Study 4153 CSR, Table 14.3.1.50

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Phase 3 Trials

Trial 4373

The proportion of subjects with AEs leading to permanent discontinuation of trial product was higher with semaglutide 2.4 mg than with placebo (7.0% vs. 3.1%), mostly due to gastrointestinal AEs (e.g., nausea, vomiting, diarrhea, constipation, and abdominal pain).

Table 66: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4373, On-Treatment

	Semaglutide N=1306	Placebo N=655
AEs leading to discontinuation	92 (7.0)	20 (3.1)
Gastrointestinal disorders	59 (4.5)	5 (0.8)
Psychiatric disorders	7 (0.5)	3 (0.5)
Skin and subcutaneous tissue disorders	5 (0.4)	2 (0.3)
Infections and infestations	4 (0.3)	1 (0.2)
Nervous system disorders	4 (0.3)	1 (0.2)
General disorders and administration site conditions	3 (0.2)	0
Metabolism and nutrition disorders	3 (0.2)	0
Eye disorders	2 (0.2)	1 (0.2)
Hepatobiliary disorders	2 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	2 (0.2)	2 (0.3)
Investigations	2 (0.2)	0
Musculoskeletal and connective tissue disorders	2 (0.2)	0
Neoplasms benign, malignant and unspecified	2 (0.2)	2 (0.3)
Ear and labyrinth disorders	1 (<0.1)	0
Renal and urinary disorders	1 (<0.1)	0
Surgical and medical procedures	1 (<0.1)	1 (0.2)
Vascular disorders	0	1 (0.2)
Blood and lymphatic system disorders	0	1 (0.2)
Cardiac disorders	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)

Source: Study 4373 CSR, Table 12-8

Trial 4374

The proportions of subjects with AEs leading to permanent discontinuation of trial product was higher with semaglutide 2.4 mg (6.2%) and semaglutide 1 mg (5.0%) than with placebo (3.5%), mostly due to gastrointestinal AEs (e.g., nausea, vomiting, and diarrhea).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 67: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4374, On-Treatment

	Semaglutide 2.4 N=403	Semaglutide 1 N=402	Placebo N=402
AEs leading to discontinuation	25 (6.2)	20 (5.0)	14 (3.5)
Gastrointestinal disorders	17 (4.2)	14 (3.5)	4 (1.0)
Nervous system disorders	2 (0.5)	0	2 (0.5)
Eye disorders	1 (0.2)	1 (0.2)	0
General disorders and administration site conditions	1 (0.2)	1 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)	0	0
Neoplasms benign, malignant and unspecified	1 (0.2)	1 (0.2)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	0
Skin and subcutaneous tissue disorders	1 (0.2)	0	2 (0.5)
Hepatobiliary disorders	0	1 (0.2)	0
Infections and infestations	0	0	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.2)	1 (0.2)
Psychiatric disorders	0	1 (0.2)	1 (0.2)

Source: Study 4374, Table 12-7

Trial 4375

The proportion of subjects with AEs leading to permanent discontinuation of trial product was higher with semaglutide 2.4 mg than with placebo (5.9% vs. 2.9%), mostly due to gastrointestinal AEs (e.g., nausea, vomiting, and diarrhea).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 68: Adverse Events Leading to Permanent Trial Product Discontinuation, Trial 4375, On-Treatment

	Semaglutide N=407	Placebo N=204
AEs leading to discontinuation	24 (5.9)	6 (2.9)
Gastrointestinal disorders	14 (3.4)	0
Psychiatric disorders	3 (0.7)	1 (0.5)
Hepatobiliary disorders	2 (0.5)	0
Nervous system disorders	2 (0.5)	0
Skin and subcutaneous tissue disorders	2 (0.5)	2 (1.0)
Injury, poisoning and procedural complications	1 (0.2)	0
Investigations	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
General disorders and administration site conditions	0	1 (0.5)
Infections and infestations	0	1 (0.5)
Musculoskeletal and connective tissue disorders	0	1 (0.5)

Source: Study 4375 CSR, Table 12-8

Trial 4376

In the 20-week semaglutide run-in period, 53 subjects (5.9%) had an AE that led to permanent treatment discontinuation. Of these, 48 subjects discontinued before randomization, and 5 subjects were randomized before subsequently permanently discontinuing trial product.

Table 69: AEs Leading to Permanent Trial Product Discontinuation, On-Treatment, Trial 4376 Run-In Period

	Semaglutide N=902	
	n	%
AEs leading to discontinuation	53	5.9
<i>By PT:</i>		
Nausea	24	2.7
Diarrhea	10	1.1
Vomiting	9	1.0
Abdominal pain	3	0.3
Abdominal pain upper	2	0.2
Constipation	2	0.2
Dyspepsia	2	0.2
Headache	2	0.2
Abdominal discomfort	1	0.1
Arthralgia	1	0.1
Atrial fibrillation	1	0.1
Bipolar disorder	1	0.1

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

	Semaglutide N=902	
Disturbance in attention	1	0.1
Dizziness	1	0.1
Eructation	1	0.1
Fatigue	1	0.1
Flatulence	1	0.1
Gastritis	1	0.1
Gastroenteritis	1	0.1
Gastroesophageal reflux disease	1	0.1
Joint noise	1	0.1
Myalgia	1	0.1
Ovarian cyst	1	0.1
Pancreatitis acute	1	0.1
Rash	1	0.1
Urticaria	1	0.1
Ventricular extrasystoles	1	0.1

Source: Reviewer created from Study 4376 ADAE.xpt dataset

In the randomized period, fewer subjects on semaglutide than placebo reported discontinuing trial product due to an adverse event (1.5% vs. 2.6%); however, 1 subject in the placebo group had 3 AEs (nausea, cholelithiasis, and abdominal pain) that were erroneously categorized as leading to permanent treatment discontinuation (the subject resumed treatment).

Table 70: AEs Leading to Permanent Trial Product Discontinuation, On-Treatment, Trial 4376 Randomized Period

	Semaglutide N=535	Placebo N=268
AEs leading to discontinuation	8 (1.5)	7 (2.6)
Gastrointestinal disorders	2 (0.4)	4 (1.5)
Blood and lymphatic system disorders	1 (0.2)	0
General disorders and administration site conditions	1 (0.2)	0
Investigations	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Neoplasms benign, malignant and unspecified	1 (0.2)	0
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0
Renal and urinary disorders	1 (0.2)	0
Hepatobiliary disorders	0	4 (1.5)
Psychiatric disorders	0	1 (0.4)

Source: Study 4376 CSR, Table 12-6

Overall, in the phase 3 pool, the proportions of subjects with AEs leading to permanent treatment discontinuation was 5.7% for semaglutide 2.4 mg (5.9 events per 100 PYE) and 3.0% for placebo (3.0 events per 100 PYE). In the phase 3 dose escalation group, AEs were the

primary cause of permanent discontinuation of product in 6.8% of semaglutide 2.4 mg subjects and 3.2% of placebo subjects.

In summary, AEs leading to permanent discontinuation of trial product was consistently higher with semaglutide 2.4 mg than with placebo, mostly due to gastrointestinal AEs.

8.4.4. Significant Adverse Events

Table 71 summarizes selected AE categories of interest in the phase 3 pool. Significant AEs of special interest are highlighted and reviewed in depth in Section 8.5, Analysis of Submission-Specific Safety Issues.

The proportion of subjects with any AE was slightly greater in the semaglutide 2.4 mg arm versus the placebo arm. More subjects on semaglutide versus placebo reported SAEs, severe AEs, AEs considered “probably” related to the drug, and AEs leading to permanent and temporary treatment discontinuation and to dose reduction.

Table 71: Overview of Selected AEs, Phase 3 Pool

	Semaglutide 2.4 mg N=2650	Placebo N=1529
All events	2348 (88.5)	1272 (83.6)
SAEs	246 (9.3)	100 (6.4)
Severe	269 (9.9)	105 (6.9)
Relationship to trial product – Probable	1048 (39.7)	282 (18.7)
Outcome – Not recovered	1034 (39.1)	605 (39.6)
Leading to:		
Permanent treatment discontinuation	149 (5.7)	47 (3.0)
Temporary interruption of trial product	233 (8.8)	59 (3.9)
Dose reduction of trial product	233 (8.8)	11 (0.7)

ISS, Appendix 7.2, Table 7.2.1

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the phase 3 pool, the most frequently observed AEs were in the ‘Gastrointestinal disorders’ SOC, with 67.1% of semaglutide 2.4 mg-treated subjects versus 43.2% of placebo-treated subjects reporting at least 1 event. Gastrointestinal disorders are described in more detail in Section 8.5.10.

AEs in the ‘Nervous system disorders’ SOC were also reported more frequently in the semaglutide arm (26.5%) versus the placebo arm (18.4%). Most AEs were related to headache and dizziness; see Table 72.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 72: Most Frequent AEs in the Semaglutide Arm ($\geq 5\%$) and Greater Than Placebo, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 %	Placebo N=1529 %
Nausea	38.3	14.0
Diarrhea	26.8	14.3
Constipation	21.8	10.2
Vomiting	21.8	5.7
Headache	12.8	8.7
Abdominal pain	8.4	4.0
Back pain	8.0	7.3
Fatigue	7.9	3.6
Decreased appetite	7.8	2.8
Dyspepsia	7.6	2.7
Abdominal pain upper	7.1	3.6
Dizziness	6.8	3.3
Eructation	6.5	0.4
Abdominal distension	6.3	4.3
Gastroenteritis	5.6	3.8
Urinary tract infection	5.3	4.0
Flatulence	5.3	3.7

Source: ISS, Appendix 7.2, Table 7.2.13

Other PTs that were reported by a higher proportion of subjects with semaglutide 2.4 mg compared to placebo included: 'Gastroenteritis viral' (3.7% vs. 2.5%, respectively), 'Alopecia' (3.3% vs. 1.4%), and 'Migraine' (2.1% vs. 1.3%). The applicant notes that the alopecia events were mainly reported as the lower level term (LLT) 'Hair loss' (2.5% vs. 1.0%), and they have proposed labeling the hair loss term.

Reviewer comment: As the other LLTs reported under the PT 'Alopecia' were 'Hair thinning,' 'Accelerated hair loss,' and 'Alopecia,' reporting only 'Hair loss' undercounts the AE. It would be reasonable to use a term such as 'Hair loss or thinning' instead of 'Alopecia' (with proportions 3.3% vs. 1.4%) to appropriately capture the event in labeling.

Because only those subjects who could tolerate the 2.4 mg dose were randomized in trial 4376, the randomized withdrawal design of trial 4376 dilutes some of the semaglutide-related AEs. Therefore, a separate analysis of PTs in the phase 3 dose-escalation group was conducted. Note that as this is a reviewer analysis, the proportions for PTs shown in Table 73 are unadjusted for study.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 73: Most Frequent AEs in the Semaglutide Arm ($\geq 2\%$) and Greater Than Placebo, Phase 3 Dose Escalation Group, On-Treatment

	Semaglutide 2.4 mg N=2116 Unadj. %	Placebo N=1261 Unadj. %
Total AEs	90.5	84.9
Nausea	44.9	15.5
Diarrhea	30.5	15.6
Constipation	24.9	10.6
Vomiting	24.7	6.0
Nasopharyngitis	20.7	19.1
Headache	14.5	9.5
Decreased appetite	9.3	3.5
Abdominal pain	9.3	4.0
Dyspepsia	9.3	3.0
Back pain	8.9	7.1
Fatigue	8.7	3.7
Abdominal pain upper	8.2	4.0
Dizziness	8.0	3.7
Eructation	7.8	0.4
Abdominal distension	7.6	4.9
Arthralgia	6.8	6.5
Flatulence	6.0	4.0
Gastroenteritis	6.0	4.4
Sinusitis	5.9	5.8
Urinary tract infection	5.8	4.0
Gastroesophageal reflux disease	5.6	2.5
Gastroenteritis viral	4.3	2.7
Abdominal discomfort	4.1	1.4
Bronchitis	3.6	3.4
Alopecia	3.5	1.3
Gastritis	3.1	1.0
Musculoskeletal pain	2.6	2.1
Insomnia	2.6	2.5
Migraine	2.4	1.1
Asthenia	2.3	1.3
Hemorrhoids	2.1	0.4
Dry mouth	2.0	0.8

Source: Reviewer created from ISS ADAE.xpt

Reviewer comment: A table similar to the above (with adjusted proportions and combining certain terms) might be appropriate for Section 6 of the prescribing information. In addition, see the alopecia comment above, which could be relevant to this data presentation as well.

The most common AEs in the 20-week semaglutide run-in period of trial 4376 were GI-related.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

A listing of the most common AEs during that period overall is presented below:

Table 74: Most Frequent AEs ($\geq 4\%$), Trial 4376, Run-In Period

	Semaglutide N=902	
	n	%
Total AEs	760	84.3
Nausea	422	46.8
Diarrhea	212	23.5
Constipation	200	22.2
Vomiting	140	15.5
Dyspepsia	103	11.4
Decreased appetite	102	11.3
Headache	96	10.6
Nasopharyngitis	92	10.2
Eructation	71	7.9
Abdominal pain	68	7.5
Fatigue	67	7.4
Gastroesophageal reflux disease	58	6.4
Abdominal distension	50	5.5
Flatulence	50	5.5
Abdominal pain upper	49	5.4
Dizziness	37	4.1

Source: Reviewer created from study 4376 ADAE.xpt dataset

By contrast to the dose-escalation group (Table 73), the incidence of AEs in the randomized phase of trial 4376 was particularly lower for GI AEs. Because all subjects received semaglutide, this table also includes common events that have a higher incidence in placebo.

Table 75: Most Frequent AEs In the Semaglutide Arm ($\geq 3\%$), Trial 4376, Randomized Period

	Semaglutide 2.4 mg N=535 %	Placebo N=268 %
Total AEs	81.3	75.0
Diarrhea	14.4	7.1
Nausea	14.0	4.9
Constipation	11.6	6.3
Nasopharyngitis	10.8	14.6
Vomiting	10.3	3.0
Headache	7.7	3.7
Influenza	7.3	7.1
Abdominal pain	6.5	3.0
Back pain	5.2	6.7
Fatigue	4.9	2.2
Arthralgia	4.7	5.2
Gastroenteritis	4.7	1.1
Urinary tract infection	4.5	3.7
Upper respiratory tract infection	4.3	4.9
Abdominal pain upper	3.7	1.1
Sinusitis	3.6	3.7
Alopecia	3.2	1.1
Dizziness	3.0	1.1

Source: Reviewer created from study 4376 ADAE.xpt dataset

Table 76 enumerates AEs considered by the investigator as “probably” or “possibly” related to the study drug. Note that because there may have been some degree of investigator and/or subject unblinding, primarily due to GI symptoms, the following table should be interpreted with caution.

Table 76: Adverse Events “Possibly” or “Probably” Related to Trial Product, On-Treatment

	Semaglutide 2.4 mg N=2650 %	Placebo N=1529 %
Gastrointestinal disorders	59.9	31.0
Nervous system disorders	11.4	4.9
<i>Headache</i>	5.5	2.7
<i>Dizziness</i>	3.9	1.2
General disorders and administration site conditions	10.6	7.0
<i>Fatigue</i>	4.1	1.4
<i>Asthenia</i>	1.4	0.5
Metabolism and nutrition disorders	9.3	4.3
<i>Decreased appetite</i>	7.6	2.6
Skin and subcutaneous tissue disorders	3.9	2.2
<i>Alopecia</i>	1.6	0.5

	Semaglutide 2.4 mg N=2650 %	Placebo N=1529 %
Infections and infestations	3.9	2.4
<i>Gastroenteritis</i>	1.9	1.3
<i>Gastroenteritis viral</i>	0.5	0.3
Investigations	3.3	2.1
<i>Lipase increased</i>	0.7	0.4
<i>Weight decreased</i>	0.5	0
Psychiatric disorders	2.5	1.7
<i>Insomnia</i>	0.8	0.6
<i>Anxiety</i>	0.5	0.1
<i>Depressed mood</i>	0.3	<0.1
Musculoskeletal and connective tissue disorders	1.7	0.8
<i>Muscle spasms</i>	0.4	<0.1
<i>Myalgia</i>	0.3	0.1
Hepatobiliary disorders	1.6	0.9
Injury, poisoning and procedural complications	1.1	0.5
Vascular disorders	1.1	0.4
<i>Hypotension</i>	0.3	0
Eye disorders	0.6	0.4
<i>Diabetic retinopathy</i>	0.3	0
Cardiac disorders	0.6	0.3
Renal and urinary disorders	0.6	0.3
Respiratory, thoracic and mediastinal disorders	0.6	0.1
Blood and lymphatic system disorders	0.5	0.3
Ear and labyrinth disorders	0.4	0.1
<i>Vertigo</i>	0.4	0.1
Reproductive system and breast disorders	0.4	0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0.2	<0.1
Endocrine disorders	0.1	<0.1

Source: ISS, Appendix 7.2, Table 7.2.18

8.4.6. Laboratory Findings

Laboratory tests that were part of reviewed safety issues are discussed elsewhere in the review; i.e., anti-semaglutide antibodies (Section 8.4.10, Immunogenicity), amylase and lipase (Section 8.5.2, Acute Pancreatitis), calcitonin (Section 8.5.4, Neoplasms), liver parameters (Section 8.5.5, Hepatic Disorders), renal parameters (Section 8.5.6, Acute Renal Failure), blood glucose (Section 8.5.7, Hypoglycemia), and certain individual cases of outlier hematological parameters (Section 8.5.11, Rare Events).

This section will summarize electrolytes, creatine kinase, and hematological parameters, with related AEs. There were no clinically important imbalances in these laboratory parameters.

Biochemistry

Table 77 summarizes categorical results of selected central laboratory biochemistry parameters from the dose escalation group. The proportions with values outside of cut-offs were similar for semaglutide and placebo. Of note, narratives for the 2 single semaglutide subjects with sodium < 120 mmol/L and potassium > 7 mmol/L suggested that in both cases there was a likely a laboratory error. Neither was reported as an AE and follow-up laboratory values were within normal limits.

Table 77: Selected Biochemistry Data, Minimum and/or Maximum Post-Baseline Values, Phase 3 Dose-Escalation Group, On-Treatment

	Semaglutide 2.4 N=2116 n (%)	Placebo N=1261 n (%)
Calcium, albumin corrected		
>ULN	33 (1.6)	15 (1.2)
>3.4 mmol/L	0	0
<LLN	48 (2.3)	39 (3.1)
<1.5 mmol/L	0	0
Potassium		
>ULN	156 (7.4)	97 (7.7)
>7.0 mmol/L	1 (<0.1)	2 (0.2)
<LLN	34 (1.6)	13 (1.0)
<2.5 mmol/L	0	0
Sodium		
>ULN	49 (2.3)	36 (2.9)
>160 mmol/L	0	1 (<0.1)
<LLN	53 (2.5)	37 (2.9)
<120 mmol/L	1 (<0.1)	0
Creatine kinase		
>ULN	364 (17.2)	243 (19.3)
>5x ULN	17 (0.8)	9 (0.7)
>10x ULN	6 (0.3)	5 (0.4)
Note that proportions are based on number of subjects with post-baseline data for each parameter		

Source: ISS, Tables 7.5.3 and 7.5.4

A review of electrolyte and related AEs demonstrated a similar proportion overall among groups, although the semaglutide group was associated with slightly more events of hypokalemia and hyponatremia.

Table 78: Electrolyte-Related AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (adj. %)	Placebo N=1529 n (adj. %)
Electrolyte and fluid balance conditions	33 (1.3)	20 (1.3)
Hypokalemia	13 (0.5)	5 (0.3)
Dehydration	11 (0.4)	10 (0.7)
Hyponatremia	4 (0.2)	0
Hyperkalemia	2 (<0.1)	3 (0.2)
Polydipsia	2 (<0.1)	1 (<0.1)
Fluid retention	1 (<0.1)	2 (0.1)
Hypernatremia	1 (<0.1)	0
Electrolyte imbalance	1 (<0.1)	0
Water, electrolyte and mineral investigations	5 (0.2)	5 (0.3)
Blood potassium increased	2 (<0.1)	0
Blood potassium abnormal	1 (<0.1)	0
Blood calcium decreased	1 (<0.1)	0
Serum ferritin decreased	1 (<0.1)	1 (<0.1)
Blood iron decreased	0	2 (0.1)
Blood sodium increased	0	1 (<0.1)

Source: ISS, Table 7.2.2

SAEs of hypokalemia and hyponatremia (all in semaglutide-treated subjects) are summarized below; note that reported laboratory data in narratives is often from local labs:

- **Hypokalemia:** NN9536-4373 (b) (6) was a 62-year-old female with a history of anxiety, dyslipidemia, hypertension, asthma, and peripheral neuropathy on hydrochlorothiazide who was on semaglutide for approximately 5 months when she presented complaining of significant mental/physical fatigue and dizziness. She was admitted to the hospital for hypokalemia; laboratory values were as follows: complete blood count WNL, eGFR 38 (ref: >60/1.73m²), urinalysis negative, sodium 134 (137-145 mmol/L); potassium 3.2 (3.5-5.1 mmol/L); chloride 93 (98-107 mmol/L); glucose 107 (74-99 mg/dL); BUN 22 (7-20 mg/dL); total protein 9.2 (6.3-8.2 g/dL). Trial drug was temporarily discontinued. The subject was treated and discharged with supplemental potassium. Several weeks later (prior to restarting the trial drug; hydrochlorothiazide had not been discontinued), potassium was again 3.2 mmol/L and she was prescribed additional potassium. Dizziness did not return. The study drug was re-introduced at a reduced dose.

- Hyponatremia: NN9536-4374 (b) (6) was a 75-year-old male who was admitted to the hospital with euvolemic hyponatremia (sodium value not provided), herpes zoster, and an acute respiratory tract infection. The subject recovered after treatment and the drug was restarted approximately 6 months later.
- Hypokalemia: NN9536-4375/ (b) (6) was a 68-year-old female with dyslipidemia, hypertension, sleep apnea, hypothyroidism, and depression/anxiety on hydrochlorothiazide. After approximately 3 months in the trial, the subject presented with hypokalemia, anorexia, back pain, chills, fever, weakness, headache, myalgia, nausea, and vomiting. She was diagnosed with a urinary tract infection, hypotension (blood pressure 80/50), and hypokalemia (blood potassium 2.2 mmol/L) and treated with rehydration, electrolyte repletion, and antibiotics. She temporarily discontinued treatment due to the AEs but restarted about 1 week later.

Separately, an SAE of 'Hyponatremic encephalopathy' was reported (also noted in study 4374 SAE Table 60):

- Subject NN9536-4374 (b) (6) was a 54-year-old male with T2D and hypertension. Approximately nine months into the trial he went on a drinking binge: he drank a 24-pack of beer, followed the next day by a 12-pack of beer to treat his hangover. He continued to not feel well and according to his wife was confused. The following day, he began drinking excessive amounts of water, and the next day was found by his wife lying on the ground and unarousable. During hospital admission, serum sodium was found to be 108 mmol/L, chloride 73 mmol/L, glucose 189 mg/dL, AST 131 U/L, ALT 81 U/L, albumin 3.4 g/dL, and lactic acid 5.6 mmol/L (elevated, no reference range provided). He recovered after treatment in the ICU. The diagnosis was reported as: "acute severe hyponatremia with acute encephalopathy secondary to beer potomania."

The events of CK > 10x ULN in the semaglutide-treated subjects are summarized below:

Study 4373:

- Subject (b) (6) was a 56-year-old female. At week 52, CK was 3262 U/L (ref: 29-168 U/L). This was reported as a non-serious AE of 'Blood creatine phosphokinase increased' of moderate severity and did not lead to changes in dosing of trial product. The investigator reported that CK 2 days later (local laboratory) was 1124 U/L. At week 68, CK was 25 U/L. The investigator suggested that the event might be caused by rosuvastatin 20 mg which was subsequently discontinued.
- Subject (b) (6) was a 42-year-old female. At week 68 (day 478), CK was 1840 U/L (ref: 29-168 U/L). This was not reported as an AE. On day 498, CK was 34 U/L (within normal

range). The investigator reported that the assessment could be caused by a laboratory error or due to the subject working out the day before the assessment.

Study 4374:

- Subject (b) (6) was a 53-year-old male. At week 68 (day 478, after last dosing), CK was 6750 U/L (ref: 30-200 U/L). This was reported as a non-serious AE of 'Blood creatine phosphokinase increased' of mild severity. The investigator reported that the subject had been engaged in physical activity on the day before laboratory evaluation and received massage.
- Subject (b) (6) was a 54-year-old male. At week 68 (day 480, after last dosing), CK was 2312 U/L, (ref: 30-200 U/L). This was not reported as an AE. On day 508 CK was 119 U/L (within normal range). The investigator reported that the cause of the event was unknown although the subject went to the gym more than once during the last month.
- Subject (b) (6) was a 44-year-old male. At week 20 (day 141), CK was 3895 U/L (ref: 30-200 U/L). This was reported as a non-serious AE of 'Blood creatine phosphokinase increased' of severe severity and led to a temporary interruption of trial product. The subject had 5 additional assessments in the following months (day 145 to day 309) which showed CK ranging from 1784-2181 U/L. At week 52, CK was 1447 U/L and at week 68 790 U/L. The investigator reported that the event was probably related to study drugs and that the subject did not perform any physical activity. No signs and symptoms were reported. At the time of the event, the subject was using atorvastatin; the medication was paused shortly after the event.

Study 4375:

- Subject (b) (6) was a 72-year-old male. At week 52, CK was 2668 U/L (ref: 30-200 U/L). This was reported as a non-serious AE of 'Blood creatine phosphokinase increased' of moderate severity and did not lead to changes in dosing of trial product. Four days later, CK was 329 U/L. At week 68, creatine kinase was 182 U/L (within normal range). The subject had an excision of a foreign body from a finger the day before the week 52 laboratory assessment. The subject had an AE reported of 'Aspartate aminotransferase increased' at the same day as the increased creatine kinase; both were reported as resolved after 5 days.

Study 4376 (not included in the table above):

- Subject (b) (6) was a 52-year-old male. At week 52 (day 365), CK was 12218 U/L; (ref: 30-200 U/L) and AST 290 U/L (ref: 5-34 U/L). Three days later, CK was 1218 U/L and AST was 100 U/L. The laboratory outliers were reported as 2 non-serious AEs ('Blood creatine phosphokinase increased' and 'Aspartate aminotransferase increased') of mild severity and did not lead to any change in dosing of trial product. According to the investigator, the subject was asymptomatic and an antibody panel to detect inflammatory myopathy was

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

negative. The subject was referred for further investigation by rheumatology. Laboratory trajectories are shown below:

Figure 65: Subject NN9536-4376 (b) (6), CK (top panel) and AST (bottom panel) Values



Source: Study 4376, Subject (b) (6) narrative

- Subject (b) (6) was a 32-year-old female. At week 20 (day 141), CK was 1917 U/L (ref: 29-168 U/L). This was reported as a non-serious AE of 'Blood creatine phosphokinase

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

increased' of severe severity and led to temporary interruption of trial product. The investigator noted that the subject had performed physical exercise prior to the event.

An additional subject had a CK > 10x ULN after having been on randomized placebo for approximately 1 year after the semaglutide run-in period.

An evaluation of AEs related to muscle and CK did not suggest a substantial imbalance among groups (Table 79).

Table 79: Muscle- and CK-Related AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (adj. %)	Placebo N=1529 n (adj. %)
Muscle disorders	106 (3.9)	53 (3.6)
Muscle spasms	47 (1.7)	23 (1.6)
Myalgia	40 (1.5)	19 (1.3)
Muscular weakness	6 (0.2)	2 (0.1)
Fibromyalgia	4 (0.1)	6 (0.4)
Muscle twitching	3 (0.1)	0
Myofascial pain syndrome	2 (<0.1)	0
Muscle tightness	2 (<0.1)	2 (0.1)
Muscle disorder	1 (<0.1)	0
Muscle fatigue	1 (<0.1)	0
Myalgia intercostal	1 (<0.1)	0
Myosclerosis	1 (<0.1)	0
Torticollis	1 (<0.1)	1 (<0.1)
Diastasis recti abdominis	0	1 (<0.1)
Blood creatine phosphokinase increased	19 (0.7)	15 (1.0)
Blood creatine phosphokinase abnormal	1 (0.1)	0

Source: ISS, Table 7.2.2

Hematology

Significant decreases in certain hematology parameters are shown for the dose-escalation group in Table 80. Slightly higher proportions of subjects on semaglutide versus placebo had values below the lower limit of normal in leukocytes (and lymphocytes); however, there were no subjects with severely low values on routine testing.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

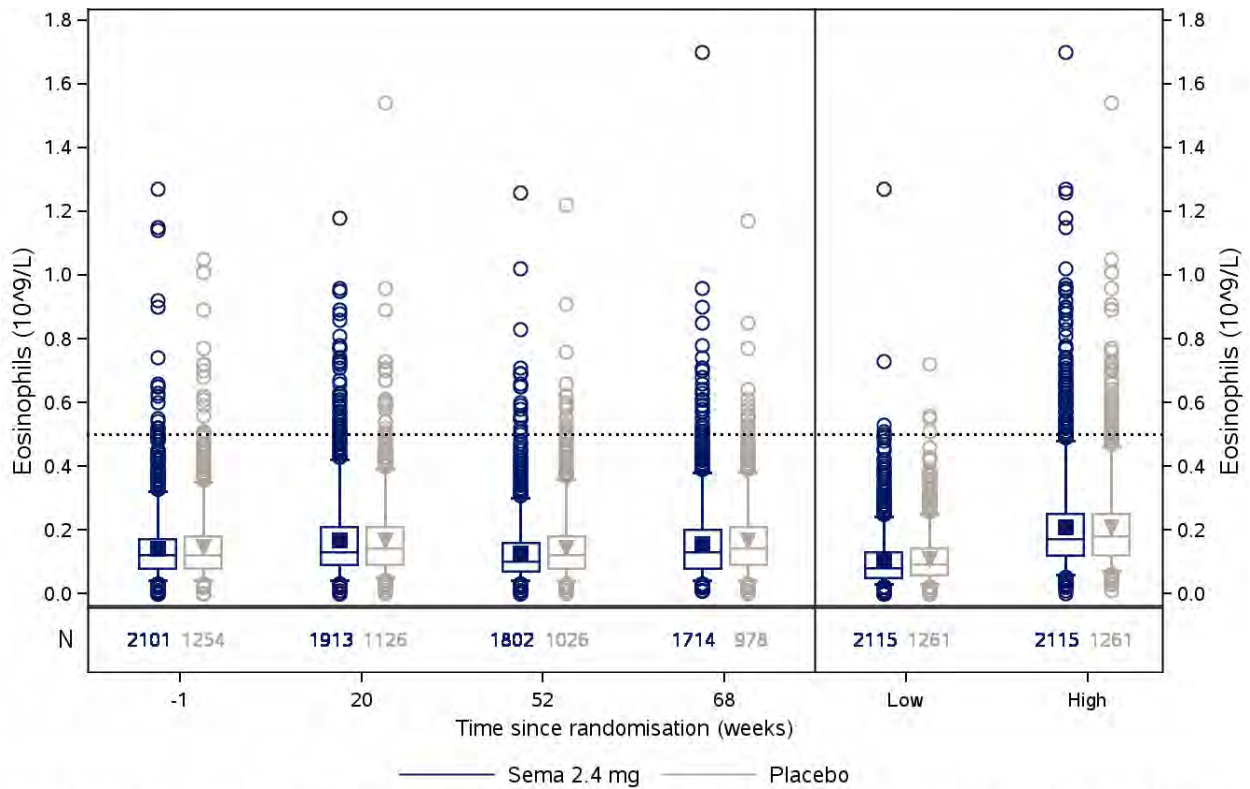
Table 80: Hematology Minimum Post-Baseline Values, Phase 3 Dose Escalation Group, On-Treatment

	Semaglutide 2.4 N=2116 n (%)	Placebo N=1261 n (%)
Platelets		
<LLN	45 (2.1)	42 (3.3)
< 25 x10 ⁹ /L	0	0
Leukocytes		
<LLN	78 (3.7)	34 (2.7)
<1 x10 ⁹ /L	0	0
Lymphocytes		
<LLN	204 (9.6)	109 (8.6)
<0.2 x10 ⁹ /L	0	0
Note that proportions are based on number of subjects with post-baseline data for each parameter		

Source: ISS, Table 7.5.24

Eosinophils and hemoglobin are also presented by week in Figure 66 and Figure 67, respectively. Semaglutide appears to be associated with somewhat more outliers for high eosinophils and low hemoglobin versus placebo; however, means and medians appear similar among groups.

Figure 66: Eosinophils by Week, Phase 3 Dose Escalation Group, On-Treatment

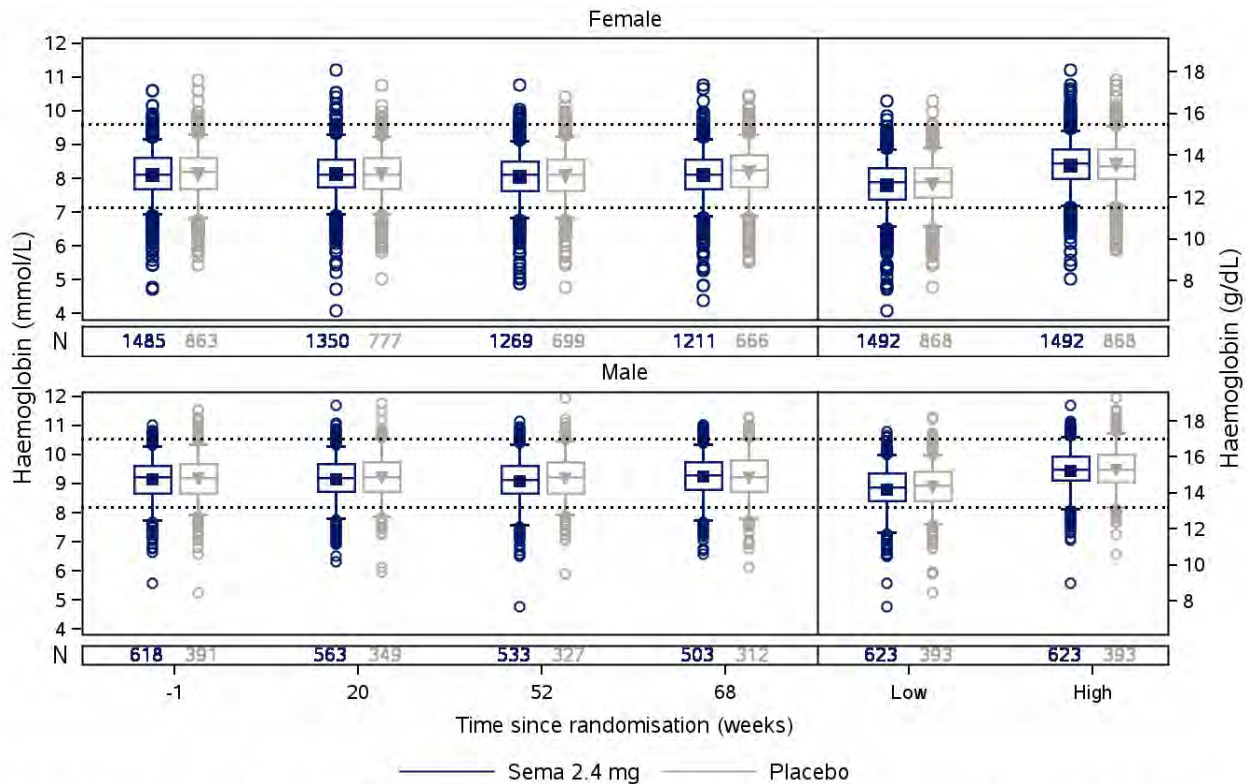


Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols in the boxes correspond to means. Whiskers correspond to the 5th and 95th percentiles. Dotted line(s) indicate normal reference range.
 Lower panel: Numbers of contributing subjects. Right panel: Low and High are per-subject minimum and maximum on-treatment values.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 14 days.

nn9536/mn9536-summary/submit_iss_20201001_er
 25SEP2020,10:32:21 - fboxplotof.sas#boxplotsot.png

Source: ISS, Figure 7.5.26

Figure 67: Hemoglobin by Week, Phase 3 Dose Escalation Group, On-Treatment



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols in the boxes correspond to means. Whiskers correspond to the 5th and 95th percentiles. Dotted line(s) indicate normal reference range.
 Lower panel: Numbers of contributing subjects. Right panel: Low and High are per-subject minimum and maximum on-treatment values. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 14 days.

nn9536/mn9536-summary/subm_iss_20201001_er
 25SEP2020:10.33.14 - fboxplotof_sas/fboxplothaemoot.png

Source: ISS, Figure 7.5.29

A review of hematology-related AEs suggests that semaglutide is associated with slightly more AEs of anemia and hemoglobin/hematocrit decreased versus placebo; the differences in proportions are small.

Table 81: Hematology-Related AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (adj. %)	Placebo N=1529 n (adj. %)
Anemias nonhemolytic and marrow depression	47 (1.8)	21 (1.4)
Anemia	37 (1.5)	18 (1.2)
Iron deficiency anemia	5 (0.2)	1 (<0.1)
Pancytopenia	2 (<0.1)	1 (<0.1)
Blood loss anemia	1 (<0.1)	0
Hypochromic anemia	1 (<0.1)	0
Pernicious anemia	1 (<0.1)	1 (<0.1)
Normocytic anemia	1 (<0.1)	1 (<0.1)
White blood cell disorders	8 (0.3)	3 (0.2)
Leukocytosis	4 (0.1)	3 (0.2)
Eosinophilia	2 (<0.1)	0
Leukopenia	2 (<0.1)	0
Platelet disorders	6 (0.2)	5 (0.3)
Thrombocytopenia	4 (0.1)	5 (0.3)
Thrombocytosis	2 (<0.1)	0
Hematology investigations (incl blood groups)	9 (0.4)	4 (0.3)
Hemoglobin decreased	6 (0.3)	2 (0.1)
Hematocrit decreased	2 (0.1)	0
Platelet count decreased	2 (<0.1)	0
Hematology test abnormal	0	2 (0.1)
Hematocrit increased	0	2 (0.1)
Hemoglobin increased	0	1 (<0.1)
Red blood cell count increased	0	1 (<0.1)
Red cell distribution width increased	0	1 (<0.1)

Source: ISS, Table 7.2.2

Separately, there were also AEs of 'Eosinophilic esophagitis' and 'Gastroenteritis eosinophilic' in 1 semaglutide-treated subject each. None of the eosinophilia (Table 81) or eosinophilic-related AEs were serious.

8.4.7. Vital Signs

Semaglutide is associated with reductions in blood pressure, and therefore, blood pressure was reviewed as an efficacy assessment (see Section 6 and Section 7). In addition, semaglutide is associated with increases in heart rate. This is discussed in detail in Section 8.5.3, Cardiovascular Disorders.

AEs related to vital signs are shown in the table below; this section will be focused on AEs of

hypotension and orthostatic hypotension.

Table 82: Vital Sign-Related AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (adj. %)	Placebo N=1529 n (adj. %)
Decreased and nonspecific blood pressure disorders and shock	38 (1.4)	6 (0.4)
Hypotension	23 (0.8)	3 (0.2)
Orthostatic hypotension	13 (0.5)	2 (0.1)
Blood pressure inadequately controlled	1 (<0.1)	1 (<0.1)
Circulatory collapse	1 (<0.1)	0
Blood pressure increased	6 (0.2)	11 (0.8)
Heart rate increased	4 (0.2)	0
Blood pressure decreased	2 (<0.1)	0
Blood pressure abnormal	1 (<0.1)	0
Pulse abnormal	1 (<0.1)	1 (<0.1)

Source: ISS, Table 7.2.2

One of the hypotension AEs was reported as serious (none of the other AEs listed in the table above was considered serious⁴⁸):

- Subject NN9536-4376 (b) (6) was a 65-year-old male with heart failure (NYHA class 2), ischemic heart disease, dyslipidemia, and hypertension, on losartan, carvedilol, and furosemide. Five days after completing the semaglutide run-in period, the subject suddenly felt sick while travelling in another part of the country. He was seen by a medical practitioner who diagnosed hypotension (BP 89/50); no action was taken, and he recovered the same day (reported as a non-serious AE). However, he continued to have fluctuating blood pressure over the next 2 months and both losartan and furosemide were withdrawn, although previously he had been on these medications for years without hypotension. Approximately 2 months later, study drug dose was reduced to 1 mg once weekly and 10-12 days later reported significant improvement in symptoms.

Reviewer comment: Fluctuations in blood pressure and hypotension with symptoms are likely related to semaglutide treatment in this subject who may have been especially vulnerable to effects of treatment given comorbidities and concomitant antihypertensive/cardiac treatment.

⁴⁸ The AE of 'Circulatory collapse' is discussed further in Section 8.4.10 (Immunogenicity), although it is not clear it was due to an allergic reaction.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In an exploratory analysis⁴⁹ by this reviewer, 5 subjects on semaglutide 2.4 mg (0.2%), 1 subject on semaglutide 1 mg (0.2%), and 1 subject on placebo (<0.1%) reported a post-baseline SBP < 80 mmHg.

In the phase 3 dose-escalation group, categorical changes in BP support the AEs shown above and the mean changes shown in the efficacy assessment, with more subjects on semaglutide than placebo experiencing more than 20 mmHg (37.9% and 26.5%, respectively) maximum BP decrease from baseline. The imbalances were observed regardless of whether baseline BP was < 110 mmHg, 110 to < 130 mmHg, or $\geq$ 130 bpm, although absolute numbers of subjects with decreases in BP increased with higher baseline BP.⁵⁰

Risk factors for events of hypotension and orthostatic hypotension were also evaluated using the phase 3 dose-escalation group:

- Use of antihypertensive medication at baseline appears to be a risk factor for events of hypotension. In the semaglutide 2.4 mg group, 66.7% of subjects with hypotension AEs and 36.1% of subjects without hypotension AEs used antihypertension medication at baseline.
- A large weight loss ($\geq$ 20%) appears to be a risk factor for events of orthostatic hypotension. In the semaglutide 2.4 mg group, 75.0% of subjects with orthostatic hypotension AEs and 26.8% of subjects without orthostatic hypotension AEs had a weight loss $\geq$ 20% at week 68.

In the phase 3 dose-escalation group, 5 subjects with AEs of hypotension or orthostatic hypotension had AEs of syncope or fall, or other information that could indicate loss of consciousness during the course of the AE. As is also discussed in Section 8.5.3, Cardiovascular Disorders, there were more events of syncope reported in the semaglutide-treated group. Three of the events in the semaglutide 2.4 mg-treated group and 1 event in the semaglutide 1 mg group were serious (narratives for these events are in Section 8.5.3).

AEs related to blood pressure increases/hypertension were explored in the randomized portion of trial 4376 using the MedDRA SMO 'Hypertension' to evaluate for a potential rebound effect (as blood pressure decreases with semaglutide). As seen in Table 83, hypertension was *not* reported more frequently in the placebo arm; in fact, it was reported more frequently in the semaglutide arm, including one event of 'Hypertension' that was reported as an SAE. ('Hypertensive crisis' in 1 subject in the semaglutide arm was reported as mild and recovered.)

⁴⁹ Unadjusted proportions

⁵⁰ Source: ISS, Table 7.6.10

Table 83: Increased Blood Pressure and Hypertension AEs

	Semaglutide 2.4 mg N=535 n (%)	Placebo N=268 n (%)
Hypertension-related AEs (Hypertension SMQ, narrow terms)	16 (3.0)	3 (1.1)
Hypertension	14 (2.6)	2 (0.7)
Blood pressure increased	1 (0.2)	1 (0.4)
Hypertensive crisis	1 (0.2)	0

Source: Reviewer created from Study 4376 ADAE.xpt dataset

A brief narrative of the hypertension SAE in the semaglutide-treated subject is as follows:

- Subject (b) (6) was a 69-year-old female with BMI of 31.2 kg/m² and history of hypertension, atherosclerosis of the renal artery, hypertensive heart disease with heart failure, and chronic kidney disease who was seen by a rheumatologist approximately 9 months in the trial and found to have a blood pressure of 240/150 mmHg. She was admitted to the intensive care unit and treated with intravenous hypertensives. After discharge, her blood pressure was apparently still high.

Reviewer comment: This event seems unlikely related to semaglutide, given the subject's comorbidities.

8.4.8. Electrocardiograms (ECGs)

In the phase 3 program, 12-lead ECGs were obtained at week 0, week 20, and week 68. The investigator was to characterize the ECG results as normal, abnormal not clinically significant (NCS), or abnormal, clinically significant (CS). Abnormal clinically significant new findings or clinically significant worsening of existing findings occurring after screening were to be reported as AEs.

In the phase 3 pool, small numbers of subjects shifted from (baseline to end-of-treatment) normal to abnormal, CS (semaglutide 2.4, 4 (0.3%); placebo, 2 (0.2%)) and from abnormal, NCS to abnormal, CS (semaglutide 2.4, 4 (0.6%); placebo, 2 (0.5%)).

Reasons for shifts in the semaglutide 2.4 mg group included: ST depression, nodal rhythm, intraventricular conduction defect/left bundle branch block, first and second degree atrioventricular block, atrial fibrillation, supraventricular extrasystoles, supraventricular tachycardia, and long QT syndrome. AEs reported related to the QT interval are discussed separately in Section 8.4.9.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In addition, 3 subjects had a shift from normal to abnormal, CS in the run-in period of trial 4376, reported as AEs of ventricular extrasystoles, atrial fibrillation, and myocardial infarction. The event of atrial fibrillation led to permanent discontinuation of trial product. The myocardial infarction was sent for adjudication by the EAC.

See Section 8.5.3, Cardiovascular Disorders, for a discussion of CV AEs seen in the semaglutide weight management program, including arrhythmias and adjudicated events.

8.4.9. QT

No events of torsade de pointes were reported in this program. Four AEs in the phase 3 pool related to QT prolongation were all reported as of mild severity; 2 on semaglutide-treated subjects and 2 in placebo-treated subjects (Table 84). (Although 1 of the placebo subjects was in trial 4376, and therefore had been exposed to semaglutide in the run-in period, the AE was reported on day 477, approximately 48 weeks since the last dose of semaglutide.)

Table 84: QT-Related AEs, Phase 3 Pool, On-Treatment

Subj ID	Sex	Age	Treatment	Verbatim term	AE start day	AE action
NN9536-4374/ (b) (6)	F	46.0	Sema 2.4 mg	PROLONGED QTC INTERVAL	480	Not Applicable
NN9536-4374/ (b) (6)	M	45.0	Placebo	MILD QT ELONGATION	139	Dose not changed
NN9536-4376/ (b) (6)	F	57.0	Sema 2.4 mg, Placebo	PROLONGED QTC-INTERVAL ON ECG	477	Not Applicable
NN9536-4376/ (b) (6)	M	50.0	Sema 2.4 mg, Sema 2.4 mg	LONG QTC SYNDROME	477	Not Applicable

Sema = semaglutide

Source: Reviewer created from ISS dataset ADAE.xpt

The effect of semaglutide on the QT interval has been evaluated in a thorough QT/QTc trial (TQT) for semaglutide SC for T2D (trial NN9535-3652). FDA agreed to cross-reference this study for the semaglutide 2.4 mg program for weight management.

The applicant maintains that the exposure-QT relationship from the TQT study covers the target population based on the following:

- There was no *in vitro* signal
- There was no QT prolongation potential; $\Delta\Delta\text{QTcF}$ (90%CI) = 0.2 ms (-2.8, 3.2) for 1.5 mg
- There was no C-QT relationship in the TQT study
- There was estimated exposure (C_{avg} or C_{max}) comparability between the TQT study in healthy volunteer and target populations. C_{max} is approximately 25% higher than C_{avg} .

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Although there is extensive overlap for exposure from the 1.5 mg used in the TQT and the 2.4 mg dose in the obese patient population, there were C_{avg} outliers. The sponsor was asked to provide QTcF data for the 3 subjects identified in trials 4373 and 4374 with C_{avg} estimated as greater than 150 nmol/L (20% above the upper bound of the TQT exposure). The results were as follows:

Table 85: QTcF Interval and ECG Interpretation, Subjects with Outlier Results for Average Semaglutide Concentrations

Trial ID/ Subject ID	Visit Number	Date of ECG	QTcF Interval (msec)	Interpretation by investigator	Comment
NN9536-4373/ (b) (6)	V2 (randomization)	(b) (6)	452	Normal	-
	V12 (week 20)		431	Normal	-
	V24 (end of treatment)		450	Normal	-
NN9536-4373/ (b) (6)	V2 (randomization)		438	Abnormal, NCS	Sinus Bradycardia; Normal ECG except for rate
	V12 (week 20)		445	Abnormal, NCS	Sinus Bradycardia
	V24 (end of treatment)		418	Abnormal, NCS	Sinus Bradycardia
NN9536-4374/ (b) (6)	V2 (randomization)		382	Normal	-
	V12 (week 20)		374	Normal	-
	V24 (end of treatment)		368	Normal	-

Abbreviation: NCS: not clinically significant

Source: Response to FDA Information Request dated May 12, 2021

The changes in QTcF in these subjects are (including C_{avg} values):

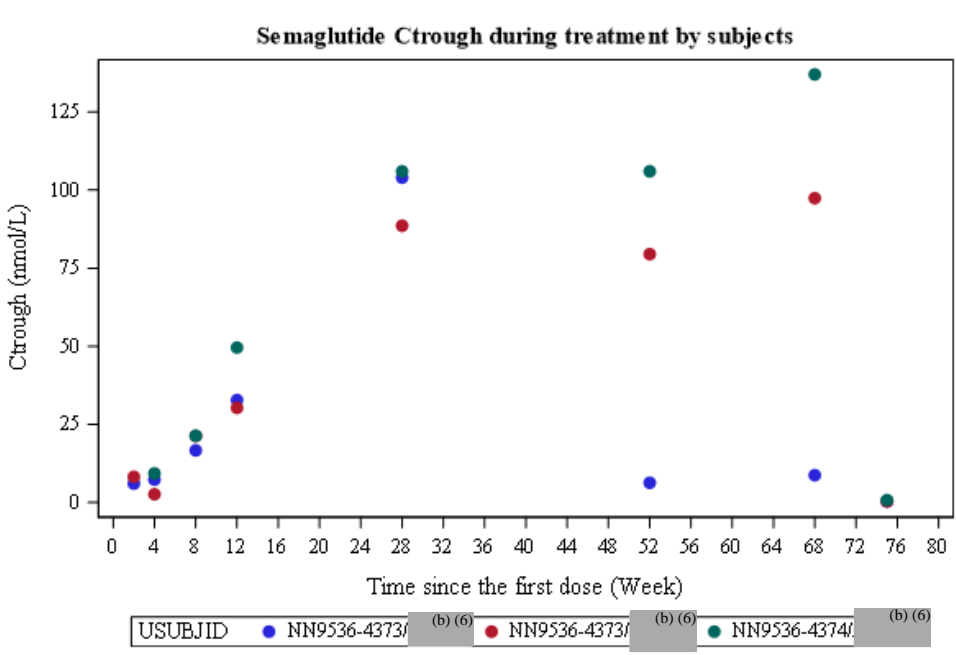
NN9536-4373/ (b) (6) (C_{avg} 156 nmol/L): week 20: -21 from baseline; week 68: -2 from baseline, +19 from week 20

NN9536-4373/ (b) (6) (C_{avg} 240 nmol/L): week 20: +7 from baseline; week 68: -20 from baseline, -27 from week 20

NN9536-4374/ (b) (6) (C_{avg} 164 nmol/L): week 20: -8 from baseline; week 68: -14 from baseline, -6 from week 20

Because C_{trough} can be more relevant for individual observations with regards to timing of ECGs, the available data are presented here as well:

Figure 68: Semaglutide Trough Concentrations by Week for Subjects with Average Concentration Outlier Values



Source: Dr. Sang Chung, OCP, personal communication

Reviewer comment: The relatively low C_{trough} for subject NN9536-4373 at weeks 52 and 68 suggests that QTcF changes from the Week 68 ECG might not be relevant for this subject. Overall, there does not appear to be a QTcF signal in these 3 subjects from the data provided.

Finally, FDA's Interdisciplinary Review Team (IRT) for QT was asked to opine on the potential for QT effects in this program, given some exposures in phase 3 above those observed in the thorough QT/QTc trial. The IRT notes: 1) a shallow exposure-response relationship between $\Delta\Delta QTcI$ and plasma concentrations of semaglutide observed in the thorough QT study; 2) peptide nature of semaglutide; and 3) no considerable impact of intrinsic and extrinsic factors of the exposures of semaglutide, the sponsor's approach of extending the findings of previous thorough QT study appears reasonable. See the memorandum from Dr. Christine Garnett, IRT reviewer, for further details.

8.4.10. Immunogenicity

As semaglutide is a peptide product, there is potential risk for immunogenicity. Semaglutide has 94% homology to endogenous GLP-1.

In the Ozempic program, 32 subjects (1.0%) developed anti-drug antibodies (ADAs) to semaglutide. Of these, 19 developed antibodies cross-reacting with native GLP-1. In the

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Rybelsus program, 14 subjects (0.5%) developed ADAs. Of these, 7 developed antibodies cross-reacting with native GLP-1. The label for both products notes that neutralizing activity is uncertain.⁵¹

This section focuses on 1) incidence and persistence of ADA, cross-reactivity to endogenous GLP-1, and neutralizing effect, 2) impact of ADA on PK, 3) impact of ADA on efficacy by change in body weight and HbA1c, 4) safety, including an evaluation of hypersensitivity and injection site reactions, and the impact of ADA on general and immunogenicity-related AEs. Refer to the review from Dr. Mohanraj Manangeeswaran, Office of Biotechnology Products (OBP) for more details.

Anti-Semaglutide Antibodies

In the weight management program, anti-semaglutide antibodies were assessed in 2 clinical pharmacology trials assessing bioequivalence (4590 and 4588), the phase 2 trial 4153, and 2 of the phase 3 trials, 4373 and 4374. The collection timepoints for antibody sampling are presented in Table 86. For the trials with semaglutide 2.4 mg, the follow-up antibody sample was taken after a drug wash-out period of 7 weeks, corresponding to approximately 7 elimination half-lives. In trial NN9535-4588 with semaglutide 1 mg, the follow-up sample was collected 5 weeks after end of treatment.

⁵¹ As per the FDA Office of Biotechnology, which reviewed the assays under the Ozempic NDA, the validation of screening and confirmatory assays used in monitoring of ADA were found suitable. At the time of the approval, the sensitivity of the neutralizing antibody (nAb) assay was considered inadequate. In response to a PMC to develop and validate a sensitive assay to “assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1,” the applicant made a good faith effort to develop a sensitive assay, and while improved, it was found that it could not be used to evaluate the levels of nAb in clinical samples. The assay development PMC (3294-3) as well as a PMC to “conduct a study to assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with semaglutide using the assays developed in 3294-3” (PMC 3294-4) were therefore released.

Table 86: Antibody Sample Collection Time-Points, Weight Management Program

Antibody sample collection time point	STEP 1 (Phase 3a)	STEP 2 (Phase 3a)	4153 (Phase 2)	4590 (Clin. Pharm.)	NN9535-4588* (Clin. Pharm.)
Week 0 (baseline)	X	X	X	X	X
Week 2	X				
Week 4	X	X	X		
Week 8	X	X	X		
Week 11					X (FU ^d)
Week 12	X	X			
Week 16			X	X	
Week 21				X	
Week 27				X (FU ^e)	
Week 28	X	X	X		
Week 40			X		
Week 52	X	X	X		
Week 59			X (FU ^b)		
Week 68	X	X			
Week 75	X (FU ^b)	X (FU ^b)			

Clin. Pharm.: clinical pharmacology trial; FU: Follow-up.

*Trial NN9535-4588 evaluated semaglutide 1.0 mg dose.

^bFollow-up: 7 weeks post end of treatment + a visit window of 0 to +5 days.

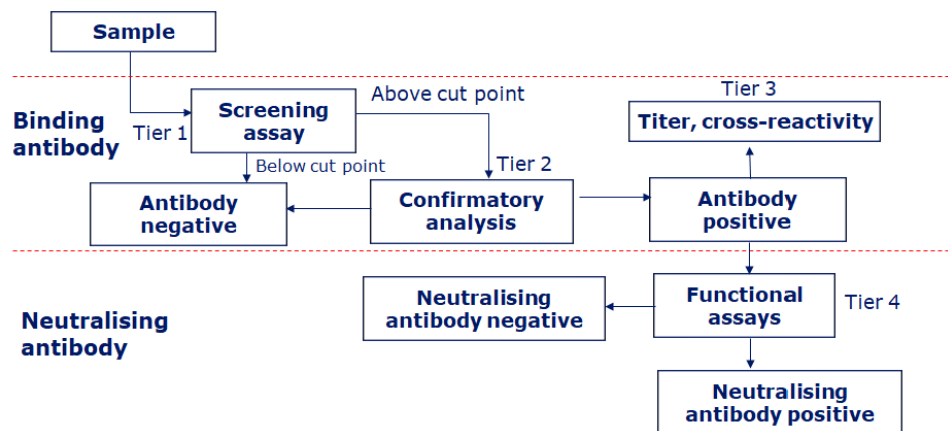
^cFollow-up: 7 weeks post end of treatment + a visit window of 0 to +4 days

^dFollow-up: 5 weeks post end of treatment + a visit window of +1 day.

Source: Integrated Summary of Immunogenicity (ISI), Table 3-1

The evaluation was performed using a tiered approach with screening analysis in tier 1, confirmatory analysis in tier 2, cross-reactivity to endogenous GLP-1 in tier 3 and *in vitro* neutralizing antibody analysis in tier 4 (Figure 69).

Figure 69: Tiered Antibody Assay Approach



Source: ISI, Figure 3-1

In the clinical pharmacology trials 4590 and 4588 and in the phase 2 dose-finding trial 4153, no subjects developed anti-semaglutide antibodies.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In the phase 3 trials 4373 and 4374, 17,101 samples were analyzed in the screening assay. Of these, 1761 samples were equal to or above cut point and therefore analyzed in the confirmatory assay, where 93 samples were confirmed positive. A total of 50 (2.9%) of semaglutide-treated subjects had positive ADAs during the trial (excluding 1 subject who had positive ADAs at baseline only), and 29 (58% of 50) of these subjects had “persistent” ADAs,⁵² whereas 21 (42% of 50) had “transient” ADAs.⁵³

Of the 29 subjects with a persistent antibody response, 19 were positive at the follow-up visit (median titer 30), and 9 were negative at the follow-up visit, but positive at other visits during the trial with at least 16 weeks separating the positive samples. One subject was positive at the end-of-treatment (week 68) visit only and did not have a follow-up visit.

Of the 21 subjects with a transient antibody response, all but 1 were ADA-positive at only a single visit during the treatment period, and 1 subject was positive at visit 8 and 14.

A total of 28 (56% of 50) subjects had ADAs that were cross-reacting with endogenous GLP-1 (5 were transient). Based on the results of the assay used (see the Office of Biotechnology Products review for further information), no ADAs had neutralizing activity.

Median titer was 30 (min 15, max 240). Of the 93 confirmed positive samples, about 80% had a titer of either 15 or 30, 15% had a titer of 60, less than 9% had a titer of 120, and 1 had a titer of 240.⁵⁴

Trial 4374 included semaglutide 2.4 mg and 1 mg arms. Although the immunogenicity focus is on the 2.4 mg dose, ADAs were evaluated for subjects in both dosing arms of this trial. The proportion of subjects positive for ADAs post-baseline was 3.0% (12 subjects) for semaglutide 2.4 mg and 1.0% (4 subjects) for semaglutide 1 mg.⁵⁵ All 4 subjects in the semaglutide 1 mg arm, and 7 of 12 subjects in the semaglutide 2.4 mg arm were also positive for antibodies cross-reacting with endogenous GLP-1.

ADA Impact on PK

For subjects in trials 4373 and 4374, the semaglutide plasma concentrations were similar for

⁵² Persistent: Subject either 1) negative at baseline, but positive at follow-up, or 2) negative at baseline and follow-up, but positive at 2 or more timepoints in between, where the first and last positive test is separated by at least 16 weeks.

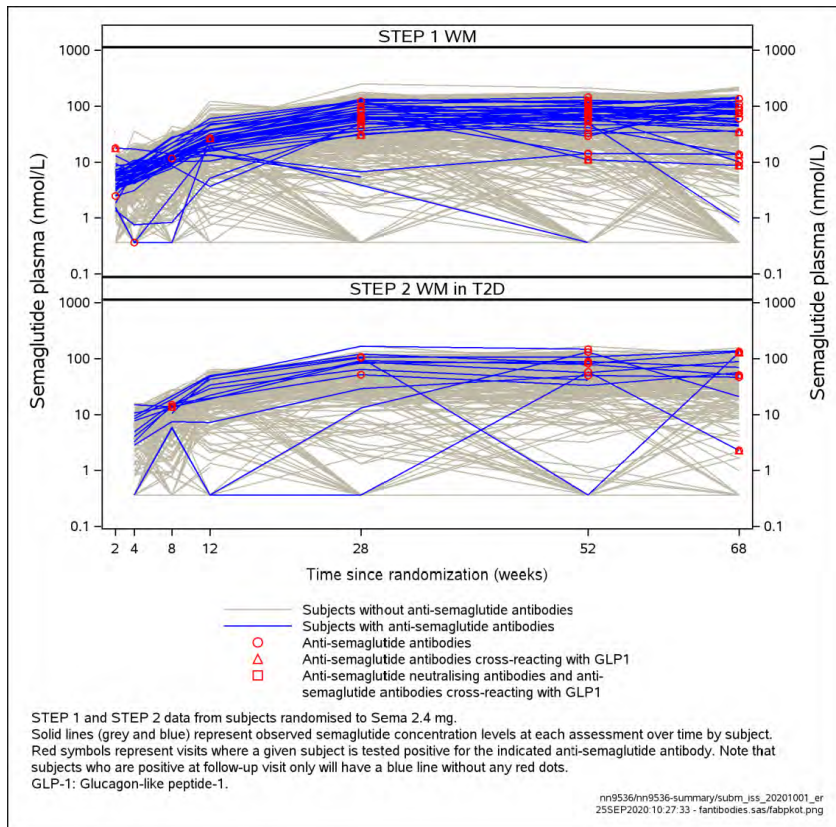
⁵³ Transient: Subject with ADAs that were negative at baseline and follow up, but positive in between.

⁵⁴ Titers were reported as minimum required dilution (MRD) adjusted titer, which was 15. Therefore, a titer of 15 is the lowest possible titer for an ADA positive sample.

⁵⁵ Of note, this is consistent with the overall incidence of ADAs observed in Ozempic trials (1.0%).

subjects with anti-semaglutide antibodies (1–26 subjects at each visit) compared to subjects without antibodies. Therefore, the presence of antibodies did not appear to affect the PK of semaglutide. Please refer to the Clinical Pharmacology review for further details.

Figure 70: Semaglutide Pharmacokinetic Concentration by Occurrence of Anti-Semaglutide Antibodies, Trials 4373 and 4374, On-Treatment



Source: ISI, Figure 4-1

ADA Impact on Efficacy

Although subjects who had ADAs appeared to have a 1.8- to 2.0-percentage point lower weight loss than subjects without antibodies, this apparent difference was attenuated in subjects with persistent ADAs (versus not) and those with occurrence of cross-reacting ADAs (versus not); Table 87. This, in addition to Figure 71, (b) (4) suggests a similar pattern of weight loss in those with and without ADAs, (b) (4)

Table 87 also presents the HbA1c data for trial 4374, which also does not suggest an attenuation in HbA1c efficacy in those with and without ADAs.

Reviewer comment:

(b) (4)

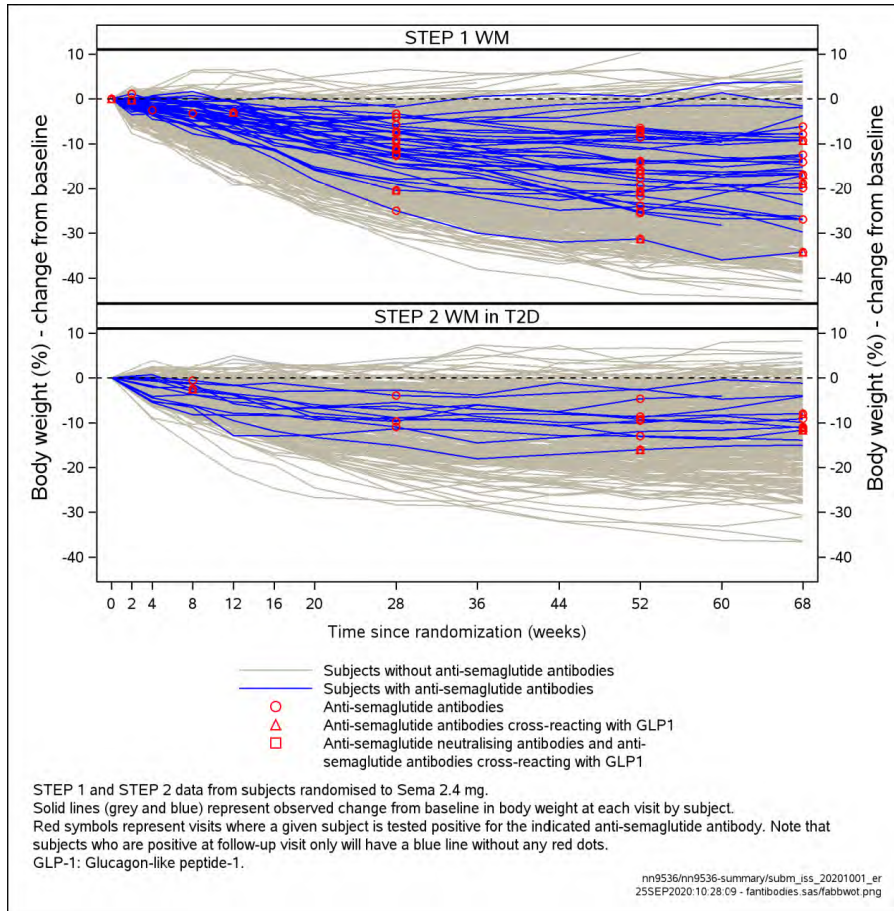
(b) (4)

Table 87: Body Weight Percent Change from Baseline (Trials 4373 and 4374) and HbA1c Change from Baseline (Trial 4374) by Occurrence of Anti-Semaglutide Antibodies, On-Treatment

	Trial 4373		Trial 4374	
	ADA			
	+	-	+	-
N	39	1267	12	391
n with weight at week 68	34	1025	11	340
Mean weight change at week 68 (SD)	-14.9	-16.9 (9.4)	-9.0 (4.3)	-10.8 (7.9)
Median	-14.4	-16.1	-9.9	-10.0
5 th percentile, 95 th percentile	-29.7, -1.6	-33.9, -2.6	-15.0, -1.2	-24.9, +0.9
Min, Max	-34.2, +3.8	-44.9, +8.5	-15.0, -1.2	-36.6, +8.2
n with HbA1c at week 68			10	340
Mean HbA1c change at week 68 (SD)			-2.3 (0.7)	-1.8 (1.1)
Median			-2.1	-1.8
5 th percentile, 95 th percentile			-3.7, -1.4	-3.4, -0.2
Min, Max			-3.7, -1.4	-4.9, +5.4
	Persistent ADA			
	+	-	+	-
N	24	1282	5	398
n	22	1037	5	346
Mean weight change at week 68 (SD)	-15.2 (9.1)	-16.9 (9.4)	-9.1 (3.2)	-10.7 (7.9)
Median	-15.6	-16.1	-10.9	-9.9
5 th percentile, 95 th percentile	-29.7, -1.6	-33.9, -2.5	-11.7, -4.0	-24.8, +0.7
Min, Max	-34.2, +3.8	-44.9, +8.5	-11.7, -4.0	-36.6, +8.2
	Cross-Reacting ADA			
N	21	1285	7	396
n	19	1040	7	344
Mean weight change at week 68 (SD)	-16.0 (10.3)	-16.9 (9.4)	-10.1 (3.4)	-10.7 (7.9)
Median	-15.2	-16.1	-10.9	-9.9
5 th percentile, 95 th percentile	-34.2, +3.8	-33.9, -2.6	-15.0, -4.0	-24.8, +0.7
Min, Max	-34.2, +3.8	-44.9, +8.5	-15.0, -4.0	-36.6, +8.2

Source: ISI, Tables 7.1.11, 7.1.13, 7.1.14, 7.1.15

Figure 71: Body Weight Percent Change from Baseline by Occurrence of Anti-Semaglutide Antibodies, Spaghetti Plot, Trials 4373 and 4374, On-Treatment



Source: ISI, Figure 7.1.12

Immune-Related Safety (Local or Systemic, Including ADA Impact on Safety)

Allergic reactions

Allergic reactions were identified in the phase 2 trial 4153 and the phase 3 program using a pre-defined MedDRA search.⁵⁶

In phase 2 trial 4153, none of the allergy events in semaglutide-treated subjects were serious (1 placebo-treated subject had an SAE of 'Hand dermatitis'). One event of 'Rash' led to treatment discontinuation in a subject treated with semaglutide 0.1 mg and 2 subjects treated with

⁵⁶ Custom Query (NNMQ Allergic reactions) – only narrow terms from the following: SMQ Anaphylactic reaction; SMQ Angioedema; SMQ Severe cutaneous adverse reactions; SMQ Anaphylactic/anaphylactoid shock conditions; SMQ Hypersensitivity

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

liraglutide 3 mg had AEs leading to discontinuation: 'Rash' and 'Rash pruritic.' None of the semaglutide-treated subjects had a severe allergy AE (2 events in 1 placebo-treated subject were considered severe: 'Eczema weeping' and 'Hand dermatitis'). Rash was the most commonly reported preferred term but did not appear dose dependent.

One non-serious event of 'Anaphylactic reaction' was reported in a semaglutide 0.4 mg-treated subject on day 111 of the trial, reported with an event of 'Urticaria' on the same day. This event was considered unlikely related to drug and the dose was not changed as a result of this event.

Reviewer comment: No further details were available about this case, but as the subject continued in the trial without dose change, I agree with the investigator assessment that the relationship of anaphylaxis to semaglutide seems unlikely.

Allergic reaction AEs in trial 4153 are summarized in Table 88.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 88: Allergic Reaction AEs, Trial 4153, On-Treatment

	Semaglutide							Lira	Placebo
	0.05 mg	0.1 mg	0.2 mg	0.3 mg	0.4 mg	0.3 mg F	0.4 mg F		
Allergy AEs	5 (4.9)	9 (8.8)	7 (6.8)	3 (2.9)	8 (7.8)	8 (7.8)	3 (2.9)	13 (12.6)	10 (7.4)
Rash	1 (1.0)	2 (2.0)	2 (1.9)	0	0	4 (3.9)	1 (1.0)	4 (3.9)	3 (2.2)
Eczema	1 (1.0)	1 (1.0)	2 (1.9)	0	0	0	0	1 (1.0)	3 (2.2)
Dermatitis	0	1 (1.0)	0	1 (1.0)	0	0	1 (1.0)	1 (1.0)	1 (0.7)
Urticaria	0	1 (1.0)	2 (1.9)	0	2 (2.0)	0	0	0	0
Dermatitis contact	1 (1.0)	1 (1.0)	0	1 (1.0)	0	0	0	1 (1.0)	0
Eyelid edema	0	0	0	0	0	2 (2.0)	1 (1.0)	1 (1.0)	0
Rhinitis allergic	1 (1.0)	1 (1.0)	1 (1.0)	0	1 (1.0)	0	0	0	0
Hypersensitivity	0	0	0	1 (1.0)	0	0	0	0	2 (1.5)
Rash pruritic	0	1 (1.0)	0	0	0	0	1 (1.0)	1 (1.0)	0
Drug hypersensitivity	0	0	0	0	0	0	0	1 (1.0)	1 (0.7)
Eye swelling	1 (1.0)	0	0	0	0	1 (1.0)	0	0	0
Injection site rash	0	1 (1.0)	0	0	0	1 (1.0)	0	0	0
Allergic sinusitis	0	0	0	0	1 (1.0)	0	0	0	0
Anaphylactic reaction	0	0	0	0	1 (1.0)	0	0	0	0
Conjunctivitis allergic	0	1 (1.0)	0	0	0	0	0	0	0
Contrast media reaction	0	0	0	0	1 (1.0)	0	0	0	0
Eczema weeping	0	0	0	0	0	0	0	0	1
Gingival swelling	0	0	0	0	1 (1.0)	0	0	0	0
Hand dermatitis	0	0	0	0	0	0	0	0	1
Injection site hypersensitivity	0	0	0	0	0	0	0	1 (1.0)	0
Laryngospasm	0	0	0	0	0	0	0	1 (1.0)	0
Lip swelling	0	0	0	0	1 (1.0)	0	0	0	0
Rash erythematous	0	0	0	0	0	1 (1.0)	0	0	0
Rash pustular	0	0	0	0	0	0	0	0	1 (0.7)
Skin reaction	0	0	0	0	0	0	0	1 (1.0)	0
Swollen tongue	0	0	0	0	1 (1.0)	0	0	0	0

Lira=liraglutide

Source: Reviewer created from Study 4153 ADAE.xpt dataset, confirmed with Study 4153 CSR, Table 14.3.1.92

Allergic reaction AEs reported from the phase 3 pool are summarized in Table 89. The proportions of subjects reporting allergic AEs were 6.9% in the semaglutide 2.4 mg arm and 6.8% in the placebo arm.

None of the semaglutide 2.4 mg-treated subjects had allergic reaction SAEs. (There was 1 SAE in a placebo subject in trial 4373 with a PT of ‘Hypersensitivity’. Additionally, in trial 4374 in the semaglutide 1 mg group – which is not in the phase 3 pool – an SAE of ‘Shock’ was reported. This SAE was thought to be cardiogenic or septic shock, i.e., not allergic.)

One event of non-serious ‘Anaphylactic transfusion reaction’ was reported in the semaglutide 2.4 mg group, not considered related to administration of trial product (verbatim term: “ANAPHYLAXIS REACTION TO BIOLOGICS INFUSION FOR ARTHRITIS”). No other anaphylactic reactions were reported.

A severe event of ‘Circulatory collapse’ was reported in the semaglutide 2.4 mg group in trial 4373 on study day 14, and the subject recovered after 1 day. This AE was thought unlikely related to the drug and the dose was not changed as a result of the event. (Although this event is captured in the allergic reactions MedDRA search, it is not clear whether this was in fact an allergic event.)

A number of PTs that included terms such as swelling or edema were noted; therefore this reviewer conducted an exploratory review of terms using the ‘Angioedema’ SMQ. Overall, the unadjusted proportions were 1.0% in the semaglutide 2.4 mg arm and 0.7% in the placebo arm. Most of the events were reported as urticaria (in both groups), but a small number of events of facial swelling were reported in the semaglutide arm. Details are shown below in Table 89.

Table 89: Allergic Reaction AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (%)	Placebo N=1529 n (%)
Allergy AEs	183 (6.9)	102 (6.8)
SAEs	0	1 (<0.1)
Severe AEs	6 (0.2)	2 (0.1)
Leading to:		
Permanent discontinuation	3 (0.1)	5 (0.3)
Temporary interruption	7 (0.3)	1 (<0.1)
Dose reduction	4 (0.1)	0
SOCS:		
Skin and subcutaneous disorders ^a	133 (5.0)	76 (5.1)
Respiratory, thoracic and mediastinal disorders ^b	21 (0.8)	12 (0.8)
Immune system disorders ^c	10 (0.4)	12 (0.8)
Injury, poisoning and procedural complications ^d	8 (0.3)	0

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

General disorders and administration site conditions ^e	7 (0.3)	1 (<0.1)
Eye disorders ^f	4 (0.1)	2 (0.1)
Gastrointestinal disorders ^g	3 (0.1)	1 (<0.1)
Vascular disorders ^h	1 (<0.1)	0
Angioedema SMQ ⁱ	27 (1.0)	10 (0.7)
Urticaria	18 (0.7)	9 (0.6)
Swelling face	2 (0.1)	0
Lip swelling	2 (0.1)	1 (0.1)
Eyelid edema	1 (<0.1)	0
Face edema	1 (<0.1)	0
Gingival swelling	1 (<0.1)	0
Swelling of eyelid	1 (<0.1)	0
Angioedema	1 (<0.1)	1 (0.1)
a Selected PTs include: rash, eczema, urticaria, dermatitis (incl. dermatitis bullous), drug eruption, angioedema, erythema nodosum b Selected PTs include: rhinitis allergic, bronchospasm, allergic cough, allergic bronchitis, hypersensitivity pneumonitis c Selected PTs include: hypersensitivity d Selected PTs include: injection related reaction, anaphylactic transfusion reaction e Selected PTs include: face edema, injection-site related PTs f Selected PTs include: eyelid edema, eye allergy g Selected PTs include: lip swelling, gingival swelling h PT: circulatory collapse i Reviewer calculated from MedDRA Desktop Browser and ISS ADAE.xpt; proportions are unadjusted		

Source: ISS, Tables 7.3.29 and 7.3.30

In the semaglutide run-in period of trial 4376, 34 allergic reaction AEs were identified from the pre-defined MedDRA search in 29 subjects (Table 90). All events were non-serious and of mild or moderate severity. Two subjects had AEs that led to permanent discontinuation of treatment (rash and urticaria).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 90: Allergic Reaction AEs, Trial 4376, Run-In Period

	Semaglutide 2.4 mg N=902 n (%)
Allergy AEs	29 (3.2)
Rash	7 (0.8)
Urticaria	5 (0.6)
Eczema	3 (0.3)
Dermatitis allergic	2 (0.2)
Dermatitis atopic	2 (0.2)
Dermatitis contact	2 (0.2)
Immediate post-injection reaction	2 (0.2)
Rash pruritic	2 (0.2)
Dermatitis	1 (0.1)
Hypersensitivity	1 (0.1)
Injection related reaction	1 (0.1)
Rhinitis allergic	1 (0.1)

Source: Reviewer created from ISS ADAE.xpt

AEs and Antibody Testing

In trials 4373 and 4374, the phase 3 trials in which ADAs were collected, 47 subjects reported AEs out of the 51 subjects positive for antibodies at any time (92.2%). Most AEs by SOC had a similar incidence in those with and without ADAs.

Table 91: On-Treatment AEs by SOC in Semaglutide-Treated Subjects with and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374

	Subjects with ADAs N=51 n (%)	Subjects without ADAs N=1658 n (%)
Any AEs	47 (92.2)	1477 (89.1)
Gastrointestinal disorders	38 (74.5)	1187 (71.6)
Infections and infestations	28 (54.9)	865 (52.2)
Nervous system disorders	10 (19.6)	463 (27.9)
Musculoskeletal and connective tissue disorders	9 (17.6)	427 (25.8)
Metabolism and nutrition disorders	8 (15.7)	247 (14.9)
General disorders and administration site conditions	7 (13.7)	353 (21.3)
Skin and subcutaneous tissue disorders	7 (13.7)	221 (13.3)
Psychiatric disorders	6 (11.8)	142 (8.6)
Respiratory, thoracic and mediastinal disorders	5 (9.8)	215 (13.0)
Neoplasms benign, malignant and unspecified	4 (7.8)	51 (3.1)
Cardiac disorders	3 (5.9)	73 (4.4)
Eye disorders	3 (5.9)	91 (5.5)
Vascular disorders	3 (5.9)	111 (6.7)
Blood and lymphatic system disorders	2 (3.9)	45 (2.7)
Ear and labyrinth disorders	2 (3.9)	63 (3.8)
Immune system disorders	2 (3.9)	32 (1.9)
Injury, poisoning and procedural complications	2 (3.9)	234 (14.1)
Investigations	2 (3.9)	131 (7.9)
Renal and urinary disorders	2 (3.9)	70 (4.2)
Reproductive system and breast disorders	2 (3.9)	106 (6.4)
Endocrine disorders	1 (2.0)	17 (1.0)
Hepatobiliary disorders	1 (2.0)	53 (3.2)
Social circumstances	1 (2.0)	0

Source: ISI, Table 7.1.3

Although there were no on-treatment SAEs in subjects positive for ADAs, 1 in-trial fatal event was reported in a subject (NN9536-4373 (b) (6)) who tested positive for ADAs in week 2 only (i.e., he was negative at weeks 4, 8, 12, and 28). The subject discontinued treatment on study day 198 due to an AE of asthenia (reported on day 141) and later reported several SAEs of loss of consciousness (days 282-303), followed by death. See the narrative for this case in Section 8.4.1.

Two of the AEs reported in subjects with ADAs were severe: 'Gastroenteritis' and 'Hypersensitivity.' The severe hypersensitivity event was reported on study day 414; the subject recovered while continuing on semaglutide.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 92 evaluates the AEs identified by the allergic reactions MedDRA search.⁵⁶ Eight of 51 subjects with ADAs (15.7%, event rate 15.5 per 100 PY) as compared to 114 of 1658 subjects without ADAs (6.9%, event rate 5.8 per 100 PY) experienced at least 1 allergy AE.

Table 92: On-Treatment Allergic Reactions in Semaglutide-Treated Subjects With and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374

	Subjects with ADA N=51	Subjects without ADA ^a N=1658
Allergic reaction AEs	8 (15.7)	114 (6.9)
Rash	2 (3.9)	31 (1.9)
Eczema	1 (2.0)	16 (1.0)
Hypersensitivity	1 (2.0) ^b	3 (0.2)
Injection site urticaria	1 (1.0)	0
Rash pruritic	1 (2.0)	4 (0.2)
Rhinitis allergic	1 (2.0)	13 (0.8)
Urticaria	1 (2.0)	12 (0.7)
a Note that only terms that occurred in subjects with ADA are shown. AEs reported in subjects without ADA (but not subjects with ADA) include: administration related reaction, anaphylactic transfusion reaction, bronchospasm, circulatory collapse, conjunctivitis allergic, dermatitis (and related terms), drug eruption, drug hypersensitivity, eye allergy, face edema, gingival swelling, injection related reaction, lip swelling, perioral dermatitis, rash maculopapular, swelling face, swelling of eyelid, vessel puncture site rash b "Severe" hypersensitivity event; see text above.		

Source: ISI, Table 7.1.4

Reviewer comment: Although there is a numerically higher rate in subjects with ADA versus without, the number of subjects in the ADA group is too small to draw conclusions about allergy with ADAs. (Furthermore, these are also not randomized comparisons and therefore the direction of any potential association is inconclusive.)

An evaluation of hypoglycemia in subjects with ADAs was also conducted. Refer to Section 8.5.7 for a discussion of hypoglycemia methodology and results in the weight management population overall. In trial 4374 (in subjects with T2D), no level 2 or 3 hypoglycemia episodes were reported in subjects positive for ADAs. In trial 4373 (in subjects without T2D), hypoglycemia AEs were not reported by any subjects positive for ADAs.

Severe Acute Hypersensitivity and Unscheduled Testing

In addition to the routine measurement of ADAs as described above, if there was a suspicion of study drug-induced severe acute hypersensitivity during any of the clinical trials, antibody samples were to be collected within 1 to 2 weeks and again 7 weeks after the event for assessment of anti-semaglutide-binding antibodies and IgE antibodies specific for semaglutide. In addition, tryptase samples could also be collected to determine whether an observed systemic acute hypersensitivity reaction could be categorized as an anaphylactic shock/anaphylactoid reaction.

No subjects in any of the weight management program trials had blood samples collected due to suspicion of severe acute hypersensitivity related to trial product; however:

- In trial 4373, 1 unscheduled sample was analyzed for anti-semaglutide binding antibodies and IgE antibodies due to a non-serious, but severe AE of eosinophilia in the semaglutide 2.4 mg group. This sample was below LLOQ in the IgE analysis and negative in the binding antibody analysis. The AE led to temporary disruption of trial product and was reported as resolved. Eosinophilia AEs are discussed in Section 8.4.6, Laboratory Findings.
- In trial 4376, 1 unscheduled sample was analyzed for anti-semaglutide binding antibodies due to an SAE of pancytopenia in a subject on semaglutide 2.4 mg; the sample was negative for antibodies. The SAE led to permanent treatment discontinuation and was not resolved at the end of trial. This case is discussed further in Section 8.5.11, Rare Events.

Injection site reactions

Injection site reactions were evaluated utilizing a pre-defined MedDRA search⁵⁷ in the phase 2 trial 4153 and the phase 3 program.

In the phase 2 trial 4153, injection site reaction AEs did not demonstrate a clear dose-relationship. However, most of the events were likely related to trauma at the injection site (injection site bruising, injection site hematoma) rather than a potential immunologic reaction (injection site pruritus, injection site erythema). All events were non-serious, and none led to treatment discontinuation in any of the semaglutide arms (1 subject on liraglutide discontinued due to injection site reaction). No severe events were reported.

In the phase 3 pool, 4.2% of semaglutide 2.4 mg subjects and 4.9% of placebo subjects reported an injection site reaction. None of the events were serious or severe. One event in a placebo subject led to permanent treatment discontinuation and 1 event in 1 semaglutide subject led to dose reduction. Most event terms were injection site pain (1.6% in each group) and injection site bruising (semaglutide 1.6%, placebo 2.6%). The PT 'Injection site reaction' was reported in 9 subjects on semaglutide 2.4 mg (0.4%) versus 1 subject on placebo (<0.1%).

Reviewer comment: The pre-defined MedDRA search includes a number of PTs that describe trauma at the injection site (bruising, hematoma, etc.) that seem to add noise to the evaluation of immunological- or irritant-based injection site reactions. More pertinent terms seem to be related to injection site reaction, erythema, pruritus, etc. In an exploratory

⁵⁷ Custom query (NNMQ Injection site reactions), both primary and secondary terms from the following: HLT Administration site reactions; HLT Application and instillation site reactions; HLT Infusion site reactions; HLT Injection site reactions

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

analysis of selected events in the phase 3 dose-escalation group, the incidence of these events is low; see Table 93 below.

Table 93: Selected Injection Site Reaction Terms, Phase 3 Dose Escalation Group

System organ class Preferred term	Sema 2.4 mg			Placebo			
	N	(Adj.%)	E	N	(Adj.%)	E	Adj.R
Number of subjects	2116			1261			
Patient years of exposure (PYE)	2765.3			1619.3			
Events	31 (1.4)	36	1.3	12 (1.0)	14	0.9	
General disorders and administration site conditions	31 (1.4)	36	1.3	12 (1.0)	14	0.9	
Injection site reaction	9 (0.4)	9	0.3	1 (<0.1)	1	<0.1	
Injection site pruritus	9 (0.4)	9	0.3	4 (0.3)	5	0.3	
Injection site erythema	7 (0.4)	7	0.3	3 (0.3)	3	0.2	
Injection site inflammation	2 (<0.1)	4	0.1	0			
Injection site paraesthesia	2 (<0.1)	2	<0.1	2 (0.2)	2	0.1	
Injection site induration	1 (<0.1)	1	<0.1	0			
Injection site swelling	1 (<0.1)	1	<0.1	1 (<0.1)	2	0.1	
Injection site urticaria	1 (<0.1)	2	<0.1	1 (<0.1)	1	<0.1	
Injection site irritation	1 (<0.1)	1	<0.1	0			

Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Sorted in descending order by system organ class and preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 patient-years of exposure, Adj.: Adjusted.
The % and R are adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

Source: Response to FDA request dated 20 May 2021, Table 6

Injection site reactions and ADAs

Table 94 evaluates the AEs identified by the injection site reactions MedDRA search by ADA.⁵⁷ Three of 51 subjects with ADAs (5.9%, event rate 12.6 per 100 PY) as compared to 74 of 1658 subjects without ADAs (4.5%, event rate 5.0 per 100 PY) experienced at least 1 injection site reaction AE.

Table 94: On-Treatment Injection Site Reactions in Semaglutide-Treated Subjects With and Without Anti-Semaglutide Antibodies, Trials 4373 and 4374

	Subjects with ADA		Subjects without ADA ^a	
	N=51 n (%)	PYE=71.2 E (R)	N=1658 n (%)	PYE=2168.0 E (R)
Injection site reaction AEs	3 (5.9)	9 (12.6)	74 (4.5)	108 (5.0)
Injection site pain	2 (3.9)	2 (2.8)	24 (1.4)	31 (1.4)
Injection site hematoma	1 (2.0)	1 (1.4)	2 (0.1)	7 (0.3)
Injection site mass	1 (2.0)	2 (2.8)	4 (0.2)	4 (0.2)
Injection site pruritus	1 (2.0)	1 (1.4)	8 (0.5)	8 (0.4)
Injection site reaction	1 (2.0)	1 (1.4)	4 (0.2)	4 (0.2)
Injection site urticaria	1 (2.0)	2 (2.8)	0	0

a Note that only terms that occurred in subjects with ADA are shown. AEs reported in subjects without ADA (but not subjects with ADA) include: application site hematoma, infusion site extravasation, injection site bruising, injection site erythema, injection site hemorrhage, injection site induration, injection site inflammation, injection site paresthesia, injection site swelling, vessel puncture site bruise, vessel puncture site rash
E: number of events; R: event rate per 100 PY

Source: ISI, Table 7.1.4

Reviewer comment: Although an association is suggested in those subjects who reported more than 1 injection site reaction, the same comment regarding comparing AEs with and without ADAs is applicable here as well, and these potential associations should be interpreted with caution.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Gallbladder-Related Disorders

Obesity and rapid weight loss are associated with an increased risk for gallstone formation.⁵⁸ GLP-1 receptor agonists have also been associated with gallstone formation, at least in part, independently from weight loss.⁵⁹ Gallstone-related disorders, including cholelithiasis and cholecystitis were reported in association with the GLP-1 receptor agonist, liraglutide, in its development program for weight management (Saxenda). In the CV outcomes trial of liraglutide for diabetes (Victoza), more SAEs of acute gallstone disease (biliary colic or acute cholecystitis) were reported versus placebo. Acute gallbladder disease is a labeled warning (Section 5) in the Saxenda and Victoza labels.

By contrast, cholelithiasis is reported as an adverse reaction only (Section 6) in the semaglutide for diabetes labels. In the Ozempic (semaglutide SC) label, cholelithiasis was reported in 1.5%

⁵⁸ Stinton LM, et al. Epidemiology of gallstones. *Gastroenterol Clin North Am* 2010 Jun; 39(2): 157-69, vii.

⁵⁹ Saxenda (liraglutide) prescribing information

and 0.4% of 0.5 mg and 1 mg Ozempic-treated subjects, respectively, as compared with no placebo-treated subjects.⁶⁰ Cholelithiasis was reported in 1% of Rybelsus 7 mg-treated subjects and not reported in Rybelsus 14 mg- or placebo-treated subjects.⁶¹

In the weight management program, gallbladder disease was an adverse event of special interest.

In the phase 2 52-week dose-ranging trial 4153, a predefined MedDRA search⁶² was utilized to identify gallbladder-related events. A higher proportion of subjects receiving daily semaglutide doses of 0.3 mg (fast escalation) and 0.4 mg (standard escalation) experienced gallbladder events compared with those receiving placebo and other semaglutide doses. No gallbladder events were reported in subjects randomized to liraglutide. The majority of events were non-serious (see Table 58 in Section 8.4.2 for an enumeration of SAEs in this trial).

Table 95: Gallbladder AEs, Study 4153

	Semaglutide							Lira	Placebo
	0.05	0.1	0.2	0.3	0.4	0.3F	0.4F		
N	103	102	103	103	102	102	103	103	136
n (%)	2 (1.9)	2 (2.0)	3 (2.9)	3 (2.9)	6 (5.9)	7 (6.9)	2 (1.9)	0	5 (3.7)
Semaglutide doses presented as mg/d Lira=liraglutide 3 mg									

Source: Study 4153 CSR, Table 12-16

In the semaglutide weight management phase 3 program, past medical history of gallbladder disease was systematically collected. At screening, 15.3% of subjects in the phase 3 pool had a history of gallbladder disease and 13.4% had previously had a cholecystectomy performed; both medical history events were well-balanced among randomized groups.

A MedDRA query for gallbladder-related disorders was predefined for the pooled analyses.⁶³

Baseline characteristics of those who experienced on randomized treatment gallbladder-related AEs are shown in Table 96, in an exploratory analysis.

⁶⁰ Ozempic (semaglutide) prescribing information

⁶¹ Rybelsus (semaglutide) prescribing information

⁶² Novo Nordisk MedDRA query 'Gallbladder related disorders' including: SMQ Biliary tract disorders; SMQ Biliary system related investigations, signs and symptoms; SMQ Gallbladder related disorders; SMQ Gallstone related disorders; SMQ Infectious biliary disorders

⁶³ Novo Nordisk MedDRA query 'Gallbladder related disorders' including narrow terms from: SMQ Functional, inflammatory and gallstone related biliary disorders; SMQ Infectious biliary disorders

Table 96: Selected Baseline Characteristics of Subjects with Gallbladder Events, Phase 3 Pool

	Semaglutide 2.4 mg N=70 n (%)	Placebo N=24 n (%)
Female sex	60 (85.7)	18 (75.0)
Mean age, years	45.2	47.9
Mean BMI, kg/m ²	37.7	37.1
Race		
White	60 (85.7)	21 (87.5)
Black	6 (8.6)	1 (4.2)
Other	4 (5.7)	2 (8.3)

Source: Reviewer created from ISS dataset ADAE

AEs of gallbladder-related disorders were identified by a predefined MedDRA search as noted above. Using this search in the phase 3 pool, adjusting for trial, 2.5% of subjects on semaglutide 2.4 mg versus 1.6% of subjects on placebo reported a gallbladder-related AE (Table 97). Since the event rates by patient-years of exposure were similar to the proportions of subjects with at least 1 event, only the numbers and proportions of subjects are shown for simplicity.

Serious AEs, severe AEs, and AEs leading to discontinuation are shown as well (Table 97); approximately half of the semaglutide events were SAEs, whereas approximately 20% of the placebo events were SAEs. Most events resulted in cholecystectomy and led to recovery without drug discontinuation. See the discussion of pancreatitis in Section 8.5.2 for additional description of events that may be related to gallstones (pancreatitis was an infrequent event).

Table 97: Gallbladder-Related Disorders, Phase 3 Pool

	Semaglutide 2.4 mg N=2650 n (%)	Placebo N=1529 n (%)
Gallbladder-related AEs	70 (2.5)	24 (1.6)
<i>Cholelithiasis</i>	45 (1.6)	16 (1.1)
<i>Cholecystitis</i>	8 (0.3)	2 (0.1)
<i>Cholecystitis acute</i>	8 (0.3)	2 (0.1)
<i>Hyperbilirubinemia</i>	4 (0.1)	1 (<0.1)
<i>Biliary colic</i>	4 (0.1)	0
<i>Blood bilirubin increased</i>	3 (0.1)	3 (0.2)
<i>Cholecystitis chronic</i>	3 (0.1)	1 (<0.1)
<i>Gallbladder disorder</i>	3 (0.1)	0
<i>Biliary dyskinesia</i>	2 (<0.1)	0
<i>Cholecystectomy</i>	1 (<0.1)	1 (<0.1)
<i>Bile duct stone</i>	1 (<0.1)	0
SAEs	34 (1.2)	5 (0.3)
<i>Cholelithiasis</i>	25 (0.9)	3 (0.2)

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

<i>Cholecystitis</i>	7 (0.2)	0
<i>Cholecystitis acute</i>	6 (0.2)	1 (<0.1)
<i>Cholecystectomy</i>	1 (<0.1)	1 (<0.1)
<i>Cholecystitis chronic</i>	1 (<0.1)	0
<i>Biliary dyskinesia</i>	1 (<0.1)	0
<i>Bile duct stone</i>	1 (<0.1)	0
Severe AEs	22 (0.8)	4 (0.3)
Leading to discontinuation	4 (0.1)	4 (0.3)

Source: SCS, Tables 2-18 and 2-19

It is also relevant to evaluate gallbladder disorders in the phase 3 trials that employed a placebo-controlled dose-escalation phase (and in which the placebo-treated subjects had not been previously exposed to semaglutide); i.e., 4373, 4374, and 4375. Notably, trial 4375, which implemented an intensive lifestyle program, reported the most events, particularly in the semaglutide group. Subjects with T2D reported the fewest events and were not substantially different among groups. This pattern was also seen with gallbladder-related SAEs, although the numbers were smaller (see Table 59, Table 60, and Table 61 in Section 8.4.2).

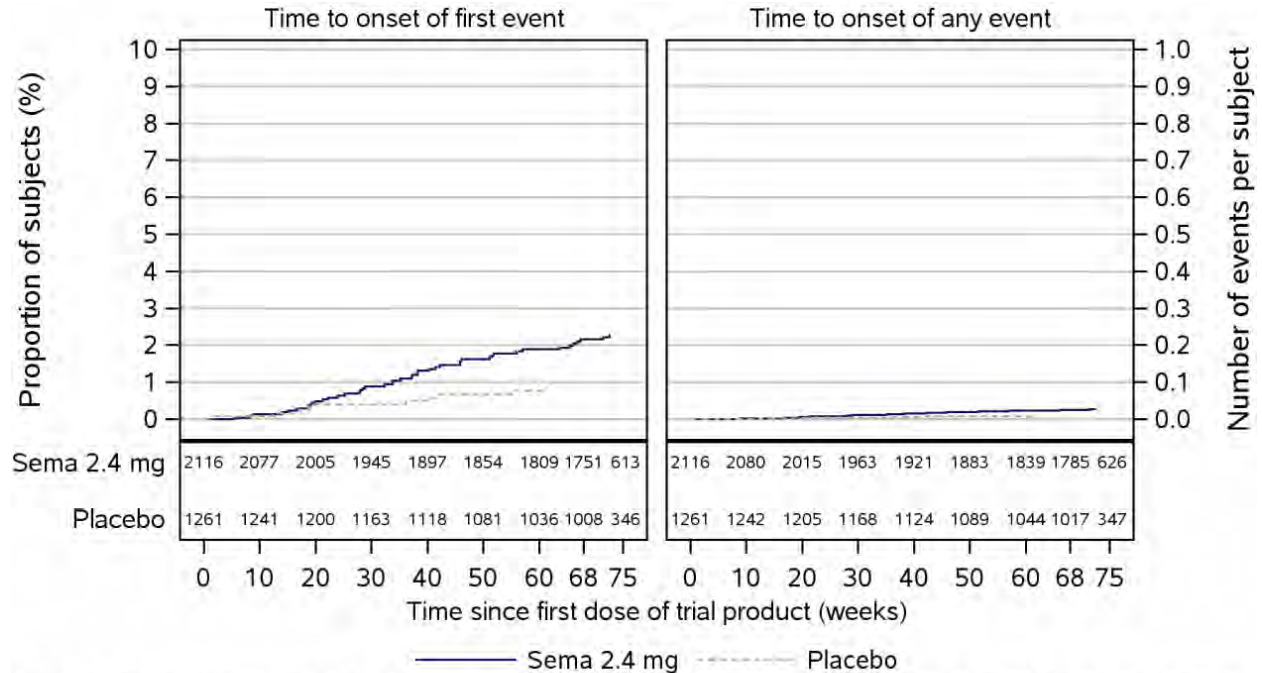
Table 98: Gallbladder-Related Disorders (MedDRA Search), Trials 4373, 4374, and 4375

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
4373	34/1306 (2.6)	-	8/655 (1.2)
4374	4/402 (1.0)	1/403 (0.2)	3/402 (0.7)
4375	20/407 (4.9)	-	3/204 (1.5)

Source: Study 4373 CSR, Table 12-13; Study 4374 CSR, Table 12-11; Study 4375 CSR, Table 12-11

The time to onset of first AEs of cholelithiasis, cholecystitis, and acute cholecystitis in the phase 3 dose-escalation group shows that first events occurred throughout the trials in the semaglutide group, whereas the occurrence of first events appeared to reach a plateau around week 40 in the placebo group.

Figure 72: Events of Cholelithiasis, Cholecystitis, and Cholecystitis Acute Over Time, On-Treatment, Phase 3 Dose-Escalation Group



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.

Numbers shown in the lower panel are subjects at risk.

Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

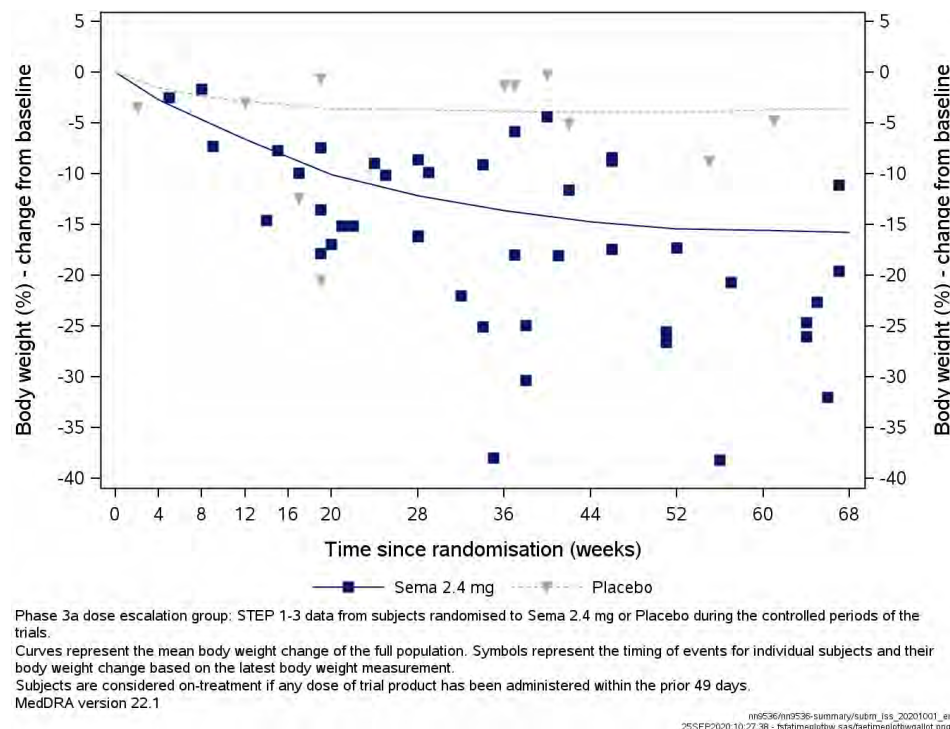
MedDRA version 22.1

nn9536/nn9536-summary/subm_iss_20201001_er
 25SEP2020 10:29:40 - faetimeplot.sas/faechovertimeplot.png

Source: SCS, Figure 2-17

Figure 73 illustrates selected gallbladder events plotted by percent weight loss at the time of the event for both treatment groups (semaglutide, blue squares; placebo, gray triangles). The lines represent the mean weight loss achieved in all subjects by group.

Figure 73: Events of Cholelithiasis, Cholecystitis, and Acute Cholecystitis and Body Weight Change Over Time, Phase 3 Dose-Escalation Group



Source: SCS, Figure 2-18

The applicant speculates that the figure suggests a lack of time dependency for the events and furthermore, that subjects on semaglutide with gallbladder events had a larger than average weight loss.

Reviewer comment: These seem to be reasonable inferences, and I agree.

In addition, the applicant conducted a *post hoc* analysis on safety by weight loss at week 68 in the phase 3 dose-escalation group. In this analysis, AEs of cholelithiasis in both treatment groups were reported with a higher frequency among those with a weight loss of $\geq 20\%$ compared to those with a weight loss $< 20\%$.

Table 99: Gallbladder AEs by Weight Loss, On-Treatment, Phase 3 Dose-Escalation Group

	Semaglutide 2.4 mg	Placebo
N		
$\geq 20\%$ weight loss	572	23
$< 20\%$ weight loss	1401	1118
missing	143	120

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Gallbladder disorder (HLGT)		
≥ 20% weight loss	19 (3.2)	1 (4.4)
< 20% weight loss	31 (2.1)	9 (0.8)
missing	2 (1.2)	1 (0.9)
Cholelithiasis (PT)		
≥ 20% weight loss	16 (2.8)	1 (4.4)
< 20% weight loss	20 (1.4)	8 (0.7)
missing	1 (0.7)	0

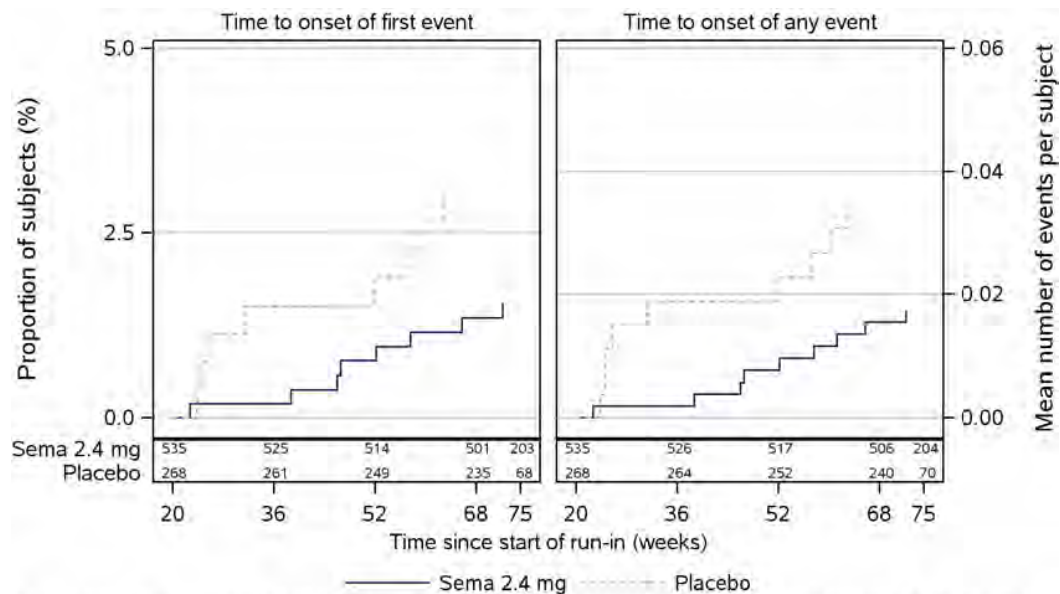
Source: ISS, Appendix 7.7, Table 7.7.53

Reviewer comment: These analyses are supportive of the observation that rapid and large weight loss increases the risk for gallstones; however, there could be other factors that are associated with large weight loss and gallstone formation, so these analyses should be considered exploratory and viewed with some caution. Furthermore, the trend is less pronounced in semaglutide arm versus the placebo arm (although the number of subjects on placebo with 20% or greater weight loss was small); this could suggest at least a partial weight-independent effect of semaglutide in gallstone formation.

In trial 4376, which implemented a 20-week run-in period of semaglutide on all subjects, 6 of the 902 subjects in the run-in (0.7%) experienced a gallstone event. All were non-serious, and 1 led to elective cholecystectomy.

In the randomized period of trial 4376, 15/535 (2.8%) of semaglutide-treated subjects and 10/268 (3.7%) of placebo-treated subjects experienced at least 1 gallbladder-related event. The pattern of events over time could suggest a withdrawal effect of semaglutide, as events on placebo were higher than semaglutide in the first few weeks of the randomized period. It should be noted that this pattern was not observed for SAEs of cholelithiasis and cholecystitis (6, 1.1% semaglutide vs. 2, 0.7% placebo; Table 63), but the numbers of SAEs were small.

Figure 74: Cholelithiasis, Cholecystitis, and Acute Cholecystitis Events Over Time, Trial 4376, On-Treatment, Randomized Period



Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Only AEs with onset in the randomized period included. Randomised period starts with week 20 visit. Lower panels: At risk tables. Only randomised subjects in the safety analysis set contribute. MedDRA version 22.1

rn9536/rn9536-4376/ctr_20200717_er
 25JUN2020 12:23:06 - faetimeplot.sas/faegalltimeplot.png

Source: Study 4376 CSR, Figure 14.3.1.55

Reviewer comment: Although this observation of greater gallbladder events on placebo is of interest, it could also be a chance finding. The applicant stated that they are not aware of any studies having shown effects of discontinuation of GLP-1 RA treatment on gallbladder motility or bile acid composition that could increase the risk of gallbladder events, as all studies that explored the impact of GLP-1 RAs on the gallbladder were conducted on-treatment. One hypothesis raised by the applicant was whether subjects who discontinue semaglutide treatment experience a return of dietary habits (e.g., sweet and high-fat foods) to pre-treatment level, which could increase the risk of gallstone disease and/or increase the risk of silent gallstone disease becoming symptomatic.

In summary, gallbladder disorders are associated with semaglutide use. This was particularly evident when evaluated in combination with an intensive lifestyle program, possibly suggesting a synergistic effect. There were also more AEs in the placebo groups versus semaglutide after a semaglutide run-in, potentially suggestive of a withdrawal effect.

8.5.2. Acute Pancreatitis

Pancreas safety, including concerns about acute pancreatitis, has historically been an area of interest with incretin mimetics. Post-marketing reports of acute pancreatitis, including fatal

and non-fatal hemorrhagic or necrotizing pancreatitis with GLP-1-based therapies have led to warnings regarding pancreatitis in drug labeling for the class. In addition, an imbalance in pancreatitis was reported in clinical trials for liraglutide (T2D and obesity populations).

Acute pancreatitis is also included in semaglutide for T2D labeling. In Ozempic glycemic control trials, acute pancreatitis was confirmed by adjudication in 7 Ozempic-treated patients (0.3 cases per 100 patient years) versus 3 in comparator-treated patients (0.2 cases per 100 patient years). In a 2-year trial, acute pancreatitis was confirmed by adjudication in 8 Ozempic-treated patients (0.27 cases per 100 patient years) and 10 placebo-treated patients (0.33 cases per 100 patient years), both on a background of standard-of-care.⁶⁰ In Rybelsus glycemic control trials, pancreatitis was reported as an SAE in 6 Rybelsus-treated patient (0.1 events per 100 patient-years) versus 1 comparator-treated patient (<0.1 events per 100 patient-years).⁶¹

[Reviewer comment: Although the applicant has cited a number of meta-analyses of randomized clinical trials that conclude no increased risk for acute pancreatitis with GLP-1 receptor agonists, all meta-analyses included – and were driven by – the results of tallied adjudicated pancreatitis events in the liraglutide cardiovascular outcomes trial, LEADER.^{64,65,66} I was the primary clinical safety reviewer for the LEADER trial. Adjudicated pancreatitis was limited by a strict case definition and the findings were therefore more nuanced than presented in the meta-analyses. Refer to the clinical safety review and discussion at the LEADER advisory committee meeting for more details.]

Events of pancreatitis were reported in the phase 2 and 3 semaglutide weight management trials and collected as events of special interest and evaluated by an events adjudication committee (EAC); no events were reported in the phase 1 trials.

Trial 4153

In the semaglutide phase 2 weight management trial 4153, subjects with a history of acute or chronic pancreatitis at any time were excluded.

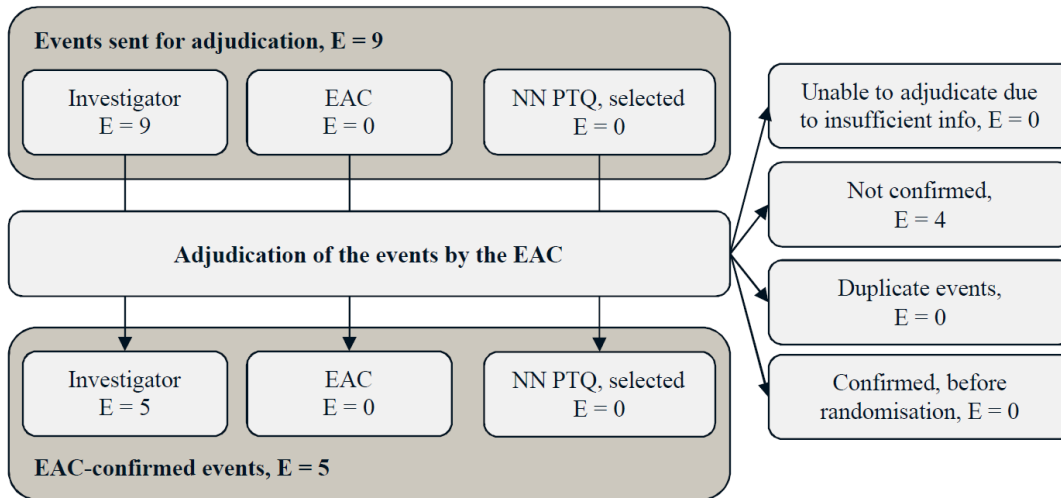
In this trial, all suspected cases of acute pancreatitis were prospectively adjudicated. A total of nine events were sent to the EAC, all of which had been initially identified by the investigator (Figure 75).

⁶⁴ Monami M, et al. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. *Diabetes Obes Metab.* 2017;19(9):1233-41.

⁶⁵ Storgaard H, et al. Glucagon-like peptide-1 receptor agonists and risk of acute pancreatitis in patients with type 2 diabetes. *Diabetes Obes Metab.* 2017;19(6):906-8.

⁶⁶ Liu Y, et al. No pancreatic safety concern following glucagon-like peptide-1 receptor agonist therapies: A pooled analysis of cardiovascular outcome trials. *Diabetes Metab Res Rev.* 2018;34(8):e3061.

Figure 75: Adjudication of Pancreatitis, Study 4153



Abbreviations: E=event; EAC= event adjudication committee; NN PTQ= Novo Nordisk preferred term query.

Source: Study 4153 CSR, Figure 12-13

Of the 9 potential pancreatitis events sent for adjudication, 5 events in 4 subjects were confirmed by the EAC. These events are described further in the table below. Of note, all subjects with confirmed pancreatitis events also reported cholelithiasis events.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 100: Pancreatitis Events Confirmed by Adjudication, Study 4153

Subject ID/ sex/age/B MI	PT/SAE (Y/N)/ causality	Day of onset ^a /duration (days)/outcome/ action	Pancreatitis event type/severity ^b status/ diagnostic criteria	Relevant details ^c
Semaglutide 0.05 mg				
(b) (6) M/47/33.0	Pancreatitis/ Y/possible	251/6/recovered/ drug withdrawn	Acute/mild/ elevated blood levels of pancreatic enzymes = 3 X UNR	Medical history: no relevant information. Concurrent reporting of cholecystitis (day 250) and cholecystectomy was performed
Semaglutide 0.3 mg F				
(b) (6) F/58/35.9	Pancreatitis acute/ Y/possible	115/4/recovered/ drug withdrawn	Acute/mild/ elevated blood levels of pancreatic enzymes = 3 X UNR	Medical history: recurrent abdominal pain Concurrent reporting of cholelithiasis (day 114) and cholecystectomy was performed after the second event of acute pancreatitis
	Pancreatitis acute/ Y/possible	156/15/recovered/ NA	Acute/mild/ elevated blood levels of pancreatic enzymes = 3 X UNR, characteristic image findings	
(b) (6) F/33/44.7	Pancreatitis acute/ Y/possible	332/10/recovered/ drug withdrawn	Acute/mild/elevated blood levels of pancreatic enzymes = 3 X UNR	Medical history: no relevant information. Previous reporting of cholelithiasis (day 176). Elective cholecystectomy was performed after the event of acute pancreatitis.
Placebo				
(b) (6) F/30/46.6	Pancreatitis/ Y/unlikely	181/13/recovered/ drug withdrawn	Acute/mild/elevated blood levels of pancreatic enzymes = 3 X UNR	Medical history: cholelithiasis Concurrent reporting of cholecystitis acute (day 176) and cholecystectomy was performed

Notes: ^aOnset day as determined by the EAC (Appendix 16.2.7, Listing 16.2.7.10), which may differ from the investigator-reported onset dates presented in Appendix 16.2.7, Listing 16.2.7.1. ^bPancreatitis event type based on EAC adjudication; severity based on revised Atlanta criteria.³⁰ ^cDetails are based on information in the case narratives from the safety database and including relevant reported PTs, concomitant medication and illness, and medical history. Causality = relationship to trial product as assessed by the investigator.

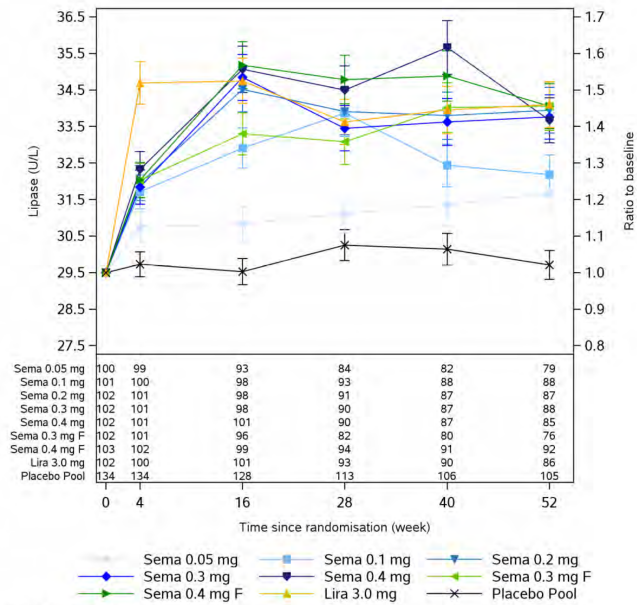
Abbreviations: BMI = body mass index; CV=cardiovascular; EAC = event adjudication committee; F = female; M = male; N = no; NA = not applicable; PT = preferred term; SAE = serious adverse event; semaglutide 0.3 mg F: semaglutide 0.3 mg fast dose escalation scheme; semaglutide 0.4 mg F: semaglutide 0.4 mg fast dose escalation scheme; UNR = upper normal range; Y = yes.

Source: Study 4153 CSR, Table 12-17

As has been described with other GLP-1 RAs, lipase and amylase were also increased with semaglutide (and liraglutide), particularly at higher doses.

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

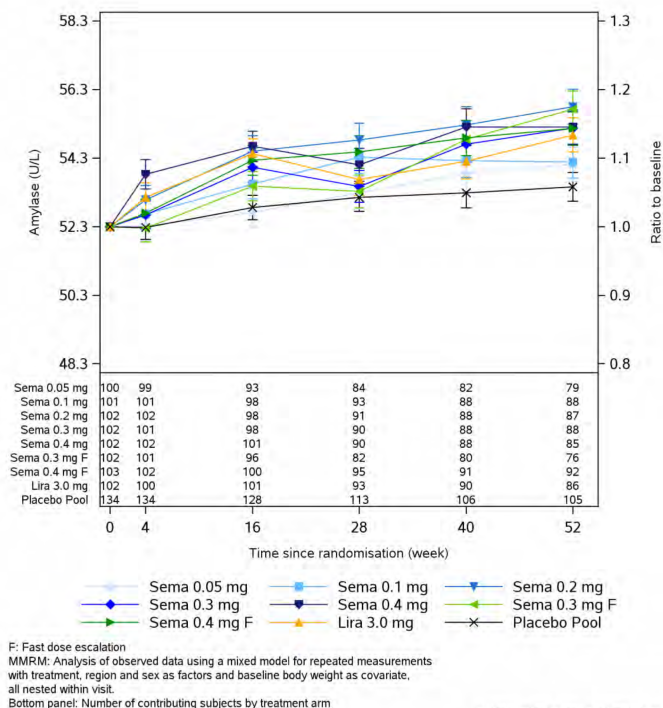
Figure 76: Change in Lipase from Baseline by Treatment Week, Study 4153



F: Fast dose escalation
 MMRM: Analysis of observed data using a mixed model for repeated measurements with treatment, region and sex as factors and baseline body weight as covariate, all nested within visit.
 Bottom panel: Number of contributing subjects by treatment arm

Source: Study 4153 CSR, Figure 12-14

Figure 77: Change in Amylase from Baseline by Treatment Week, Study 4153



Source: Study 4153 CSR, Figure 12-17

Table 101: Proportion with at Least One Post-Baseline Abnormal Lipase and Amylase Value Meeting Cut-Off, Study 4153

	Semaglutide							Lira	Pbo
	0.05	0.1	0.2	0.3	0.4	0.3F	0.4F		
N	103	102	103	103	102	102	103	103	136
Lipase, % meeting cut-off									
>ULN	11.0	9.9	17.6	14.7	20.6	15.7	22.3	19.6	5.2
>1.5xULN	6.0	6.9	12.7	4.9	6.9	7.8	8.7	9.8	1.5
>2xULN	3.0	5.9	2.9	2.9	4.9	6.9	3.9	4.9	1.5
>3xULN	2.0	4.0	1.0	2.0	2.9	3.9	2.9	0	0
>5xULN	0	2.0	1.0	0	2.9	2.9	1.9	0	0
Amylase, % meeting cut-off									
>ULN	3.0	3.0	2.0	2.9	6.9	5.9	5.8	5.9	2.2
>1.5xULN	0	3.0	0	0	2.0	2.9	1.9	0	0.7
>2xULN	0	0	0	0	1.0	1.0	1.0	0	0
>3xULN	0	0	0	0	0	0	0	0	0

Lira=liraglutide, Pbo=placebo

Source: Study 4153 CSR, Tables 12-18 and 12-19

Phase 3 Trials

In the phase 3 weight management trials, subjects with recent acute pancreatitis (within 180 days prior to screening), and subjects with a history or presence of chronic pancreatitis were excluded.

In the phase 3 trials, acute pancreatitis was assessed by 1) an on-treatment pre-defined MedDRA search,⁶⁷ and 2) the outcome of adjudication by EAC of possible cases of pancreatitis with severity⁶⁸ (Table 102). Trial product was to be discontinued in case of suspicion of acute pancreatitis.

Table 102: Acute Pancreatitis – Diagnostic Criteria and Severity

Event category	Description for evaluation of diagnosis	Adjudication outcome(s)
Acute pancreatitis	The diagnosis of acute pancreatitis required two of the following three features: - Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back) - Serum lipase activity (and/or amylase activity) at least three times greater than the upper limit of normal - Characteristic findings of acute pancreatitis on imaging	Acute pancreatitis by severity (Atlanta classification ⁶⁸): - Mild - Moderately severe - Severe

Source: SCS, Table 2-20

MedDRA search

According to the pre-specified MedDRA search, 4 events of acute pancreatitis were reported in the randomized phase 3 program: 3 on semaglutide (3/2650, 0.1%) and 1 on placebo (1/1529, <0.1%). (The placebo subject was *not* from study 4376, and therefore had not been previously exposed to semaglutide.) In the semaglutide group, 2 of the 3 events were SAEs (subjects with SAEs recovered and the subject with the non-serious SAE recovered with sequelae), and in the placebo group the 1 event was an SAE (the subject recovered).

In addition, 1 AE of acute pancreatitis (1/902, 0.1%) was reported during the 20-week open-label semaglutide run-in period of study 4376. This event was non-serious, led to permanent discontinuation of trial product, and resolved.

⁶⁷ Novo Nordisk MedDRA query 'Pancreatitis' including: SMQ Acute pancreatitis, narrow terms only; HLT Acute and chronic pancreatitis, primary and secondary terms

⁶⁸ Banks PA, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-11.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Adjudicated events

Ten events of possible acute pancreatitis in the in-trial period were sent for adjudication: 8 events identified by the investigator and 2 events identified by a pre-defined MedDRA search. One subject ((b) (6), study 4373, semaglutide 2.4 mg) had 2 events of EAC-confirmed acute pancreatitis in-trial but *not* on-treatment as noted in Table 104 (this subject also had 1 EAC-confirmed on-treatment event).

Eight events were identified as on-treatment in the phase 3 pool; 5 (in 4 subjects) were confirmed by the EAC in the semaglutide arm and 1 in the placebo arm. Results of adjudication are shown in Table 103 (including severity by Atlanta criteria).

Note that the phase 3 pool does not include the run-in period of 4376, during which time 1 subject had an event of EAC-confirmed acute pancreatitis (included in Table 104); this subject was never randomized.

Table 103: Acute Pancreatitis, EAC-Confirmed and Not Confirmed, On-Treatment, Phase 3 Pool

	Semaglutide		Placebo	
	N=2650 n (%)	PYE=3309.5 E (adj R)	N=1529 n (%)	PYE=1885.4 E (adj R)
EAC-confirmed acute pancreatitis	4 (0.2)	5 (0.2)	1 (<0.1)	1 (<0.1)
<i>Severity (Atlanta criteria)</i>				
<i>Mild</i>	3 (0.1)	3 (<0.1)	1 (<0.1)	1 (<0.1)
<i>Moderately severe</i>	1 (<0.1)	2 (<0.1)	0	0
SAE	3 (0.1)	3 (<0.1)	1 (<0.1)	1 (<0.1)
Not EAC-confirmed events	2 (0.1)	2 (<0.1)	0	0

EAC: event adjudication committee
PYE: patient-years of exposure
E: number of events, adj R: adjusted event rate per 100 PYE

Source: SCS, Table 2-23

Details of the events confirmed by EAC are in the table below. Two semaglutide subjects and 1 placebo subject with EAC-confirmed pancreatitis events had gallstones seen on imaging (suggesting the potential for gallstone pancreatitis).

Table 104: Details of EAC-Confirmed Acute Pancreatitis Events, On-Treatment (Including Run-In Period)

Trial / ID / Age / Sex / BMI	Investigator-reported information		EAC-reported information	Additional information
	PT / Study day / Confounders	Seriousness / Severity / Causality / Action / Outcome	Severity / Study day / Criteria fulfilled / Source / Documentation	
<i>Semaglutide</i>				
4373 / █ ^{(b) (6)} / 40 / F / 45.0	Lipase increased / 260 / None	Serious / Severe / Probable / Permanent treatment discontinuation / Recovered	Mild / 260 / 1) Pain and 2) Enzymes / Investigator / Full	Imaging consistent with gallstones, not acute pancreatitis; later diagnosed with cholecystitis and had a cholecystectomy
4373 / █ ^{(b) (6)} / 37 / F / 36.3	Pancreatitis acute / 234 / History of acute pancreatitis and alcohol consumption	Serious / Moderate / Possible / Permanent treatment discontinuation / Recovered	Mild / 232 / 1) Pain and 2) Enzymes / Investigator / Full	An additional 2 events of EAC- confirmed acute pancreatitis were reported for the in-trial period several months after drug discontinuation
4373 / █ ^{(b) (6)} / 32 M / 35.5	Pancreatitis acute / 508 ^a / None	Serious / Mild / Unlikely / Not applicable / Recovered	Mild / 508 / 1) Pain and 2) Enzymes / Investigator / Full	Imaging consistent with gallstones, not acute pancreatitis Subject had a rapid weight loss
4374 / █ ^{(b) (6)} / 61 / M / 39.1	Pancreatitis acute / 84 / None	Non-serious / Moderate / Probably / Permanent treatment discontinuation / Recovered with sequelae	Moderately severe / 87 / 1) Pain and 2) Enzymes / Investigator / Full	No imaging data were available at the time of the investigator- reported events Imaging data were available at day 140 due to an SAE of chronic pancreatitis (co-reported with pancreatic pseudocyst at day 149): sequelae after acute pancreatitis as well as signs of chronic pancreatitis
	Pancreatic pseudocyst / 149 / No additional data was provided ^b	Non-serious / Mild / Probable / Not Applicable / Not recovered	Moderately severe / 84 / 1) Pain and 2) Enzymes / PT search / Full	An additional non-serious pancreatic event was reported by the investigator (after on- treatment period, day 225); reported with PT pancreatic necrosis but not confirmed by EAC as imaging results showed chronic not acute pancreatitis
4376 / █ ^{(b) (6)} / 56 / F / 32.1	Pancreatitis acute / 104 / None	Non-serious / Moderate / Probably / Permanent treatment	Mild / 469 / 1) Pain and 2) Enzymes / Investigator / Full	Imaging did not show pancreatitis but also did not visualize pancreatic tail

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

		discontinuation / Recovered		Event start day was reported by investigator as day 104 and the subject was never randomized. It is unclear why the EAC considered the event start day to be 469 (looks like an error)
<i>Placebo</i>				
4374 / (b) (6) / 52 / M / 29.3	Obstructive pancreatitis / 254 / None	Serious / Moderate / Unlikely / Dose not changed / Recovered	Mild / 253 / 1) Pain and 2) Enzymes / Investigator / Full	Event co-reported with events of cholecystitis acute, cholelithiasis, and liver cirrhosis
a The event had onset in the 7-week follow-up period after last dose of trial product b Additional data were to be collected in the case of acute pancreatitis				

Source: SCS, Table 2-24; subject (b) (6) added by reviewer from data in study 4376 ADADJ.xpt and Table 16.2.7.20

AEs that were sent for adjudication but ultimately were not confirmed as they did not meet diagnostic criteria were reviewed:

- Trial 4373: 1 event of asymptomatic hyperlipasemia was reported in a subject treated with semaglutide 2.4 mg. One lipase value of 273 was just over the 3x ULN cut-off (ref: 234). A CT scan was cancelled because repeat lipase values were decreasing, and the subject remained asymptomatic.
- Trial 4374: 1 event of 'pancreatic necrosis' was reported in a subject treated with semaglutide 2.4 mg; this is described in Table 104 above as an event of chronic pancreatitis (subject (b) (6)).

See the discussion of lipase and amylase below for a case of elevated lipase in the setting of cholecystitis that was not sent to the EAC for adjudication.

Lipase and Amylase

Lipase and amylase were also evaluated in the phase 3 trials – the dose-escalation group of trials 4373, 4374, and 4375 allowed for a useful comparison to placebo given similar study designs. In this pool, lipase and amylase had increased by a mean of 39% and 16%, respectively, in the semaglutide group at week 68 as compared to placebo, which had stable values (-3% and +4%, respectively) over the same period. A categorical summary of elevated lipase and amylase is shown in Table 105 below; as in the phase 2 trial, semaglutide is consistently associated with lipase elevations, although the proportions of subjects with values >3x ULN is small.

Table 105: Categorical Summary of Lipase and Amylase, Phase 3 Dose-Escalation Group

	Semaglutide N=2116	Placebo N=1261	Semaglutide N=2116	Placebo N=1261
	<i>Lipase</i> % meeting cut-off		<i>Amylase</i> % meeting cut-off	
Week -1				
>ULN	2.2	4.0	1.0	0.9
>3xULN	0.2	<0.1	0	0
Week 20				
>ULN	7.3	4.0	1.7	1.5
>3xULN	0.4	0.5	0	0
Week 68				
>ULN	6.8	2.8	1.7	0.9
>3xULN	0.8	<0.1	0	0
Maximum post-baseline				
>ULN	11.2	5.9	2.7	2.1
>3xULN	1.2	0.8	<0.1	0

Source: SCS, Table 2-26

Upon review of a narrative for cholecystitis (see Section 8.5.1 for a further discussion of gallbladder-related disorders), a local laboratory lipase value of 2797 U/L (ref. 73-393) was reported as part of the case presentation:

- Subject NN9536-4375/ (b) (6) was a 55-year-old male who presented with right upper quadrant pain and had an urgent cholecystectomy due to gallstones and presumed cholecystitis. Laboratory values provided on the date of hospital admission included a lipase of 2797 U/L (ref. 73-393). CT and MRI scan both showed abnormal imaging suspicious for acute cholecystitis. The event of lipase increase was not reported as a separate AE, as the lipase increase was considered part of the clinical event of cholecystitis. The subject had a cholecystectomy and recovered from the AE.

Reviewer comment: As this event of lipase increase in the setting of cholelithiasis/ cholecystitis could be consistent with gallstone pancreatitis, it should have been sent for EAC adjudication.

The applicant was asked to review phase 3 narratives for local labs with amylase and/or lipase values $\geq 3x$ ULN. They identified 7 cases. Of these, 4 were adjudicated and confirmed as acute pancreatitis. The remaining 3 cases included a benign pancreatic neoplasm, cholecystitis (discussed above), and appendicitis.

Table 106: Cases with Amylase and/or Lipase $\geq$ 3x ULN

Case number/ Trial ID/Patient ID	Lab test	Result (U/L)	Preferred term	Symptoms of abdominal pain	Relevant imaging	Comment
Semaglutide 2.4 mg						
743603/ NN9536-4375 (b) (6)	Amylase	1216	Benign pancreatic neoplasm	Left flank pain	CT: 4 cm cystic lesion in pancreatic tail.	Not included in CTR as event was reported in July 2020. Included in the original NDA in the safety summary as new SAE from completed clinical trials.
649700/ NN9536-4373 (b) (6)	Lipase	263	Increased Lipase	Significant upper abdominal pain	Ultrasound and CT showed multiple lithiases with no sign of complication, and was not consistent with acute or chronic pancreatitis	EAC-confirmed mild acute pancreatitis event
661853/ NN9536-4373 (b) (6)	Lipase	186	Acute pancreatitis, Colitis	Epigastric pain	No CT evidence of pancreatitis	EAC-confirmed mild acute pancreatitis event
707153/ NN9536-4373 (b) (6)	Lipase	698	Acute cholecystitis, acute pancreatitis, cholelithiasis	Upper abdominal pain	Ultrasound and MRI consistent with presence of gallstones but not consistent with acute or chronic pancreatitis.	EAC-confirmed mild acute pancreatitis event
678372/ NN9536-4375 (b) (6)	Lipase	2797	Cholecystitis	Pain in upper right abdomen quadrant	CT scan: interval development of pericholecystic fluid with possible gallbladder stones, MRI: gallbladder wall thickening and pericholecystic fluid. Suspicion of gallstones and cholecystitis	
659856/ NN9536-4375 (b) (6)	Lipase	289	Appendicitis	Lower quadrant abdominal pain	CT scan revealed acute appendicitis and normal appearing pancreas.	
Placebo						
663039/ NN9536-4374 (b) (6)	Lipase	5264	Obstructive pancreatitis, Acute cholecystitis	Pain in upper right abdomen quadrant	Unspecified imaging was abnormal and showed enlarged gallbladder, acute pancreatitis, obstructive gallstone and dilated common bile duct.	EAC-confirmed mild acute pancreatitis event

Abbreviations: CT: Computed tomography; CTR: Clinical trial report; MRI: Magnetic resonance imaging; EAC: Event adjudication committee

Source: Response to FDA request dated 20 May 2021, Table 1

In summary, pancreatitis was reported infrequently in the semaglutide program. In approximately half of the cases, gallstones were observed in association with pancreatitis. Semaglutide also appears to be associated with elevations in pancreatic enzymes, but these elevations were infrequently captured as pancreatitis events.

At this time, it is not possible to conclude that semaglutide is *not* associated with pancreatitis, as the events might occur too infrequently for such a determination. The program was not specifically designed to conclusively determine whether semaglutide is associated with a risk for pancreatitis.

8.5.3. Cardiovascular Disorders

This section primarily discusses cardiovascular (CV) adverse events, adjudicated major adverse cardiovascular events (MACE), and AEs related to arrhythmia. Additionally, changes in heart rate (HR) are described.

There were too few events to conclude a difference from placebo in the rate of MACE. There was a trend suggesting an increased incidence of supraventricular arrhythmias (primarily atrial fibrillation and supraventricular extrasystoles) in patients with diabetes; however, the numbers were small. Although this finding was not observed in other studied populations, the increase

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

in HR associated with semaglutide in theory could predispose vulnerable individuals to adverse cardiac events.

GLP-1 RAs, including semaglutide, increase HR. In placebo-controlled trials with Ozempic, a mean increase of 2 to 3 beats per minute (bpm) was observed with Ozempic (semaglutide 0.5 and 1 mg), versus a mean decrease in HR of 0.3 bpm in the placebo arm.⁶⁰

Semaglutide has been evaluated to date in 2 CV outcomes trials in subjects with established CV disease and T2D: PIONEER 6 (Ozempic) and SUSTAIN 6 (Rybelsus). Ozempic was shown to significantly reduce the occurrence of MACE; the estimated hazard ratio for time to first MACE was 0.74 (95% CI: 0.58, 0.95) over a median observation time of 2.1 years. In the trial with Rybelsus, non-inferiority to placebo (risk margin of 1.3) was established, with a hazard ratio of 0.79 (95% CI: 0.57, 1.11) over the median observation time of 16 months. Based on these 2 CVOTs, Ozempic was approved for an indication to reduce the CV risk in patients with T2D and established CV disease. The CV safety of Rybelsus was confirmed and the trial is labeled as a safety study.

Other GLP-1 RAs have been evaluated in CVOTs and have demonstrated no increased CV risk or CV benefit.

The effect of semaglutide 2.4 mg SC once weekly on MACE in a patient population with established CV disease and obesity (and without diabetes) is currently underway. The applicant states that reporting of results from this trial is expected in 2024. In addition, a CVOT to assess the CV benefit of oral semaglutide (Rybelsus) in T2D is currently underway.

Cardiovascular Events

Trial 4153

In the phase 2 trial 4153, pre-defined events were set for adjudication: acute coronary syndrome, cerebrovascular event, coronary revascularization procedure, heart failure requiring hospitalization, and death.

In this trial, 10 events were identified for event adjudication of which 7 events in 6 subjects were confirmed by the EAC. All 10 events were identified by the investigator.

One event was a non-CV death; this was the only fatality in the trial (see Section 8.4.1).

Within the event type 'acute coronary syndrome,' 2 events (chest pain and angina unstable) in 2 subjects (1 semaglutide 0.4 mg and 1 placebo) were sent for adjudication; none was a confirmed event by the EAC.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

No events of heart failure were identified to be sent for adjudication.

Events in the other 2 adjudicated categories, 'cerebrovascular events' and 'coronary revascularization events,' are described in the table below. All but 1 subject had a medical history of CV disease.

Table 107: EAC-Confirmed CV Events, Study 4153

Arm	ID / sex / age / BMI	PT / SAE	Severity	Study day	Outcome / action	EAC classification	History of CVD
<i>Cerebrovascular events</i>							
Sema 0.05	(b) (6) / F / 56 / 36.3	Ischemic stroke / Y	Severe	164	Recovered with sequelae / drug withdrawn	Ischemic stroke	Heart failure NYHA class II, hypertension, peripheral arterial disease
Sema 0.1	(b) (6) / F / 39 / 40.5	Transient ischemic attack / N	Moderate	325	Recovered / dose not changed	Transient ischemic attack	None
Sema 0.1	(b) (6) / F / 56 / 35.7	Transient ischemic attack / Y	Severe	59	Recovered / drug interrupted	Transient ischemic attack	Ischemic heart disease, percutaneous coronary intervention, hypertension
<i>Coronary revascularization</i>							
Sema 0.4	(b) (6) / M / 53 / 41.6	Percutaneous coronary revascularization / Y	Severe	80	Recovered / dose not changed	Percutaneous coronary intervention	Ischemic heart disease
Placebo	(b) (6) / M / 63 / 33.1	Coronary artery stenosis / N	Moderate	117	Not recovered / dose not changed	Percutaneous coronary intervention	Ischemic heart disease, percutaneous coronary intervention, coronary artery bypass graft, hypertension
		Angina pectoris / N	Moderate	120	Recovered / dose not changed	Percutaneous coronary intervention	
Sema=semaglutide EAC=external adjudication committee CVD=cardiovascular disease NYHA=New York Heart Association							

Source: Study 4153 CSR, Tables 12-25 and 12-26

Phase 3 Trials

In the phase 3 program, CV events were evaluated based on a pre-defined MedDRA search⁶⁹ as well as by adjudication by the EAC (see discussion and Table 112, below). [The MedDRA search includes a broader swath of *potential* CV events than the adjudication process; note that it also includes events that are not necessarily cardiovascular-specific, such as 'Edema peripheral,' 'Dyspnea,' 'Blood creatine phosphokinase increased,' 'Acute kidney injury,' and 'Septic shock.'] The in-trial observation period (rather than on-treatment) was used due to the potentially long latency between onset and diagnosis.⁷⁰

Adverse events of CV disorders as identified by the MedDRA search were reported in 8.7% of semaglutide subjects and 10.9% of placebo subjects; SAEs were 1.6% and 1.8%, respectively. In the phase 3 pool, preferred terms (PTs) that were reported more frequently in semaglutide-treated subjects than placebo-treated subjects included 'Syncope' (0.8% vs. 0.4%) and 'Orthostatic hypotension' (0.5% vs. 0.1%); these AEs are discussed further below and in Section 8.4.7, Vital Signs.

PTs from the pre-defined search with incidence $\geq 0.5\%$ in the semaglutide 2.4 mg group and greater than placebo are presented by trial for 4373, 4374, and 4375 below; in addition, AEs in the 'Cardiac disorders' SOC were included for completeness:

Table 108: CV Events, MedDRA Search, Study 4373, In-Trial

Study 4373	Semaglutide N=1306	Placebo N=655
CV Events (pre-defined MedDRA search)	107 (8.2)	75 (11.5)
Syncope	11 (0.8)	2 (0.3)
Orthostatic hypotension	8 (0.6)	0
Cardiac disorders SOC, on-treatment	54 (4.1)	33 (5.0)
Cardiac disorders SOC, in-trial	58 (4.4)	35 (5.3)

Source: Study 4373 CSR, Tables 12-17, 14.3.1.4, and 14.3.1.5

⁶⁹ Novo Nordisk MedDRA Query 'Cardiovascular disorders' included broad and narrow terms from the following: SMQ Central nervous system vascular disorders; SMQ Vasculitis; SMQ Ischemic heart disease; SMQ Cardiac arrhythmias; SMQ Cardiac failure; SMQ Cardiomyopathy; SMQ Embolic and thrombotic events; SMQ Shock; SMQ Torsade de pointes/QT prolongation

⁷⁰ As a reminder, subjects in trial 4376 randomized to placebo had been treated with semaglutide for 20 weeks prior to randomization.

Table 109: CV Events, MedDRA Search, Study 4374, In-Trial

Study 4374	Semaglutide 2.4 N=403	Semaglutide 1 N=402	Placebo N=402
CV Events	50 (12.4)	35 (8.7)	39 (9.7)
Atrial fibrillation	6 (1.5)	2 (0.5)	2 (0.5)
Supraventricular extrasystoles	4 (1.0)	0	0
Blood creatine phosphokinase increased	3 (0.7)	2 (0.5)	1 (0.2)
Acute kidney injury	3 (0.7)	2 (0.5)	2 (0.5)
Tachycardia	2 (0.5)	1 (0.2)	0
Carotid arteriosclerosis	2 (0.5)	0	1 (0.2)
Heart rate increased	2 (0.5)	2 (0.5)	0
Carotid artery stenosis	2 (0.5)	1 (0.2)	0
Cerebrovascular accident	2 (0.5)	0	1 (0.2)
Syncope	2 (0.5)	2 (0.5)	1 (0.2)
Cardiac disorders SOC, on-treatment	22 (5.5)	20 (5.0)	13 (3.2)
Cardiac disorders SOC, in-trial	24 (6.0)	22 (5.5)	13 (3.2)

Source: Study 4374 CSR, Tables 12-15, 14.3.1.4, and 14.3.1.5

Table 110: CV Events MedDRA Search, Study 4375, In-Trial

Study 4375	Semaglutide N=407	Placebo N=204
CV Events	40 (9.8)	22 (10.8)
Syncope	7 (1.7)	0
Orthostatic hypotension	3 (0.7)	0
Loss of consciousness	2 (0.5)	0
Atrioventricular block first degree	2 (0.5)	0
Thrombosis	2 (0.5)	0
Cardiac disorders SOC, on-treatment	11 (2.7)	9 (4.4)
Cardiac disorders SOC, in-trial	12 (2.9)	9 (4.4)

Source: Study 4375 CSR, Tables 12-13, 14.3.1.4, and 14.3.1.5

In the run-in period of trial 4376, the most frequently reported AEs were 'Palpitations' (6 events) and 'Chest pain' (5 events). Five SAEs were reported in 5 subjects: 2 'Acute myocardial infarction,' and 1 of each of 'Syncope,' 'Pulmonary embolism,' and 'Hemiparesthesia.' All 5 SAEs were resolved; 4 of the 5 without changes in dosing of trial product and 1 (syncope) led to a dose reduction. In addition, 2 events, 'Atrial fibrillation' and 'Ventricular extrasystoles' led to permanent discontinuation of trial product.

During the randomized period, more subjects on placebo versus semaglutide reported a CV event according to MedDRA search, in part driven by more events of peripheral edema in the

placebo arm. Because both groups initially received semaglutide, AEs $\geq 5\%$ in either randomized group and 'Cardiac disorders' SOC are shown below.

Table 111: CV Events, MedDRA Search, Study 4376, In-Trial

Study 4376	Semaglutide N=535	Placebo N=268
CV Events	26 (4.9)	30 (11.2)
Blood creatine phosphokinase increased	7 (1.3)	5 (1.9)
Syncope	3 (0.6)	3 (1.1)
Palpitations	3 (0.6)	3 (1.1)
Edema peripheral	2 (0.4)	7 (2.6)
Atrial fibrillation	1 (0.2)	2 (0.7)
Cardiac disorders SOC, on-treatment	13 (2.4)	11 (4.1)
Cardiac disorders SOC, in-trial	13 (2.4)	11 (4.1)

Source: Study 4375 CSR, Tables 12-13, 14.3.1.5, and 14.3.1.7

Overall, in the phase 3 pool there were 21 subjects on semaglutide 2.4 mg (0.8%) with an AE of 'Syncope' versus 6 subjects on placebo (0.4%). Given the potential for semaglutide to cause hypotension and orthostatic hypotension (see Section 8.4.7, Vital Signs), serious syncopal episodes were reviewed:

- NN9536-4374/ (b) (6) (semaglutide 2.4 mg) was a 45-year-old male with T2D, hypertension, generalized edema, hypothyroidism, anemia, and nonrheumatic aortic valve insufficiency, who was treated in the trial for approximately 13 months when as he was walking up an incline, he felt fatigued and lightheaded. He fell forward and apparently had a syncopal episode. He was admitted to the hospital where laboratory and imaging tests were all negative/normal. During the hospitalization, he was placed on a nicardipine drip for uncontrolled blood pressure. He recovered and had no change to study drug.
- NN9536-4375/ (b) (6) (semaglutide 2.4 mg) was a 71-year-old female with dyslipidemia and chronic kidney disease stage 3 who was in the trial for approximately 470 days when she fainted at her Weight Watchers appointment causing her to fall and break her left hip. The subject reported standing more than 10 minutes and had decreased oral intake. The subject and the PI both felt that the cause of the syncope was dehydration. The cause of the syncope was not felt to be cardiogenic (a non-serious AE of occasional premature ventricular complexes on ECG was reported on day 488). She had surgery on her hip and recovered. No change was made to the study drug.
- NN9536-4376/ (b) (6) (run-in and randomized: semaglutide 2.4 mg) was a 43-year-old female with a history of hypermenorrhea and suicidal ideation due to trauma.

Approximately 2 months into the run-in period the subject had a syncopal episode during a routine gynecological surgery thought to be due to hypovolemia versus vasovagal. She was hospitalized for 1 night and recovered after receiving fluids. The semaglutide dose was reduced for 1 week.

- NN9536-4374/ (b) (6) (semaglutide 1 mg) was a 70-year-old male with T2D, dyslipidemia, hypertension, obstructive sleep apnea, peripheral vascular disease, diabetic nephropathy, and diabetic neuropathy on glimepiride and propranolol. The subject presented with right lower extremity cellulitis on day 1 of treatment and passed out on day 3. He was admitted to the hospital with dehydration, sepsis, lactic acidosis, syncope, acute kidney injury, and hypotension. He was treated and recovered with no change to the study drug.

Reviewer comment: All of the events had confounding factors, but a contribution of semaglutide, at least in part, cannot be dismissed in some cases (e.g., volume depletion leading to orthostatic hypotension). These syncopal episodes were not reported to have been caused by arrhythmia. Notably, all subjects recovered and remained on semaglutide.

Certain CV events were submitted for adjudication to an independent adjudication committee. Events submitted for adjudication as shown in Table 112 could be identified via reported AEs (either direct reporting for adjudication by the investigator or a MedDRA preferred term search) or by the EAC during review of source documentation.

Table 112: Adjudication of CV Events, Phase 3 Program

Event type	Description	Adjudication outcome(s)
Death	All-cause death	• Cardiovascular death (including undetermined cause of death) • Non-cardiovascular death
Acute Coronary Syndrome	Acute coronary syndrome conditions include all types of acute myocardial infarction and hospitalisation for unstable angina pectoris	• Acute myocardial infarction (including subgroup classifications) • Hospitalisation for unstable angina pectoris
Cerebrovascular events	Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction	• Ischaemic stroke • Haemorrhagic stroke • Undetermined stroke • Transient Ischaemic Attack
Coronary artery revascularisation	A coronary revascularisation procedure is a catheter-based (PCI) or a surgical procedure (CABG) designed to improve myocardial blood flow	• Coronary revascularisation procedure
Heart failure	Presentation of the patient for an urgent, unscheduled clinic/office/emergency department visit or hospital admission, with a primary diagnosis of heart failure (new episode or worsening of existing heart failure)	• Heart failure hospitalisation • Urgent heart failure visit

Source: SCS, Table 2-27

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

All event types excluding death underwent primary adjudication (death events went to a death adjudication meeting). Two adjudicators of relevant specialty were assigned to events for primary adjudication and independently evaluated each event. If the 2 primary adjudications matched, the adjudication was complete. Events with disagreements or those directly advanced from primary adjudication were adjudicated by a consensus committee consisting of a minimum of 2 adjudicators of the relevant specialty and an EAC Chair or Vice-Chair.

In the phase 3 pool, there was a total of 32 EAC-confirmed CV events in-trial, with 15 subjects (0.6%) in the semaglutide 2.4 mg arm (17 events; 0.5 events per 100 PYO) and 11 subjects (0.7%) in the placebo arm (15 events; 0.7 events per 100 PYO).

Deaths are not included in this analysis, but as seen under the 3-component MACE evaluation (Table 116) as well as the evaluation of all deaths in the weight management program (Section 8.4.1), 3 of the 6 deaths in the phase 3 pool were categorized as CV death, all in semaglutide 2.4 mg-treated subjects. An additional death of cardiorespiratory arrest (EAC reported as 'undetermined') occurred in a subject randomized to semaglutide 1 mg (Table 55).

Table 113: EAC-Confirmed CV Events (Not Including CV Death), Phase 3 Pool, In-Trial

	Semaglutide 2.4 N=2650 PYO=3556.8		Placebo N=1529 PYO=2048.9	
	n (adj %)	E (adj R)	n (adj %)	E (adj R)
CV events	15 (0.6)	17 (0.5)	11 (0.7)	15 (0.7)
Stroke	5 (0.2)	5 (0.2)	3 (0.2)	3 (0.1)
Acute myocardial infarction	4 (0.2)	4 (0.1)	5 (0.3)	5 (0.3)
Coronary artery revascularization	3 (0.1)	3 (<0.1)	3 (0.2)	4 (0.2)
Unstable angina pectoris	2 (<0.1)	2 (<0.1)	0	0
Transient ischemic attack	2 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Heart failure	1 (<0.1)	1 (<0.1)	2 (0.1)	2 (<0.1)

Source: SCS, Table 2-30

Table 114 presents the numbers and proportions of subjects with confirmed events by EAC-determined category by trial. As expected, CV events occurred more frequently in trial 4374, which studied subjects with T2D. Overall, the numbers of subjects with events were small.

Table 114: Subjects with EAC-Confirmed CV Events (Not Including CV Death), By Trial

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo	Semaglutide run-in
4373	6/1306 (0.5)	-	4/655 (0.6)	-
Acute coronary syndrome	4 (0.3)	-	3 (0.5)	-
Cerebrovascular events	1 (<0.1)	-	1 (<0.1)	-
Coronary artery revascularization	3 (0.2)	-	0	-
4374	6/403 (1.5)	6/402 (1.5)	5/402 (1.2)	-
Acute coronary syndrome	2 (0.5)	3 (0.7)	1 (0.2)	-
Cerebrovascular events	3 (0.7)	1 (0.2)	3 (0.7)	-
Coronary artery revascularization	0	3 (0.7)	1 (0.2)	-
Heart failure	1 (0.2)	0	2 (0.5)	-
4375	2/407 (0.5)	-	0	-
Cerebrovascular events	2 (0.5)	-	0	-
4376	1/535 (0.2)	-	2/268 (0.7)	3/902 (0.3)
Acute coronary syndrome	0	-	1 (0.4)	2 (0.2)
Cerebrovascular events	1 (0.2)	-	0	1 (0.1)
Coronary artery revascularization	0	-	2 (0.7)	0

Source: Study 4373 CSR, Table 12-18; Study 4374 CSR, Table 12-16; Study 4375 CSR Table 12-14; Study 4376 CSR, Tables 12-13 and 12-14

To further evaluate the adjudication process for CV events, this reviewer evaluated the cases that did not meet diagnostic criteria in trial 4373 (the largest trial); see Table 115.

Reviewer comment: Based on this assessment, it appears that the adjudication process worked as designed. Nevertheless, it is relying on appropriately coded AEs for events to undergo EAC review.⁷¹

⁷¹ For example, subject NN9536-4373 (b) (6) in the semaglutide 2.4 mg arm had an AE based on an abnormal, CS ECG with the verbatim term "JUNCTIONAL RHYTHM W ACUTE ST CHANGES, ASYMPTOMATIC." However, the PT was coded as 'Nodal rhythm'. This is discussed under Section 8.3.2, Categorization of Adverse Events.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 115: CV Events Sent for Adjudication, Not Confirmed, Study 4373

Treatment	Subj ID	Age/Sex/Race	AE Term	Start day	Evaluation	Adjudicator 1 Comment ^a	Adjudicator 2 Comment ^a	Committee Comment ^a
Sema	(b) (6)	69/F/NR	DIPLOPIA	141	CONSENSUS MEETING	Consider stroke	Not consistent with ischemia	Transient symptoms and no supporting evidence of stroke
Sema	(b) (6)	66/M/W	WORSENING OF PERIPHERAL ARTERY OCCLUSIVE DISEASE DUE TO OCCLUSION OF STENT IN RIGHT FEMORAL ARTERY	104	PRIMARY ADJUDICATION	Peripheral arterial disease, no signs or symptoms of stroke or TIA	Similar comment to adjudicator 1	
Sema	(b) (6)	52/M/W	LOBULATION IN RIGHT ICA WITH OSSEOUS EROSION	442	PRIMARY ADJUDICATION	No symptoms described to suggest stroke and no CT lesions consistent with stroke.	Similar comment to adjudicator 1	
Sema	(b) (6)	53/F/W	SUBDURAL HEMATOMA	219	PRIMARY ADJUDICATION	Traumatic SDH/SAH (motor vehicle accident) without clear evidence of stroke	Similar comment to adjudicator 1	
Sema	(b) (6)	56/F/W	EXPRESSIVE APHASIA	304	CONSENSUS MEETING	Transient speaking difficulty with multiple episodes of syncope diagnosed with primary psychiatric disorder and negative imaging	Symptoms consistent with partial aphasia	3 syncope events before presentation with questionable transient speech problems that may have been related to hypotension post syncope so did not feel this was a TIA
Placebo	(b) (6)	65/F/W	SIEZURES	388	CONSENSUS MEETING	MRI negative ischemic stroke	Seizure	Prior stroke 6 months earlier, unclear if presenting symptoms were truly different from chronic neurological deficits after original stroke, no brain imaging evidence of a new stroke
Sema=semaglutide a: Reviewer condensed comment NR: not reported								

Source: Reviewer created/modified from Study 4373 ADADJ.xpt dataset

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Adjudicated 3-component MACE, composed of cardiovascular death (including undetermined cause of death as per the EAC), non-fatal myocardial infarction, and non-fatal stroke, was analyzed in the randomized phase 3 pool. Twenty MACE were confirmed by the EAC; 0.5% in each treatment group with a hazard ratio of 0.991 (95% CI 0.400, 2.456). All MACE in the phase 3 program were 'first MACE,' as no subjects experienced more than 1 MACE during the trials.

Notably, the events were few and therefore the confidence interval is wide, with an upper bound of the 95% CI greater than 2.0. Nevertheless, the semaglutide in T2D experience (including the 2 completed CVOTs described above) provide confidence that semaglutide is unlikely to cause CV harm in this patient population; a similar conclusion was drawn with liraglutide (Saxenda) based on the Victoza experience.⁵⁹ The Division agreed that this program could cross-reference the T2D program and the weight management program did not need to prespecify a noninferiority margin for unacceptable CV risk assuming that no unanticipated CV safety concerns were identified in the phase 3 program.⁷²

⁷² EOP2 meeting minutes, signed 22 Nov 2017

Table 116: EAC-Confirmed MACE, Phase 3 Pool, In-Trial

	Semaglutide 2.4 N=2650 PYO=3556.8		Placebo N=1529 PYO=2048.9	
	n (adj %)	E (adj R)	n (adj %)	E (adj R)
First MACE	12 (0.5)	12 (0.4)	8 (0.5)	8 (0.4)
Stroke	5 (0.2)	5 (0.2)	3 (0.2)	3 (0.1)
Ischemic stroke	5 (0.2)	5 (0.2)	3 (0.2)	3 (0.1)
Acute myocardial infarction (MI)	4 (0.2)	4 (0.1)	5 (0.3)	5 (0.3)
ST elevation MI	2 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Type 1 MI	2 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Indeterminate	1 (<0.1)	1 (<0.1)	3 (0.2)	3 (0.1)
Type 1 MI	1 (<0.1)	1 (<0.1)	3 (0.2)	3 (0.1)
Non-ST elevation MI	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Type 2 MI	1 (<0.1)	1 (<0.1)	0	0
Type 1 MI	0	0	1 (<0.1)	1 (<0.1)
CV death	2 (<0.1)	2 (<0.1)	0	0
Undetermined cause of death	1 (<0.1)	1 (<0.1)	0	0
Type 1 MI: MI caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) ⁷³				
Type 2 MI: ischemic myocardial injury in the context of a mismatch between oxygen supply and demand (excluding acute atherothrombotic plaque disruption) ⁷³				

Source: SCS, Table 2-31

Arrhythmias

In the phase 2 trial 4153, no SAEs of arrhythmia were reported. The most frequently reported AEs in the 'Cardiac arrhythmia' HLGt semaglutide groups by PT were 'Palpitations' and 'Tachycardia'.

In phase 3 trials, the most frequently reported events on-treatment were atrial fibrillation, atrioventricular block first degree, and tachycardia. The incidence of these events was similar in the semaglutide 2.4 mg and placebo groups in the overall phase 3 pool.

⁷³ Thygesen K, et al: the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). Circulation. 2018; 138: e618-51.

Table 117 presents the 'Cardiac arrhythmias' HLG by trial on-treatment (note that numbers are slightly different than the MedDRA CV AE search in the subsection above, which was based on the in-trial experience).

In trial 4374, the imbalance in the semaglutide 2.4 mg group was driven by atrial fibrillation (semaglutide 2.4 mg n=5, placebo n=2) and supraventricular extrasystoles (semaglutide 2.4 mg n=4, placebo n=0).

Table 117: Cardiac Arrhythmias HLG by Phase 3 Trial

Study	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo	Semaglutide run-in
4373	32/1306 (2.5)	-	17/655 (2.6)	-
SAEs	3 (0.22)	-	1 (0.15)	-
4374	13/403 (3.2)	10/402 (2.5)	4/402 (1.0)	-
SAEs	3 (0.74)	2 (0.50)	2 (0.50)	-
4375	7/407 (1.7)	-	3/204 (1.5)	-
SAEs	0	-	0	-
4376	7/535 (1.3)	-	5/268 (1.9)	5/902 (0.6)
SAEs	2 (0.37)	-	2 (0.75)	0

Source: Study 4373 CSR, Table 14.3.1.4; Study 4374 CSR, Table 14.3.1.4; Study 4375 CSR, Table 14.3.1.4; Study 4376 CSR, Tables 14.3.1.5 and 14.3.1.6

Overall, the incidence of SAEs was similar among groups: semaglutide 2.4 mg n=8 (0.3%) vs. placebo n=5 (0.3%).⁴⁹ Atrial fibrillation was the most frequently reported SAE, and the incidence was similar among groups: semaglutide 2.4 mg n=5 (0.2%) vs. placebo n=5 (0.3%).⁴⁹ Other SAEs of cardiac arrhythmias in the semaglutide 2.4 mg group were atrial tachycardia (n=1) and supraventricular tachycardia (n=2). A description of the SAEs in the semaglutide 2.4 mg is as follows:

- NN9536-4373/ (b) (6): this was a 58-year-old female with a past medical history of arrhythmia (not further described). She presented after 1 year and 3 months on treatment with atrial tachycardia at 156 beats/min. She was treated in the hospital with adenosine and bisoprolol, action was reported as drug discontinued temporarily, and the outcome of the event was reported as "not recovered".
- NN9536-4373 (b) (6): this was a 54-year-old male with 3 SAE reports of atrial fibrillation/paroxysmal atrial fibrillation. He was treated with cardioversion twice and then flecainide treatment. Atrial fibrillation was reported 2 times again after flecainide treatment, both times after drinking alcohol. Action taken was reported as no change to the drug.
- NN9536-4373 (b) (6): this was an 84-year-old female with a past medical history of atrial fibrillation (since 2013), who presented after approximately 4.5 months with palpitations and was found to atrial fibrillation with rapid ventricular response (heart rate: 151 bpm). Troponin I was 0.04 ng/mL and troponin 0.076 ng/mL (ref for both: <0.033). By report,

cardiac catheterization ruled out acute coronary syndrome. Heart rate was controlled and she was discharged with no change made to semaglutide.

- NN9536-4374/ (b) (6): this was a 55-year-old female with T2D, hypertension, and sleep apnea, who was found during a routine study ECG after approximately 4.5 months on study drug to have atrial fibrillation. Trial product was discontinued temporarily and restarted at a lower dose. The condition was considered chronic.
- NN9536-4374/ (b) (6): this was a 60-year-old male with T2D who presented after 1 year of treatment with atrial fibrillation, tachycardia (heart rate: 132 bpm), and congestive heart failure. It was reported that the events were exacerbated by “excess salt and excess alcohol intake”. The trial product was permanently discontinued as a result of the atrial fibrillation.
- NN9536-4374/ (b) (6): this was a 55-year-old male with a medical history of T2D, hypertension, and alcoholism who presented with worsening depression and tachycardia in the first 2-4 months of the trial. He was started on Wellbutrin. At visit 12 (~4.5 months), an abnormal ECG was noted and the subject was sent to the ER with supraventricular tachycardia (SVT). Adenosine and electric cardioversion were unsuccessful and the subject underwent SVT ablation. Trial drug was discontinued temporarily and then restarted at 0.25 mg weekly. The event was considered resolved.
- NN9536-4376/ (b) (6): this was a 42-year-old female with a history of paroxysmal SVT who presented after 1 year and 3 months on treatment with AV nodal reentrant tachycardia (PT: ‘Supraventricular tachycardia’), which improved after radiofrequency ablation. On the same day, there was also a report of a non-serious AE of “metabolic dishormonal cardiomyopathy,” which was “confirmed not to be a symptom of this event.” No change was taken to the drug and the event was considered recovered.
- NN9536-4376/ (b) (6): this was a 35-year-old female who was treated in the trial for 1 year and 3 months. Approximately 6 weeks after drug was discontinued, the subject presented to the ER atrial fibrillation with rapid ventricular response (heart rate: 170 bpm). She had reported ~3 weeks of intermittent palpitations. It was thought that caffeine was the most likely cause. She was treated with IV diltiazem and recovered.

Reviewer comment: Most events have confounding factors. Heart rate increases with semaglutide that could contribute to atrial arrhythmias cannot be ruled out as a theoretical concern.

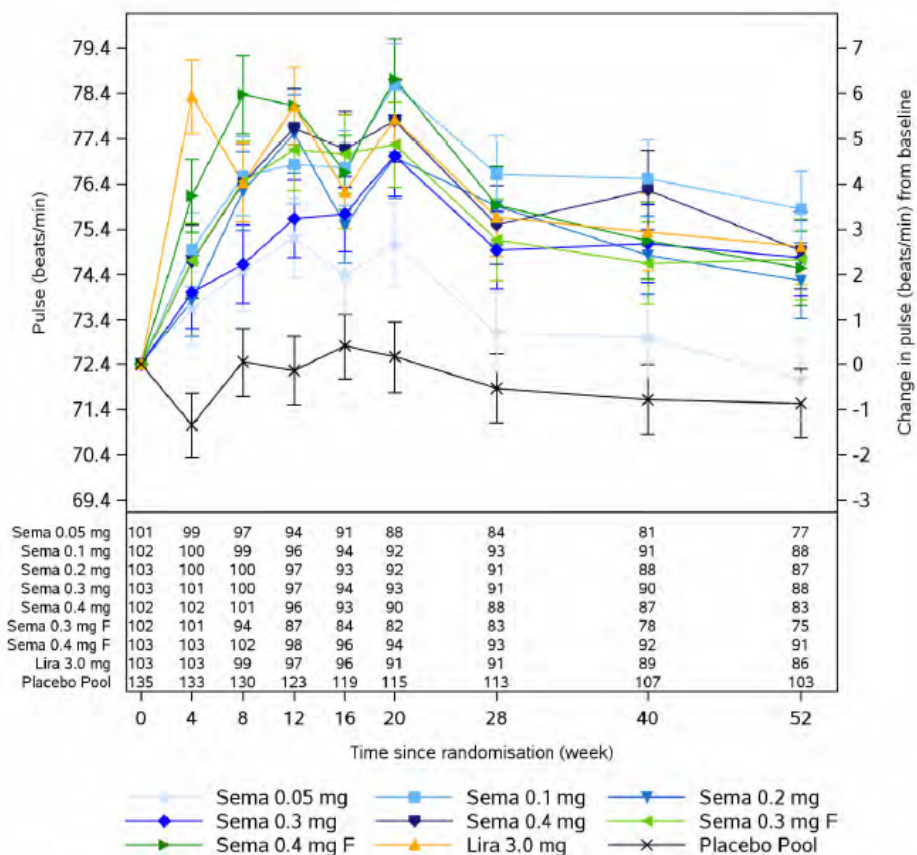
Heart Rate

As discussed in the introduction to this section, heart rate (HR) increases have been observed with the GLP1 RAs, including semaglutide. HR was evaluated versus placebo (all trials), for dose response (phase 2 trial 4153 and phase 3 trial 4374), and after study drug withdrawal (phase 3 trial 4376).

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

In the phase 2 trial 4153, an increase in HR was observed versus placebo for all semaglutide arms of 0.1 mg daily and above without a clear dose relationship, as well as the liraglutide 3 mg arm. The changes from baseline ranged from a mean of approximately 3 to 4 bpm over placebo after 52 weeks of treatment.

Figure 78: Change in HR from Baseline by Treatment Week, MMRM



F: Fast dose escalation
 MMRM: Analysis of observed data using a mixed model for repeated measurements with treatment, region and sex as factors and baseline body weight as covariate, all nested within visit.
 Bottom panel: Number of contributing subjects by treatment arm

Source: Study 4153 CSR, Figure 12-26

In the phase 3 trials, treatment difference in HR at week 68 from baseline ranged from approximately 1 to 4 bpm as shown in Table 118. Note that the absolute HR change is decreased in the randomized portion of study 4376 (STEP 4 in the table), which included a 20-week semaglutide run-in period prior to randomization.

Table 118: Heart Rate, Change from Baseline at Week 68

	Semaglutide 2.4 mg	Placebo
STEP 1		
N (baseline/week 68)	1306/950	655/443
Baseline	72	72
Change from baseline at week 68	3.52	-0.74
Treatment difference [95% CI] at week 68	4.26 [3.38; 5.15]*	
STEP 2		
N (baseline/week 68)	403/320	402/313
Baseline	75	76
Change from baseline at week 68	2.49	-0.23
Treatment difference [95% CI] at week 68	2.71 [1.43; 3.99]*	
STEP 3		
N (baseline/week 68)	407/290	204/139
Baseline	71	71
Change from baseline at week 68	3.05	2.10
Treatment difference [95% CI] at week 68	0.96 [-0.72; 2.63]	
STEP 4		
N (baseline/week 68)	535/470	268/220
Baseline	76	76
Change from baseline at week 68	-1.97	-5.25
Treatment difference [95% CI] at week 68	3.28 [1.93; 4.62]*	

* p<0.0001

Bpm: beats per minute; N: Number of subjects, CI: Confidence interval.

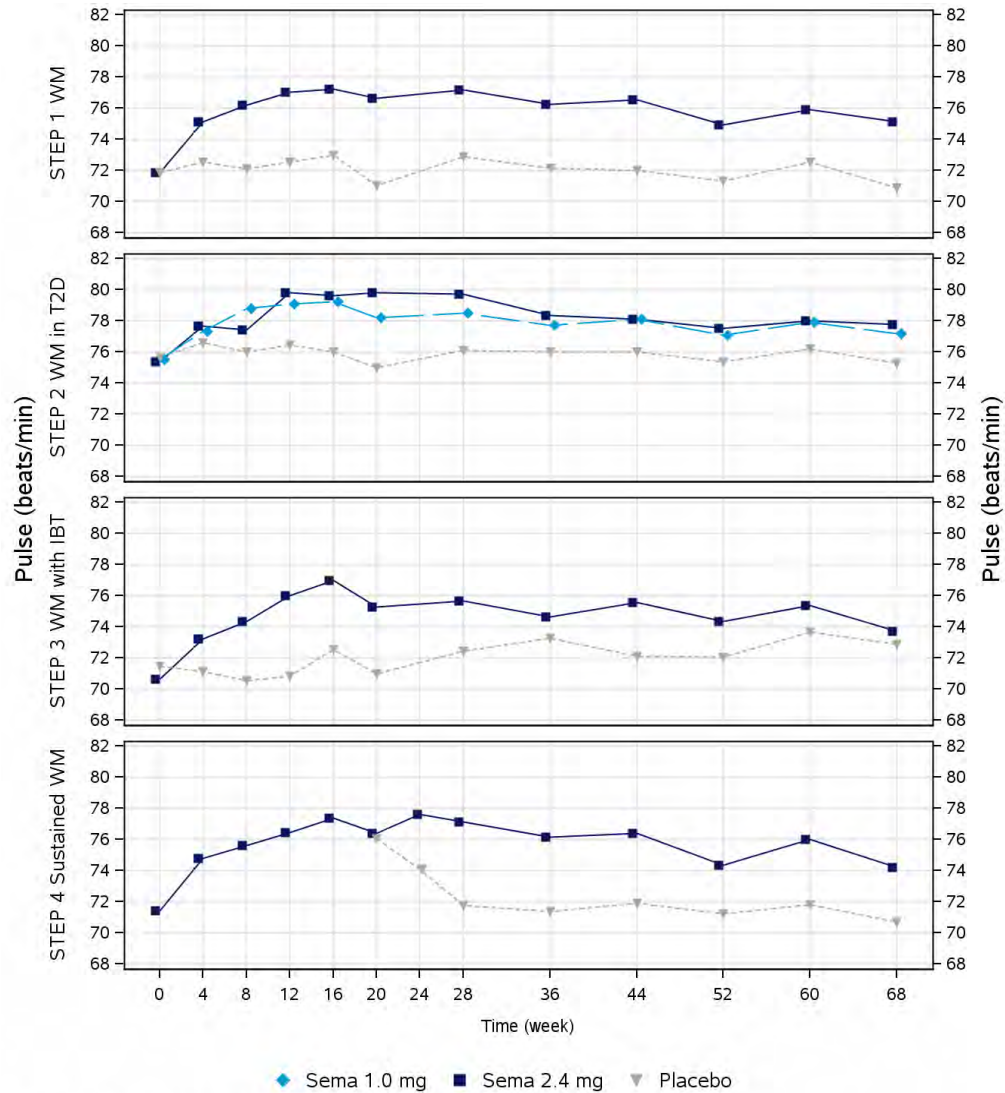
Analysis of data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. MMRM: All responses for all randomised subject prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline pulse as covariate, all nested within visit.

STEP 1=study 4373, STEP 2=study 4374, STEP 3=study 4375, STEP 4=study 4376

Source: SCS, Table 2-32

The figures below illustrate the trajectory of mean HR over time (raw values), with an approximate 2 to 5 bpm increase over placebo and a return toward baseline after week 68 (supported by the randomized withdrawal period in study 4376). The semaglutide 1 and 2.4 mg arms in study 4374 did not appear substantially different, supporting the absence of a clear dose effect at higher semaglutide doses in study 4153.

Figure 79: Pulse by Week, On-Treatment, Phase 3 Trials



WM: Weight management, T2D: Type 2 diabetes, IBT: Intensive behavioural therapy
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 14 days.
 During the run-in period for STEP 4 only assessments from subjects that were randomised at week 20 are shown.
nn9536/nn9536-summary/summ_iss_20201001_er
 25SEP2020:10:27:41 - fmeantrial.sas/fmeantrial/pulse.png

Source: ISS, Figure 7.6.3

In the phase 3 dose-escalation group, categorical changes in HR support the mean changes shown above, with more subjects on semaglutide than placebo experiencing 10 to < 20 bpm (41.0% and 34.5%, respectively) and ≥ 20 bpm (26.0% and 15.6%, respectively) maximum HR

change from baseline. The imbalances were observed regardless of whether baseline HR was < 60 bpm, 60 to < 80 bpm, or ≥ 80 bpm.⁷⁴

8.5.4. Neoplasms

Neoplasms were evaluated in the phase 2 and 3 weight management trials. There was no evidence of an increased risk of malignancy overall with semaglutide, and there was no evidence of an increased risk of any individual malignancy, including malignancies classified as events of special interest.

Neoplasms are of particular interest in this review because of GLP-1 RA class concerns (pancreatic cancer, medullary thyroid cancer [MTC]), as well as specific concerns raised in the Saxenda (liraglutide for weight management) program (breast cancer, benign and malignant colorectal neoplasms, and melanoma and non-melanoma skin cancer).

The semaglutide for T2D program did not raise any concerns regarding neoplasms. However, a recently published article reporting the results of a 72-week phase 2 trial with semaglutide versus placebo in subjects with biopsy-proven nonalcoholic steatohepatitis (NASH) reported malignant neoplasms in 3 out of 239 subjects (1%) on semaglutide and in no subjects out of 80 who received placebo, and overall, benign, malignant, and unspecified neoplasms were reported in 15% of the patients in the semaglutide groups and in 8% of those in the placebo group, with no pattern of occurrence in specific organs.⁷⁵

In the phase 2 and 3 weight management trials, subjects were not eligible for inclusion if they had:

- a history of malignant neoplasm within 5 years (except basal and squamous cell skin cancer or any carcinoma in situ)
- personal or first-degree relative history of multiple endocrine neoplasia syndrome type 2 or MTC
- calcitonin ≥ 100 ng/L at screening (≥ 50 ng/L in the phase 2 trial 4153)

Trial 4153

Neoplasms, including thyroid neoplasms, were identified as a safety area of interest in the phase 2 trial 4153. In this trial, all suspected cases were prospectively adjudicated by an oncologist in order to confirm the diagnosis and classify the neoplasms into benign, malignant, premalignant/carcinoma in situ/borderline, and unclassified, as well as by organ system. For

⁷⁴ Source: ISS, Table 7.6.2

⁷⁵ Newsome PN, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *New Engl J Med* 2021; 384: 1113-24.

thyroid neoplasms, an endocrinologist with expertise in thyroid neoplasms was included in the EAC.

In this trial, 70 events were sent for adjudication; 42 identified by the investigator and 28 from a preferred term search. No events were sent directly from the EAC for adjudication. Of these 70 potential events, 47 were not confirmed, 1 was considered a duplicate, and 1 was unable to adjudicate due to insufficient information. Therefore, 21 in-trial events (20 non-thyroid neoplasm events and 1 thyroid neoplasm event) in 19 subjects were confirmed by the EAC:

- One pre-malignant and 9 malignant neoplasms were confirmed by the EAC (6 with semaglutide, 2 with liraglutide 3 mg and 2 with placebo). Five of the 6 malignant/pre-malignant neoplasms in semaglutide-treated subjects were skin cancers. The other malignancy was the metastatic ovarian cancer in the subject treated with semaglutide 0.4 mg F (discussed in Section 8.4.1, under deaths). In the liraglutide group, squamous cell carcinoma of skin and invasive ductal breast carcinoma were confirmed malignancies. In the placebo group, transitional cell cancer of the renal pelvis and ureter and papillary thyroid cancer were confirmed malignancies. No MTCs were reported in any of the treatment arms. Except for the metastatic ovarian cancer, which was classified as stage IV by the EAC, all malignant neoplasms were categorized as stage 1 (localized). Onset days ranged from 98–404 days for the malignant/pre-malignant neoplasms.
- A total of 11 benign neoplasms in 10 subjects were confirmed by the EAC: 6 with semaglutide, 1 with liraglutide 3 mg, and 4 with placebo. Except for 1 case of uterine leiomyoma, all benign neoplasms were colorectal neoplasms (polyps and adenomas).

Neoplasms as identified by the predefined MedDRA search did not suggest any clustering or dose-related concerns.

Table 119: Neoplasms AEs, Trial 4153, MedDRA Search, In-Trial

	Semaglutide							Lira N=103	Placebo N=136
	0.05 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
Neoplasms [Prespecified MedDRA search]	11 (10.7)	7 (6.9)	4 (3.9)	2 (1.9)	7 (6.9)	4 (3.9)	6 (5.8)	4 (3.9)	9 (6.6)
Neoplasms benign, malignant and unspecified (incl cysts) [SOC]	4 (3.9)	1 (1.0)	2 (1.9)	1 (1.0)	4 (3.9)	3 (2.9)	2 (1.9)	3 (2.9)	6 (4.4)
Lira=liraglutide									

Source: Study 4153 CSR, Table 14.3.1.129

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Phase 3 Trials

In the weight management phase 3 program, neoplasms did not undergo a separate independent adjudication process.

Reviewer comment: This was agreed upon with the Division; nevertheless, the lack of adjudication could have led to some misclassification or under-reporting. For example, a couple of instances of AEs captured as diagnostic procedures or complications of procedures (thyroidectomy, postoperative anemia), obscured the known neoplasm (papillary thyroid cancer in a semaglutide subject, colonic polyp in a placebo subject; see Table 53 in Section 8.3.2). Furthermore, adjudication can ensure more consistent classification of tumor types, although it can suffer limitations when there is insufficient information. Overall, I do not have concerns that there was a systemic effort to obscure or misclassify neoplasms in this program.

The applicant conducted a pre-defined MedDRA search of investigator-reported AEs to evaluate neoplasms overall (benign and malignant), malignant neoplasms, and specific focus areas of breast neoplasms, skin neoplasms, colorectal neoplasms, and pancreatic cancer. Events were evaluated based on the in-trial period to account for potential lag-time for development of neoplastic growth. The applicant analyzed these events based on the phase 3 pool, which includes trial 4376. Because all subjects in trial 4376 were exposed to semaglutide during the run-in period, AEs are also presented by trial to ensure that no events were masked by the pooling.

Table 120: Neoplasms Summary (Benign and Malignant), Phase 3 Pool and By Trial, In-Trial Period

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Phase 3 pool	N=2650		N=1529
All AEs – pre-specified MedDRA search	187 (6.9)		108 (7.1)
SAEs	27 (1.0)		13 (0.8)
Neoplasms benign, malignant and unspecified SOC	88 (3.3)		53 (3.5)
Trial 4373	N=1306		N=655
All AEs	93 (7.1)		49 (7.5)
Neoplasms benign, malignant and unspecified SOC	46 (3.5)		26 (4.0)
Trial 4374	N=403	N=402	N=402
All AEs	21 (5.2)	29 (7.2)	28 (7.0)
Neoplasms benign, malignant and unspecified SOC	10 (2.5)	14 (3.5)	13 (3.2)
Trial 4375	N=407		N=204
All AEs	43 (10.6)		15 (7.4)
Neoplasms benign, malignant and unspecified SOC	12 (2.9)		8 (3.9)
Trial 4376	N=535		N=268
All AEs	30 (5.6)		16 (6.0)
Neoplasms benign, malignant and unspecified SOC	20 (3.7)		6 (2.2)

Source: SCS, Table 2-36; Study 4373 CSR, Table 14.3.1.61; Study 4374 CSR, Table 14.3.1.68; Study 4375 CSR, Table 14.3.1.61; Study 4376 CSR, Table 14.3.1.75

In the semaglutide run-in period of trial 4376, the MedDRA search for all neoplasms identified 15 AEs in 13 subjects; all were single events by PT except for 2 events of jaw cyst. Three of the events were SAEs: endometrial cancer, ovarian cyst, and biliary cyst. Endometrial cancer was the only malignancy identified in the semaglutide run-in phase. This subject with endometrial cancer subsequently died due to metastatic lung cancer in the randomized period (placebo group); see narrative in Section 8.4.1.

Regarding malignant neoplasms in the entire phase 3 program (phase 3 pool), similar proportions were reported in each treatment group (semaglutide 2.4 mg 1.1%, placebo 1.1%); Table 121. Three of these events had a fatal outcome; all were randomized to the placebo group, although as discussed above, 1 of these subjects with a malignancy leading to death had previously received semaglutide 2.4 mg during the run-in period. See Table 55 and narratives in Section 8.4.1 for a discussion of all fatal events in the weight management program.

Table 121: Malignant Neoplasms, Phase 3 Pool and By Trial, In-Trial Period

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Phase 3 pool	N=2650		N=1529
All Malignant AEs	28 (1.1)		17 (1.1)
SAEs	17 (0.6)		10 (0.6)
Trial 4373	N=1306		N=655
All Malignant AEs	14 (1.1)		7 (1.1)
Trial 4374	N=403	N=402	N=402
All Malignant AEs	5 (1.2)	7 (1.7)	8 (2.0)
Trial 4375	N=407		N=204
All Malignant AEs	3 (0.7)		1 (0.5)
Trial 4376	N=535		N=268
All Malignant AEs	6 (1.1)		1 (0.4)

Source: SCS, Table 2-40; Study 4373 CSR, Table 14.3.1.35; Study 4374 CSR, Table 14.3.1.35; Study 4375 CSR, Table 14.3.1.35; Study 4376 CSR, Table 14.3.1.49

All malignancies identified from the MedDRA search in the phase 3 pool were from the 'Neoplasms benign, malignant and unspecified' SOC, so malignant neoplasms by SOC are not presented separately.⁷⁶ Specific malignant neoplasm AEs by PT are shown in the table below. Only 1 subject reported malignant events (lung cancer metastatic and metastases to central nervous system) in the placebo group from the randomized portion of trial 4376 (i.e., after having been exposed to semaglutide in the run-in period). Therefore, the events are only presented as pooled, as this analysis fairly reflects the randomized treatment. (The run-in period from trial 4376, including malignant neoplasms, is discussed above.)

⁷⁶ Note that 1 papillary thyroid cancer in a semaglutide 2.4 mg subject was not identified in the MedDRA search (PT: 'Thyroidectomy'); see Section 8.3.2.

Table 122: Malignant Neoplasms by PT, Phase 3 Pool, In-Trial Period

	Semaglutide 2.4	Placebo
	N=2650	N=1529
Malignant neoplasms	28 (1.1)	17 (1.1)
Basal cell carcinoma	5 (0.2)	4 (0.2)
Intraductal proliferative breast lesion	3 (0.1)	1 (<0.1)
Squamous cell carcinoma	2 (<0.1)	0
Invasive ductal breast carcinoma	2 (<0.1)	0
Malignant melanoma	2 (<0.1)	0
Breast cancer	2 (<0.1)	0
Papillary thyroid cancer ⁷⁶	2 (<0.1)	0
Chronic lymphocytic leukemia	1 (<0.1)	0
Gastrointestinal lymphoma	1 (<0.1)	0
Myeloid leukemia	1 (<0.1)	0
Nasal cavity cancer	1 (<0.1)	0
Endometrial adenocarcinoma	1 (<0.1)	0
Invasive breast carcinoma	1 (<0.1)	0
Marginal zone lymphoma	1 (<0.1)	0
Cervix carcinoma stage 0	1 (<0.1)	0
Dermatofibrosarcoma protuberans	1 (<0.1)	0
Gastrointestinal stromal tumor	1 (<0.1)	0
Prostate cancer	1 (<0.1)	3 (0.2)
Gastric cancer	0	1 (<0.1)
Gastric cancer stage IV	0	1 (<0.1)
Glioblastoma	0	1 (<0.1)
Hairy cell leukemia	0	1 (<0.1)
Hepatocellular carcinoma	0	1 (<0.1)
Invasive lobular breast carcinoma	0	1 (<0.1)
Keratinizing squamous cell carcinoma of nasopharynx	0	1 (<0.1)
Lobular breast carcinoma in situ	0	1 (<0.1)
Lung cancer metastatic	0	1 (<0.1)
Malignant melanoma in situ	0	1 (<0.1)
Metastases to central nervous system	0	1 (<0.1)
Note: % are adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials		

Source: SCS, Table 2-41

Breast Cancer

At screening, 0.6% of female subjects in the semaglutide 2.4 mg group and 1.2% of female subjects in the placebo group reported a personal history of breast cancer. A similar proportion (0.3%) of female subjects reported a personal history of carcinoma in situ of the breast.

Breast cancer was observed only in females⁷⁷ in the phase 3 program: 8/1920 female subjects (0.4%) in the semaglutide 2.4 mg group and 3/1073 female subjects (0.3%) in the placebo group reported malignant breast neoplasms in the in-trial period.

- Of the 8 events in the semaglutide group, 1 event was reported on day 1 of the trial (PT: 'Breast cancer'), and 3 events were reported after 5–7 months in the trials (1 event of 'Invasive breast carcinoma' and 2 events of 'Intraductal proliferative breast lesion'). The remaining 4 events were reported after approximately a year (1 event of 'Breast cancer,' 1 event of 'Intraductal proliferative breast lesion,' and 2 events of 'Invasive ductal breast carcinoma').
- The 3 AEs of malignant breast neoplasms in the placebo group were reported after less than 2 months for 1 event ('Invasive lobular breast carcinoma') and after approximately a year for the remaining 2 events (1 'Intraductal proliferative breast lesion' and 1 'Lobular breast carcinoma in situ').

Colorectal Neoplasms

At screening, 4.9% of semaglutide-treated subjects and 4.6% of placebo-treated subjects had a history of colorectal neoplasms; almost all were classified as benign.

In the phase 3 pool during the in-trial period, the proportion of subjects reporting AEs of colorectal neoplasms (benign and malignant) was similar in the semaglutide 2.4 mg and placebo groups (0.8% in both⁷⁸). All events were non-serious, mild or moderate in severity and the majority were reported as resolved. The majority were large intestinal polyps; a smaller number were rectal polyps and colon adenomas.

Skin Neoplasms

At screening, a similar proportion of subjects (3.6%) per group had a history of skin cancer; the majority was basal cell carcinoma (2.6% per group).

In the phase 3 pool during the in-trial period, the proportion of subjects reporting AEs of skin neoplasms (benign and malignant) was similar with semaglutide 2.4 mg (0.8%) and placebo (1.1%). Only 1 SAE of skin neoplasm was reported; this event (malignant melanoma) occurred in a subject in the semaglutide 2.4 mg group, was considered of mild severity and resolved. Overall, 2 subjects in the semaglutide 2.4 group reported malignant melanoma and 1 subject in placebo reported malignant melanoma in situ. The majority of events in the semaglutide group

⁷⁷ One male subject in trial 4376 (semaglutide 2.4) reported a benign breast neoplasm; this event was non-serious, mild in severity, and reported as resolved.

⁷⁸ This information is from the applicant's MedDRA search as presented in the Summary of Clinical Safety and does not include 1 event of colonic polyp in a patient randomized to placebo, reported as 'anemia postoperative'

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

were 'Melanocytic nevus' and 'Basal cell carcinoma.' It should be noted that there were 2 non-serious on-treatment AEs of basal cell carcinoma that were not identified via AE reporting, as they were not included in the pre-specified MedDRA search (see Table 53).

Pancreatic Cancer

No events of pancreatic cancer occurred in the weight management program.

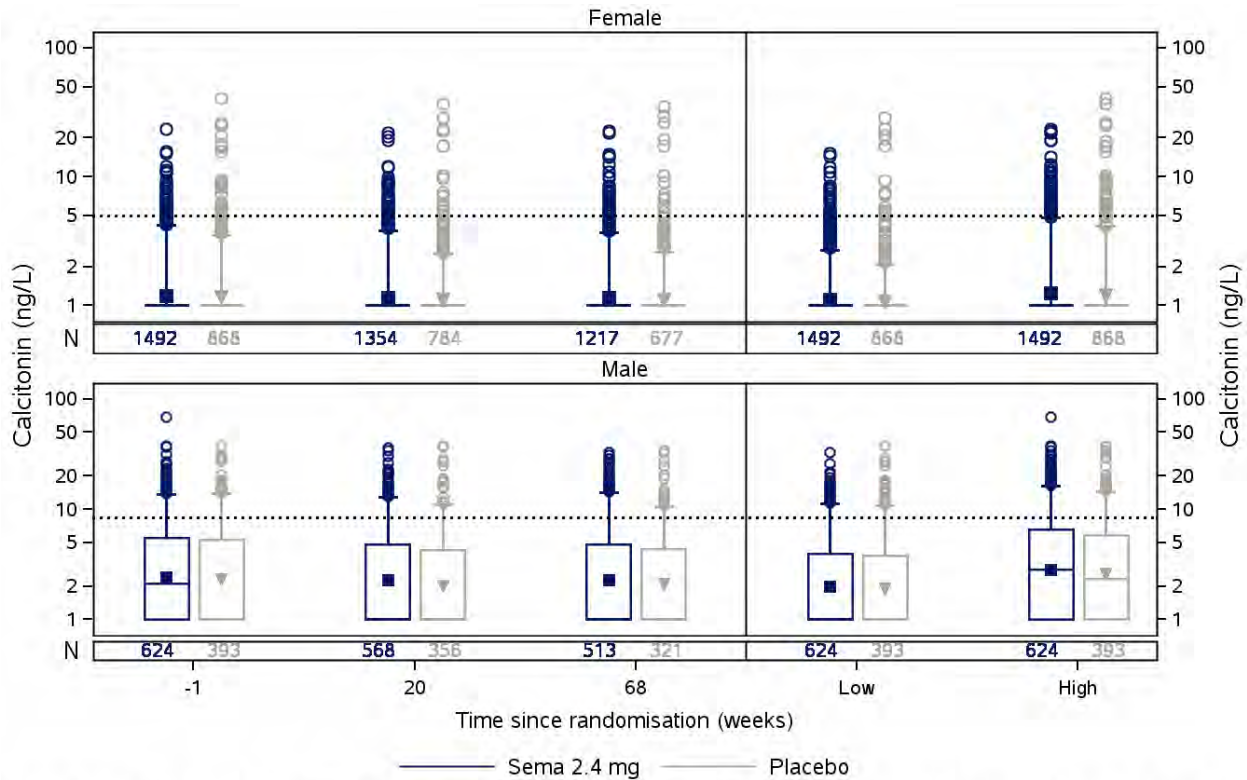
Medullary Thyroid Cancer and Calcitonin

No events of MTC occurred in the weight management program.

Calcitonin was measured in this program to monitor for C-cell hyperplasia. Calcitonin is not a routinely recommended test for monitoring patients treated with GLP-1 RAs, including semaglutide. On average, calcitonin values were higher for males than females and did not change substantially over time.

Figure 80 presents a box plot of calcitonin values by week in trials 4373, 4374, and 4375, as well as the minimum and maximum on-treatment values in those trials. Note that the minimum and maximum values *include* baseline values, as they are considered on-treatment for the purposes of the laboratory analysis.

Figure 80: Calcitonin by Week and Minimum and Maximum Values, Trials 4373, 4374, and 4375



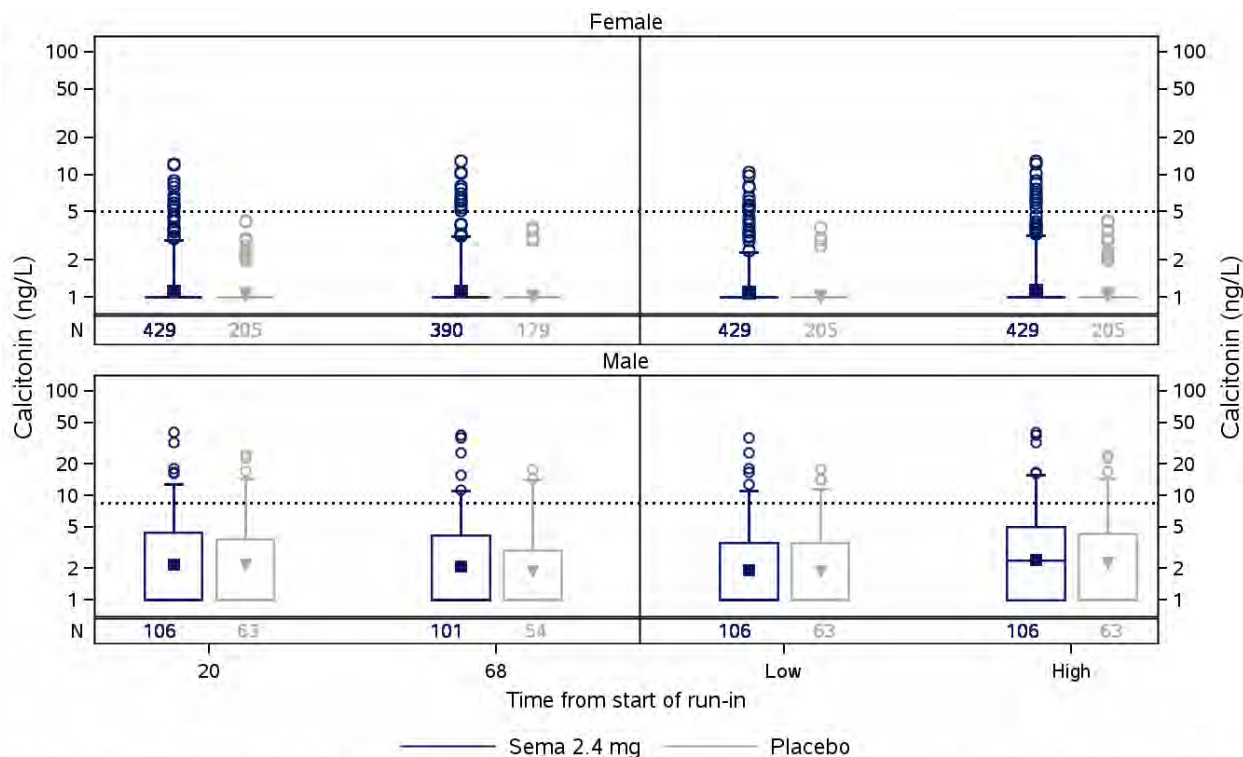
Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols in the boxes correspond to means. Whiskers correspond to the 5th and 95th percentiles. Dotted line(s) indicate normal reference range.
 Lower panel: Numbers of contributing subjects. Right panel: Low and High are per-subject minimum and maximum on-treatment values.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 14 days.

nn9536/mn9536-summary/subm_iss_20201001_ar
 25SEP2020;10:27:36 - fboxplotot.sas/fboxplotcalot.png

Source: ISS, Appendix 7.5, Figure 7.5.13

In trial 4376, more individual subjects randomized to semaglutide versus placebo (i.e., after the semaglutide run-in) experienced calcitonin values above the ULN (Figure 81).

Figure 81: Calcitonin by Week and Minimum and Maximum Values, Trial 4376 (Randomized Period)



Observed data from on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 14 days. Randomised period starts with week 20 visit.
 Boxes correspond to the 25th, 50th (median) and 75th percentiles and symbols in the boxes correspond to geometric means. Whiskers correspond to the 5th and 95th percentiles. Low and High are the per-subject minimum and maximum values over the on-treatment observation period including assessments taken outside the planned visit schedule. Dotted line(s) indicate normal reference range. Lower panel: Numbers of contributing subjects. Right panel: Low and High are per-subject minimum and maximum on-treatment values.
 Only randomised subjects in the safety analysis set contribute.

nr9536/m9536-4376/ctr_20200717_ar
 25JUN2020.12:23:04 - fboxplotb_sas%calcitoboxplotot.png

Source: Study 4376 CSR, Figure 14.3.5.13

One subject ((b) (6) in trial 4374, semaglutide 2.4 mg) experienced a calcitonin value ≥ 50 ng/L during the screening period (69.1 ng/L). This subject was advised to see a thyroid specialist and was later diagnosed with papillary thyroid carcinoma.

Aside from this subject, no subject in the trial had a calcitonin value ≥ 50 ng/L. Subjects with post-baseline values ranging from 36.5 to 44.6 ng/L are shown in the table below; all had elevated calcitonin at baseline and were similar among treatment groups.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 123: Calcitonin, Outlier Post-Baseline Values

Study/Subject ID	Randomized Group	Baseline ^a	Maximum Post-Baseline ^b
NN9536-4374 (b) (6)	Placebo	18.4	36.6
NN9536-4374	Sema 1 mg	28.2	44.6
NN9536-4374	Placebo	20.8	36.5
NN9536-4374	Placebo	38	37.7
NN9536-4376	Sema 2.4 mg	32.3	40.2
NN9536-4376	Sema 2.4 mg	15	38.1

a in trial 4376, baseline is defined as before run-in
b on-treatment period
Sema=semaglutide

Source: Reviewer created from ISS dataset ADLB.xpt

Finally, an exploratory analysis of AEs related to calcitonin increase was conducted. All were considered of mild severity and none was an SAE. Incidence (unadjusted) was similar among the groups:

Table 124: Calcitonin AEs, Phase 3 Pool

	Semaglutide 2.4 N=2650 Unadj %	Placebo N=1529 Unadj %
Calcitonin events, on-treatment	4 (0.2)	2 (0.1)
Blood calcitonin increased	4 (0.2)	1 (0.1)
Hypercalcitoninemia	0	1 (0.1)

Source: Reviewer created from ISS dataset ADAE.xpt

In addition, there was 1 subject randomized to semaglutide 1 mg who had an AE of hypercalcitoninemia.

In summary, notwithstanding some limitations in data collection and reporting, there does not appear to be a signal for neoplasms (malignant or benign) overall or of specific types. Any observed imbalances were small and there was not a pattern of neoplasm type identified.

8.5.5. Hepatic Disorders

Drug induced liver injury (DILI) was not identified as a safety concern in the pre-marketing reviews of semaglutide for diabetes (Ozempic and Rybelsus), although the Ozempic reviewer did note an imbalance in ALT >5X ULN.⁷⁹ The semaglutide products do not include liver safety information in their labeling.

⁷⁹ Lungu A. Clinical review of NDA 209637, dated 27 Nov 2017. DARRTS ref. ID 4186415

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In the semaglutide weight management program, there was no evidence of increased risk of hepatic AEs or SAEs with semaglutide. There was no imbalance in transaminase elevations, except for a single case of ALT >5x ULN on semaglutide versus no cases on placebo, described further in this section.

The Office of Surveillance and Epidemiology (OSE) was contacted in July 2020 by a hepatologist whose patient developed cholestatic jaundice approximately 6 months after starting Rybelsus (oral semaglutide). Work-up, including liver biopsy, was suggestive of DILI. As a result of receiving this case, a preliminary FAERS search by OSE identified additional reports suggestive of DILI with semaglutide, including 2 fatal reports and 8 hospitalizations. According to Dr. Amy Chung, Division of Pharmacovigilance-I (DPV-I),⁸⁰ 1 of the fatal reports described a 45-year-old female patient who developed hepatorenal syndrome approximately 3 months after starting semaglutide injections for T2DM. A second fatal report described a 77-year-old male patient who developed cholestatic jaundice after 2 doses of semaglutide injection; liver biopsy in this case showed prominent cholestasis and hepatocellular injury.

OSE subsequently expanded their preliminary review to include the GLP-1 RA class. An additional FAERS search identified serious reports for exenatide, liraglutide, dulaglutide, and lixisenatide, including 2 fatal reports of hepatic failure with use of exenatide (1 reporting intrahepatic cholestasis), 2 reports of hospitalization for cholestasis and DILI with liraglutide, and 2 published literature case reports (autoimmune hepatitis with liraglutide and cholestatic liver injury with dulaglutide). In pre-marketing reviews of liraglutide, imbalances in transaminases were observed for liraglutide (Saxenda and Victoza; these are labeled) and cases of mild hepatocellular injury with albiglutide (labeled, but no longer marketed).

NISS 1004209 was recently opened to assess DILI with the GLP-1 RA class, and an information request was sent to all the marketed GLP-1 RAs, including semaglutide, for additional information regarding DILI cases in pre- and post-marketing databases.

To evaluate the hepatic safety of semaglutide 2.4 mg in the weight management program, hepatic disorders were considered events of special interest and were identified via a pre-defined MedDRA search⁸¹ and the following liver parameters: ALT, AST, ALP, GGT, and TBL.

All data on hepatic disorders and laboratory data were evaluated based on the on-treatment period, except for the following 2 evaluations:

⁸⁰ Personal communication.

⁸¹ MedDRA SMQ: Drug related hepatic disorders – comprehensive search

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- Cases of concurrent elevations in ALT/AST > 3x ULN and total bilirubin > 2x ULN were evaluated for the in-trial period of the phase 3 weight management trials (4373, 4374, 4375, and 4376) and the semaglutide run-in period of trial 4376, and included scheduled and unscheduled visits (no cases were identified).
- Subjects with ALT > 5x ULN at any time post-baseline (including scheduled and unscheduled visits) were evaluated for the in-trial period of the phase 3 weight management trials and the run-in period of trial 4376.

This review evaluated the applicant's outputs by MedDRA AE search, focusing on SAEs and AEs that could potentially be DILI events, and the laboratory liver parameters. In addition to the pooled phase 3 data, an evaluation was conducted of the phase 2 data and run-in period of trial 4376, a local laboratory data search in narratives, and a review of blinded and ongoing trial data. New post-marketing data available through the NISS evaluation is discussed in Section 8.9.1.

Adverse Events

Trial 4153

In the phase 2 trial 4153, no hepatic AEs were serious, severe, or led to treatment discontinuation. The highest proportion of events in the trial was in the placebo group (6.6%). AEs in the semaglutide groups ranged from 0 to 2.9% in a non-dose-dependent manner. The only subject with the PT 'Drug-induced liver injury' was randomized to the liraglutide 3 mg group (verbatim term: "HEPATITIC REACTION : IMMUNO-ALLERGY HEPATIC REACTION AFTER DRUG INJECTION (ELEVATED ALT AND AST)").

Phase 3 Trials

In the phase 3 pool, similar proportions of subjects reported AEs of hepatic disorders for semaglutide (2.3%) and placebo (2.7%); see Table 125.

Three events in 2 subjects randomized to semaglutide 2.4 mg (<0.1%) were SAEs versus 1 event in 1 subject randomized to placebo (<0.1%); this SAE in the placebo subject was a fatal event (hepatocellular carcinoma, see Section 8.4.1). In addition, the subject in the semaglutide 2.4 mg arm who had 2 hepatic disorder SAEs on-treatment had a third hepatic disorder SAE in-trial (not on-treatment). Narratives for all the semaglutide-treated SAEs are presented further below.

Three events led to permanent treatment discontinuation: 1 each randomized to semaglutide 2.4 mg (hepatic enzyme increased), semaglutide 1 mg (liver disorder), and placebo (hepatocellular carcinoma); the narratives for the semaglutide-treated subjects are presented further below.

Table 125: Hepatic Disorders, Predefined MedDRA Search, Phase 3 Pool

	Semaglutide 2.4		Placebo	
	N=2650 n (adj%)	PYE 3309.5 E (adj R)	N=1529 n (adj%)	PYE 1885.4 E (adj R)
Hepatic disorder events	60 (2.3)	70 (2.1)	42 (2.7)	54 (2.7)
Hepatic steatosis	13 (0.5)	13 (0.4)	15 (1.0)	15 (0.8)
Hepatic enzyme increased	7 (0.3)	7 (0.2)	6 (0.4)	6 (0.3)
Gamma-glutamyltransferase increased	7 (0.2)	7 (0.2)	3 (0.2)	3 (0.2)
Aspartate aminotransferase increased	5 (0.2)	5 (0.1)	6 (0.4)	6 (0.3)
Liver function test increased	4 (0.2)	4 (0.1)	1 (<0.1)	1 (<0.1)
Hyperbilirubinemia	4 (0.1)	5 (0.2)	1 (<0.1)	1 (<0.1)
Hepatic cyst	3 (0.1)	3 (<0.1)	2 (0.1)	2 (<0.1)
Blood bilirubin increased	3 (0.1)	3 (<0.1)	3 (0.2)	3 (0.2)
Alanine aminotransferase increased	3 (0.1)	3 (<0.1)	8 (0.5)	8 (0.4)
Hemangioma of liver	2 (<0.1)	2 (<0.1)	0	0
Hepatic function abnormal	2 (<0.1)	2 (<0.1)	0	0
Nonalcoholic fatty liver disease	2 (<0.1)	2 (<0.1)	0	0
Liver function test abnormal	2 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Hypertransaminasemia	1 (<0.1)	3 (<0.1)	0	0
Hepatic encephalopathy	1 (<0.1)	1 (<0.1)	0	0
Hepatic lesion	1 (<0.1)	1 (<0.1)	0	0
Hepatic neoplasm	1 (<0.1)	1 (<0.1)	0	0
Hepatic pain	1 (<0.1)	1 (<0.1)	0	0
Hypoalbuminemia	1 (<0.1)	1 (<0.1)	0	0
Liver disorder	1 (<0.1)	1 (<0.1)	0	0
Non-alcoholic steatohepatitis	1 (<0.1)	1 (<0.1)	0	0
Transaminases increased	1 (<0.1)	1 (<0.1)	2 (0.1)	2 (<0.1)
Blood alkaline phosphatase increased	0	0	1 (<0.1)	1 (<0.1)
Drug-induced liver injury	0	0	1 (<0.1)	1 (<0.1)
Hepatic cirrhosis	0	0	1 (<0.1)	1 (<0.1)
Hepatocellular carcinoma	0	0	1 (<0.1)	1 (<0.1)
Portal hypertension	0	0	1 (<0.1)	1 (<0.1)
Varices esophageal	0	0	1 (<0.1)	1 (<0.1)

Source: ISS, Table 7.3.18

Note that preferred terms of AEs observed in the placebo arm could still be attributed to semaglutide in the event they occurred in study 4376, which had a semaglutide run-in period. The reported PTs in Table 125 from the randomized portion of trial 4376 were: hepatic enzyme increased, blood bilirubin increased, and hyperbilirubinemia; none was serious.

In a separate analysis of only the 3 trials contributing to the dose-escalation group (4373, 4374, and 4375), hepatic AEs by MedDRA search were 49/2116 (2.3%) for semaglutide 2.4 mg and

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

38/1261 (3.0%) for placebo. The incidence in trial 4376 during the randomized portion was 11/535 (2.1%) for semaglutide 2.4 mg and 4/268 (1.5%) for placebo.

A review of the hepatic disorders AEs from the semaglutide run-in period from trial 4376 are listed below; all events were non-serious.

Table 126: Hepatic Disorders AEs from Trial 4376 Run-In Period

Subj ID	Preferred term
NN9536-4376/ (b) (6)	Gamma-glutamyltransferase increased
NN9536-4376/ (b) (6)	Blood alkaline phosphatase increased
NN9536-4376/ (b) (6)	Focal nodular hyperplasia
NN9536-4376/ (b) (6)	Hepatic cyst
NN9536-4376/ (b) (6)	Cholestasis ^a

a Note that the verbatim term was: "CHOLETHASIS WITHOUT SIGNS OF ACUTE CHOLECYSTITIS" suggesting that the AE was possibly cholelithiasis, not cholestasis, and perhaps misclassified due to a spelling error

Source: Reviewer created from ISS dataset ADAE.xpt

The hepatic disorders SAEs in the semaglutide-treated subjects are discussed in the narratives below:

- NN9536-4373/ (b) (6) (PT: 'Hypertransaminasemia')

This subject was a 39-year-old female with a medical history of obesity (BMI 33 kg/m²), polycystic ovarian syndrome, irritable bowel syndrome, non-toxic multinodular goiter, cholecystitis/cholecystectomy, and gout. By report she did not regularly drink alcohol; it was unknown if there had been an episode of excessive (binge) drinking in the last 30 days prior to the event. She had been on semaglutide for approximately 4.5 months prior to the event. Six days after the most recent dose, the subject came to the study site for visit 12 and had laboratory data collected. According to the narrative, results included ALT 116 U/L (ref. 5-38) and GGT 180 U/L (ref 5-50). [However, the laboratory data as provided in the dataset demonstrated ALT 231 U/L and GGT 202 U/L. All other liver parameters were within normal limits (WNL).] An SAE of hypertransaminemia was reported (reason for serious classification: "other medically important serious event").

Serological tests were negative for acute viral infection.

Approximately 1 month later, repeat blood tests were performed: ALT 120 U/L and GGT 121 U/L. At an unknown date, blood tests were repeated, and ALT was "halved" (results, units, and reference ranges not reported). Liver ultrasound showed normal size, contour, and echotexture. There was no evidence of any focal lesions or intrahepatic duct dilatation. Cholecystectomy was noted and the common duct was not dilated.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

No action was taken was taken to the trial drug. Two months later, the outcome for the AE was considered "recovered". However, approximately 2 months later, the subject had a new event of hypertransaminasemia, reported as non-serious. Study drug was temporarily discontinued. Transaminase values were not reported. A third non-serious AE of hypertransaminasemia was reported during the off-drug follow-up period.

Of note, ALT and GGT at weeks 52 and 68 were WNL. Finally, it should be noted that there was a non-serious AE reported for this subject of Sjogren's syndrome on study day 454. No further information was provided.

Reviewer comment: Although a contribution of semaglutide to increases in ALT and GGT cannot be completely dismissed, it is notable that the subject improved (for some period of time) while on drug. Furthermore, the case appears confounded by a new diagnosis of Sjogren's syndrome, which can be associated with hepatic abnormalities.⁸²

- NN9536-4374/ (b) (6) (PTs: 'Hepatic encephalopathy,' 'Non-alcoholic steatohepatitis,' and 'Hepatorenal syndrome')

The subject was a 64-year-old female with a history of obesity, T2D, thrombocytopenia, dyslipidemia, hypertension, and NASH with fibrosis/cirrhosis (diagnosed in 2015, followed by hepatology). This case was reported by an investigator as "Hepatic Encephalopathy" and "worsening NASH". Prior to onset of this event, the subject presented with intermittent nausea (reported as non-serious event) as she was progressing through the dose escalations and gastroesophageal reflux disease-like symptoms.

After about 2.5 months in the trial, the subject was seen by her liver specialist and had a fibroscan performed; no particular concerns were noted by the hepatologist.

About 2 weeks later, the subject was re-assessed by investigator. She reported that she had had issues with her memory and confusion.

Several days later, the subject's confusion apparently worsened, and she presented to the emergency department where she was diagnosed with hepatic encephalopathy and admitted to the hospital. Symptoms were nausea, vomiting, and confusion. Computerized tomogram of the head showed no definitive acute intracranial abnormality. The most likely cause of the event was reported as NASH. There were no recent drinking episodes reported. She was discharged from the hospital 2 days later.

⁸² www.uptodate.com Clinical manifestations of Sjogren's syndrome: Extraglandular disease. Accessed 01 Mar 2021.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

The study drug was discontinued (reportedly due to an AE of “vomiting”).

Several days later, the subject was seen by the investigator for follow-up. The subject's condition had improved although her sister reported that she was not fully back to baseline. The subject had difficulty tolerating the lactulose used to treat the encephalopathy. The subject's condition worsened (including seizures) shortly thereafter and she was readmitted requiring intensive care, propofol infusion, and intubation. Blood bilirubin was 37.0 µmol/L (ref. 3.4 - 17.1) and INR was 1.4 (ref. 0.9 - 1.1). EEG showed moderate generalized encephalopathy, consistent with hepatic etiology.

The subject continued to improve and was transferred to the medicine floor. Laboratory data included: ALT 50 U/L (ref. 0-33), alkaline phosphatase 84 U/L (ref. 35-104), AST 92 U/L (ref. 0-32), albumin 34 g/L (ref. 35-52). EEG showed very clear improvement.

During hospitalization, the subject also sustained an acute kidney injury, thought to be due to decreased oral intake and dehydration due to treatment with lactulose prior to her admission. Kidney function improved during the hospitalization.

She also had a worsening of her pre-existing thrombocytopenia. Pancytopenia during admission was also noted, which appears to have resolved, with only the thrombocytopenia remaining.

Five days and again several weeks after discharge the subject visited the site and appeared to be functioning back at her baseline. The AEs were considered resolved.

Approximately 1 year later, the subject was admitted to the hospital with elevated creatinine and ascites and was diagnosed with hepatorenal syndrome. She was hospitalized for approximately 1 month and recovered.

Reviewer comment: The case of hepatic encephalopathy appears to be a worsening of pre-existing NASH cirrhosis. The hepatorenal syndrome event occurred after being off drug for over 1 year.

In addition to the SAEs reported above, 2 subjects treated with semaglutide (1 randomized to semaglutide 2.4 mg and 1 randomized to semaglutide 1 mg) discontinued drug treatment due to liver-related AEs.

- NN9536-4373 (b) (6) (PT: 'Hepatic enzyme increased')

This subject was a 23-year-old female with a BMI of 38.1 kg/m², anxiety, depression, and incontinence, on concomitant citaprolam and ethinylestradiol/levonorgestrel. The subject was

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

dosed for 134 days and trial day of permanent discontinuation was 149. On day 140 of treatment, the subject had ALT > 5x ULN (397 U/L, ref. 0-55; result was ~30x baseline, see Table 127 below) and AST approximately 4x ULN. Total bilirubin and alkaline phosphatase were WNL (total bilirubin: BL 0.27 mg/dL, day 140 0.69 mg/dL, ref. 0-1.2; alkaline phosphatase: BL 88 U/L, day 140 72 U/L, ref. 40-150).

The event was reported as an AE of hepatic enzyme increased and the subject permanently discontinued trial product on day 149 due to the event. After 45 days, the outcome was reported as resolved (normalized after approximately 1.5 months after the week 20 assessment; data not provided).

Of note, the subject had an SAE of 'Gastroenteritis' (symptoms: eructation, vomiting, diarrhea, and epigastric pain) approximately 2 months prior to this event where ALT was increased (204 U/L and 298 U/L; total bilirubin and alkaline phosphatase were WNL and eosinophils were $0.65 \times 10^9/L$ (ref. 0.02-0.5)). In the hospital, she was given IV paracetamol, morphine, and as needed antiemetics. A work-up, including abdominal ultrasound (excluding gallstones), hepatitis screen, and amylase was negative. The cause of the event was thought to be a viral illness.

This led to a temporary interruption of trial product, after which ALT decreased.

A compilation of ALT values in relationship to semaglutide de-challenge and re-challenge is presented below (Table 127):

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 127: Subject NN9536-4373 (b) (6), ALT Values (Including from Local Labs)



(b) (6)

Source: Reviewer created from case narratives (trial 4373 CSR) and ISS dataset ADLB.xpt

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Concomitant medications are presented below:

Table 128: Concomitant Medications, Subject NN9536-4373/ (b) (6)



Source: Case narrative (trial 4373 CSR)

Reviewer comment: The de-challenge and re-challenge data provided in this report are suggestive of a causal relationship of transaminase elevations to semaglutide, however, there may be some confounding by concomitant medications (e.g., flucloxacillin⁸³) or underlying infections.

- NN9536-4374 (b) (6) (PT: 'Liver disorder'); note: this subject was randomized to semaglutide 1 mg

This was a 58-year-old male subject with a BMI of 37.5 kg/m² and a medical history of atrial fibrillation, dyslipidemia, deafness, hypertension, hyperbilirubinemia, hyperuricemia, congestive cardiomyopathy, sleep apnea, and peripheral venous disease, who had an event of liver disorder (verbatim term: "chronic hepatopathy (chronic event)") on day 267 leading to permanent discontinuation on day 296. Concomitant medications included simvastatin, ramipril, furosemide, metformin, empagliflozin, metoprolol, and dabigatran. No further information was provided.

⁸³ LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Penicillins (2nd Generation) [Updated 2020 Oct 20]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548033/>

Laboratory Data

Trial 4153

In the phase 2 trial 4153, 1 subject ((b) (6), semaglutide 0.3 mg fast escalation arm), a 53-year-old female with a BMI of 31.4 kg/m² and a history of hepatic steatosis, chronic cholecystitis, biliary tract disorder, hypercholesterolemia, and hypertension, was observed to have an ALT value >5x ULN. Of note, at baseline, ALT for this subject was 313 U/L. Liver parameters are shown in the table below. She completed the trial on-treatment.

Table 129: Subject (b) (6) (Trial 4153), Liver Parameters

Laboratory assessments: Liver parameters - ALT, ALP, AST, and Bilirubin

Date/trial day	ALT (U/L) ULN 55	ALP (IU/L) ULN 150	AST (U/L) ULN 34	Total Bilirubin (μmol/L) ULN 20.5
(b) (6)-13	285	70	111	25.1
(b) (6)-1	313	76	82	23
(b) (6)-29	318	76	90	10.3
(b) (6)-113	351	57	150	25.8
(b) (6)-99	197	54	93	34.2
(b) (6)-281	151	61	.	15.2
(b) (6)-290	136	65	98	19.8
(b) (6)-367	154	53	160	10.8

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN = upper limit of normal.

Source: Study 4153 CSR, Narrative for Subject ID: (b) (6)

Phase 3 Trials

In the phase 3 program dose-escalation group (trials 4373, 4374, and 4375), baseline values of ALT, AST, total bilirubin, and alkaline phosphatase were similar among groups. At week 68, ALT decreased in both treatment groups, but to a greater extent with semaglutide 2.4 mg compared to placebo (decreases of 26% vs. 13%). AST and alkaline phosphatase decreased with semaglutide 2.4 mg from baseline to week 68 (12% and 10%, respectively) to a greater extent than placebo (4% and 3%, respectively). Mean total bilirubin *increased* by 15% with semaglutide 2.4 mg and by 6% with placebo at week 68.

A similar pattern was observed in trial 4376, which included a semaglutide run-in period: mean ALT decreased during the run-in period and slightly decreased further in the semaglutide 2.4 mg group in the randomized period whereas mean ALT in the placebo group was stable. Mean AST and alkaline phosphatase slightly decreased in the semaglutide 2.4 mg group from week 0 to week 68. Mean total bilirubin *increased* during the run-in period. In the randomized period,

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

mean total bilirubin remained stable in the semaglutide 2.4 mg group and slightly decreased in the placebo group.

Throughout the entire phase 3 program, including the semaglutide run-in period of trial 4376, there was only 1 report of ALT > 5x ULN in a subject randomized to semaglutide 2.4 mg. This event is described in the discontinuation AE narrative above [NN9536-4373/ (b) (6) (PT: 'Hepatic enzyme increased')]. There was also 1 subject randomized to placebo in trial 4373 with an ALT value > 5x ULN.

As noted above, there were no reports of biochemical Hy's law (ALT/AST > 3x ULN concurrent with total bilirubin > 2x ULN) in the weight management program observed in the central laboratory through routine monitoring.

A summary of maximum post-baseline liver parameters on-treatment in trials 4373, 4374, and 4375 is presented in the table below.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 130: Maximum Post-Baseline Liver Parameter Values, On-Treatment, Trials 4373, 4374, and 4375

	Semaglutide 2.4 N=2116	Placebo N=1261
<i>ALT</i>	n=1963	n=1172
>ULN	110 (5.2)	105 (8.3)
>3x ULN	5 (0.2)	7 (0.6)
>5x ULN	1 (<0.1)	1 (<0.1)
>10x ULN	0	0
<i>Alkaline phosphatase</i>	n=1963	n=1173
>ULN	18 (0.9)	16 (1.3)
>1.5x ULN	0	0
<i>AST</i>	n=1963	n=1171
>ULN	159 (7.5)	151 (12.0)
>3x ULN	6 (0.3)	10 (0.8)
>5x ULN	2 (<0.1)	3 (0.2)
>10x ULN	0	0
<i>GGT^a</i>	n=1590	n=985
>ULN	262 (12.4)	219 (17.4)
>5x ULN	7 (0.3)	8 (0.6)
<i>Total bilirubin</i>	n=1963	n=1172
>ULN	190 (9.0)	115 (9.1)
>1.5x ULN	37 (1.7)	23 (1.8)
>2x ULN	8 (0.4)	6 (0.5)
>3x ULN	1 (<0.1)	0
>10x ULN	0	0
a Only measured in 4373 and 4374		

Source: ISS, Table 7.5.3

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 131: Liver Parameter Values, On-Treatment, Trial 4376 at Randomization (Post Semaglutide Run-In Period)

	Semaglutide 2.4 – post-run-in (week 20) N=803
<i>ALT</i>	
>ULN	29 (3.6)
>3x ULN	1 (0.1)
>5x ULN	0
<i>Alkaline phosphatase</i>	
>ULN	3 (0.4)
>1.5x ULN	2 (0.2)
>2x ULN	0
<i>AST</i>	
>ULN	34 (4.2)
>3x ULN	1 (0.1)
>5x ULN	0
<i>Total bilirubin</i>	
>ULN	42 (5.2)
>1.5x ULN	8 (1.0)
>3x ULN	1 (0.1)
>10x ULN	0

Source: Study 4376 CSR, Table 14.3.5.3

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 132: Liver Parameter Values, On-Treatment, Trial 4376 at Week 68

	Semaglutide 2.4 N=535	Placebo N=268
<i>ALT</i>	n=488	n=232
>ULN	15 (3.1)	7 (3.0)
>3x ULN	1 (0.2)	0
>5x ULN	0	0
<i>Alkaline phosphatase</i>	n=494	n=233
>ULN	2 (0.4)	1 (0.4)
>1.5x ULN	0	0
<i>AST</i>	n=491	n=231
>ULN	15 (3.1)	8 (3.5)
>3x ULN	0	0
<i>Total bilirubin</i>	n=488	n=232
>ULN	39 (8.0)	7 (3.0)
>1.5x ULN	10 (2.0)	1 (0.4)
>3x ULN	0	0

Source: Study 4376 CSR, Table 14.3.5.3

A summary of clinical information regarding subjects with ALT or AST > 5x ULN during the trials is presented in the table below.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 133: Details of ALT/AST Outliers, Phase 3 Trials

Trial Subject ID Age / Sex / BMI	Week / Trial day	Value (U/L)	Normal range (U/L)	PT / Seriousness / Severity / Causality / Action / Outcome	Relevant details
<i>Semaglutide</i>					
4373 (b) (6) 23 / F / 38.1	20 / 140	ALT 397	0-55	Hepatic enzyme increased / Non-serious / Severe / Probable / Permanent discontinuation / Recovered	Additional ALT assessment after 1.5 months showed normalized levels (local laboratory)
4373 (b) (6) 50 / F / 32.9	20 / 153	AST 183	5-34	Aspartate aminotransferase increased / Non-serious / Moderate / Possible / No changes / Recovered	AST normalized after 15 days. AE of gastroenteritis on day 148. Hepatic steatosis is concomitant illness.
4375 (b) (6) 46 / F / 30.8	52 / NR	AST 176	5-34	Not reported as an AE	The event was asymptomatic. AST levels normalized without treatment after approximately 4 weeks: 34 U/L
4376 (b) (6) 52 / M / 33.1	52 / NR	AST 290	5-34	Aspartate aminotransferase increased / Non-serious / Mild / Possible / No changes / Recovered	Concurrently reported with CK 12216 U/L (ref. 30-200). 3 days later: CK 1218, AST 100. Subject asymptomatic.
<i>Placebo</i>					
4373 (b) (6) 53 / F / 41.3	20 / 145	ALT 314 AST 316	0-55 5-34	Not reported as AEs	Cholelithiasis prior to the event. NAFLD as concomitant illness. Both ALT and AST normalized after 15 days.
4373 (b) (6) 42 / F / 43.1	52 / 376	AST 200	5-34	Aspartate aminotransferase increased / Non-serious / Moderate / Unlikely / No changes / Recovered	Additional AST assessment after 2 weeks: 37 U/L
4373 (b) (6) / 45 / F / 35.6	68 / 492	AST 230	5-34	Aspartate aminotransferase increased / Non-serious / Mild / Unlikely / Not applicable / Not recovered	Additional AST assessment on day 512: 90 U/L and day 538: 93 U/L; reported to be possibly alcohol-induced
4374 (b) (6) 28 / F / 41.7	68 / 478	AST 257	5-34	Not reported as an AE	Elevated AST at screening: 69 U/L. Non-alcoholic fatty liver disease is concomitant illness.
a Narrative provided above b Narrative in Section 8.4.6					

Source: Study 4373 CSR, Table 12-29; Study 4374 CSR, Table 12-28; Study 4375 CSR, Table 12-24; Study 4376 CSR, Table 12-34

Upon FDA request, the applicant also searched their narrative database for *local* laboratory results of cases of elevations of ALT/AST > 3x ULN concurrent with total bilirubin > 2x ULN

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

and/or cases of elevation of ALT or AST > 5x ULN (i.e., laboratory data that would not be identified via the study database, which utilizes results from a central laboratory).

Based on this search, the applicant identified 15 subjects (11 with semaglutide 2.4 mg, 1 with semaglutide 1 mg, and 3 with placebo) not previously captured in the above tables. The applicant notes that all 15 cases had alternative etiologies in which liver enzyme abnormalities can be expected as part of the clinical course. The majority of cases were attributed to gallbladder disease (7 semaglutide 2.4 mg, 2 placebo).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 134: Subjects with Abnormal Liver Enzymes Based on Local Laboratory Data

Trial ID/ Subject ID (Case ID)	Treatment group ^a	Preferred Term	On treatment ^a	Onset day ^{a,b}	Brief alternative aetiology/Comments
AST/ALT >3x ULN concurrent with TBL >2x ULN					
NN9536-4373/ (b) (6)	Sema 2.4 mg	Hepatitis E	Yes	311	Abnormal laboratory values occurred concurrently with event of hepatitis E
NN9536-4373/ (b) (6)	Sema 2.4 mg	Cytomegalovirus infection	Yes	312	Abnormal laboratory values occurred concurrently with event of cytomegalovirus infection
NN9536-4373/ (b) (6)	Sema 2.4 mg	Cholecystitis/ Cholelithiasis	Yes	295/295	Abnormal laboratory values occurred concurrently with events of cholecystitis and cholelithiasis
NN9536-4375/ (b) (6)	Sema 2.4 mg	Cholecystitis	Yes	199	Abnormal laboratory values occurred concurrently with event of cholecystitis
NN9536-4376/ (b) (6)	Sema 2.4 mg	Cholecystitis	Yes	429	Abnormal laboratory values occurred concurrently with event of cholecystitis
NN9536-4374/ (b) (6)	Placebo	Cholecystitis acute/Obstructive pancreatitis	Yes	253/254	Abnormal laboratory values occurred concurrently with events of cholecystitis and obstructive pancreatitis
ALT/AST >5x ULN					
NN9536-4373/ (b) (6)	Sema 2.4 mg	Cholecystitis	Yes	468	Abnormal laboratory values occurred concurrently with event of cholecystitis
NN9536-4373/ (b) (6)	Sema 2.4 mg	Cholecystitis acute	Yes	130	Abnormal laboratory values occurred concurrently with event of cholecystitis
NN9536-4373/ (b) (6)	Sema 2.4 mg	Cholecystitis acute/ Pancreatitis acute/ Cholelithiasis	Yes	508/508/ 508	Abnormal laboratory values occurred concurrently with event of cholecystitis, pancreatitis and cholelithiasis
NN9536-4373/ (b) (6)	Sema 2.4 mg	Tonsillitis	Yes	176	Abnormal laboratory values occurred concurrently with event of tonsillitis
NN9536-4374/ (b) (6)	Sema 2.4 mg	Gastroenteritis	Yes	104	AST reported as 90 IU/L and occurred concurrently with invasive gastroenteritis, negative re-challenge
NN9536-4374/ (b) (6)	Sema 1.0 mg	Cardio-respiratory arrest	No	393	Abnormal laboratory values occurred concurrently with event of multi-organ dysfunction
NN9536-4376/ (b) (6) c	Sema 2.4 mg	Cholelithiasis	Yes	364	Abnormal laboratory values occurred concurrently with event of cholelithiasis
NN9536-4373/ (b) (6)	Placebo	Pneumonia/ Septic shock/Urinary tract infection	Yes	348	Abnormal laboratory values occurred concurrently with events of pneumonia, septic shock and urinary tract infection

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Trial ID/ Subject ID (Case ID)	Treatment group ^a	Preferred Term	On treatment ^a	Onset day ^{a,b}	Brief alternative aetiology/Comments
NN9536-4376/ (b) (6) c	Placebo	Cholelithiasis/ abdominal pain	Yes	179/209	Abnormal laboratory values occurred concurrently with event of cholelithiasis

^a Treatment group, On treatment and Onset day are from Listings 16.2.7.1 in the clinical study reports.

^b Onset day from randomisation to onset for the Preferred Term for the event.

^c Subject received treatment with semaglutide 2.4 mg during the 20-week uncontrolled run-in period of STEP 4.

Source: Response to IR, 15 Mar 2021, Table 2-1

Blinded/Ongoing Trial Data

Blinded data from ongoing clinical trials, including the CVOT SELECT, were presented in the NDA Summary of Clinical Safety. These data are limited.

- No fatal cases in the 'Hepatobiliary' SOC were reported.
- Two fatal cases of PT 'Hepatocellular carcinoma' were reported:
 - 79-year-old male
 - 54-year-old male (also with acute kidney injury)
- The majority of SAEs in the 'Hepatobiliary' SOC were related to gallbladder disorders (e.g., cholelithiasis and cholecystitis). SAEs (by PT) specifically related to the liver included:
 - 51-year-old male with SAEs of 'Liver injury', 'Aspartate aminotransferase increased', 'Blood bilirubin increased'; all recovered
 - 59-year-old male with SAE of 'Alcoholic liver disease'; recovered
 - 61-year-old male with SAEs of 'Jaundice cholestatic'; recovered and 'Hepatocellular carcinoma'; not recovered
 - 62-year-old female with SAE of 'Hepatic cirrhosis'; recovered with sequelae

Separately, in a response to the 74-day letter (see more details in Section 8.9.1), the applicant tabulated cases of Hy's Law from ongoing blinded trials, including ongoing trials from the semaglutide for weight management program. None of the alternative etiologies provided suggest DILI.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 135: Cases Meeting the Biochemical Definition of Hy’s Law, Ongoing (Blinded) Weight Management Trials

Trial	Subj ID	Onset day	Brief alternative etiology
NN9536-4382 (Phase 3 trial in East Asian subjects)	(b) (6)	138	Gallstone disease
		129	Cholelithiasis
144		Gallbladder sludge and statin treatment	
EX9536-4388 (SELECT CVOT)		153	Large alcohol consumption prior to the event
		161	Acute viral hepatitis (A)
		112	Pancreatic cancer
		1	Hepatocellular carcinoma
FDA is aware of the treatment allocation for some of these subjects due to IND safety reports and an information request (IND 126360): a semaglutide, b placebo			

Source: Response to 74-day letter, Table 3-7

One case of DILI that led to acute hepatic failure was reported in the ongoing SELECT CVOT was not captured in the above listing due to the data cut-off; FDA requested additional information from the applicant in an information request:

- Subject EX9536-4388 (b) (6) (semaglutide 2.4 mg) is a 45-year-old female with history of migraine, ischemic stroke, and stroke of undetermined etiology on atorvastatin and acetylsalicylic acid. She had normal liver enzymes at baseline and approximately 1 week before the SAE of DILI. Alcohol intake was described as “would occasionally drink 1 glass of wine with meals.” She was in the trial for approximately 2 months at the time of the event. One week prior to the event, the subject was admitted to the hospital for a lumbar puncture to work up old brain MRI findings. The lumbar puncture was normal. Post-procedure, the subject developed a headache for which she took paracetamol 4g daily. Four days later, she developed unspecified malaise, nausea, and headache. She was seen in the ER and discharged with “symptomatic medication.” She returned after fainting from an orthostatic headache and was hospitalized. Labs are listed below (Table 136). Test for viral hepatitis and HIV were negative. CT showed no dilation of the bile ducts, slight hepatic heterogeneity with stratification of the vesicular wall without vesicular distension. The next couple of days, lab values worsened (Table 136), and she was transferred to another hospital with jaundice, encephalopathy, and thrombocytopenia. She was supposed to receive a hepatic transplant, but her values improved after N-acetylcysteine (NAC) treatment, and the transplant was no longer considered necessary. Drug was discontinued temporarily; on day 78, semaglutide was restarted. The outcome of the event is considered resolved.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 136: Liver Labs for Subject (b) (4) in SELECT Trial



Source: Response to FDA Information Request dated 13 April 2021

As part of the evaluation of this case, the applicant was asked to comment on the potential of semaglutide to impact the pharmacokinetics of acetaminophen over repeat dosing of acetaminophen and they concluded that the likely impact is low: (1) Gastric emptying delay likely to lead to slightly reduced acetaminophen concentrations and (2) based on the earlier in vitro DDI studies performed with semaglutide, and due to the size and permeability characteristics of semaglutide, the applicant considers it highly unlikely that the semaglutide molecule could reach the hepatic sub-cellular compartments in order to either inhibit acetaminophen conjugation or to directly interact with and induce CYP2E1, the primary oxidative enzyme that causes acetaminophen toxic DDIs. Furthermore, they provided some data from a mouse NASH model that they interpret to suggest that semaglutide treatment does not affect the levels of glutathione in the liver; however, the dose administered was 0.2-fold the maximum clinical dose of 2.4 mg based on BSA, making it difficult to draw any conclusion about the role semaglutide may play in influencing glutathione levels.⁸⁴

Reviewer comment: The details in this case do not suggest that semaglutide is the likely cause of DILI: the timeline is consistent with acetaminophen toxicity, clinical data improved with NAC, there was complete resolution, and semaglutide rechallenge was negative. In addition, based on the information provided, data do not suggest that semaglutide would lead to acetaminophen toxicity via a DDI.

⁸⁴ Personal communication, Braithwaite E., FDA toxicologist

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In summary, although there is at least 1 case that suggests that semaglutide might be associated with transaminase elevations; overall, the weight management phase 3 clinical trial data do not suggest to-date that semaglutide is causal for DILI. DILI can be a rare and idiosyncratic event, however, and the review of post-marketing and trial data being undertaken by OSE as part of a NISS will help clarify the potential for a causal relationship for DILI with semaglutide and other GLP-1 RAs.

8.5.6. Acute Renal Failure

GLP-1 RAs, including semaglutide, are labeled with a warning for acute kidney injury and worsening of chronic renal failure, as a result of dehydration/hypovolemia due to drug-related GI adverse effects (e.g., nausea, vomiting, diarrhea).

In the semaglutide weight management program there were small imbalances in renal adverse events, specifically acute kidney injury, associated with semaglutide. No events were associated with permanent treatment discontinuation.

Trial 4153

In the phase 2 trial 4153, renal insufficiency or failure was not an exclusion criterion. One subject had a history of nephrotic syndrome (semaglutide 0.05 mg) and 1 subject had a history of acute kidney injury (semaglutide 0.3 mg) at screening.

Two events of renal disorder AEs were reported in 2 subjects; 1 subject from the semaglutide 0.3 mg arm and 1 subject from the semaglutide 0.4 mg arm. Both events were reported within the first 16 weeks of the trial.

- Subject (b) (6) (semaglutide 0.4 mg): this was an SAE reported in a 39-year-old male subject with a history of sleep apnea and peripheral edema; PT: 'Acute kidney injury,' and additional SAEs of 'Dehydration,' 'Vomiting,' and 'Diarrhea'). The event happened when the subject was titrating to semaglutide 0.2 mg.

On day 63, the subject experienced dehydration due to nausea, vomiting, and diarrhea and treatment was permanently discontinued. At day 65, the subject was hospitalized with acute renal failure secondary to severe dehydration due to the GI events. (At screening, creatinine was 0.87 mg/dL, at time of event, creatinine was 2.15 mg/dL, at the end-of-treatment visit 3 weeks later, creatinine was 0.76 mg/dL.) The subject fully recovered within 2 days after treatment with intravenous hydration.

- Subject (b) (6) (semaglutide 0.3 mg): this event was non-serious and mild (PT: 'Acute kidney injury'). The subject fully recovered and completed the trial.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In addition, 1 subject experienced 2 occasions of creatinine > 3x baseline:

- Subject (b) (6) (semaglutide 0.4 mg): the subject was a 61-year-old female with a BMI of 51.6 kg/m² and a medical history of dyslipidemia, hypertension, and asthma who had a progressive increase in serum creatinine during the trial (Figure 82). Creatinine was > 3x baseline at week 40 and at week 52. A non-serious, severe, AE of 'Blood creatinine increased' was reported at week 52. By report, the subject did not recover. There were no associated GI AEs reported around this time, although notably, she presented with a complete acute thrombosis of the left brachial artery about 2 weeks after completing the trial (she was reportedly found to be antithrombin III deficient). Management with thrombolytics and anticoagulants did not resolve the condition and she required left below-the-elbow amputation.

Figure 82: Serum Creatinine by Treatment Week, Subject NN9536-4153 (b) (6)



Source: Study 4153 CSR, Figure 14.3.5.118

Reviewer comment: Although the creatinine increase was temporally related to semaglutide, this subject had other confounding conditions, such as the event of arterial thrombosis that was refractory to medical management. This subject's clinical course seems unlikely related to semaglutide and more likely related to antithrombin III deficiency and other co-morbid conditions.

Phase 3 Trials

In the phase 3 trials, the following estimated glomerular filtration rate (eGFR) criteria were used for inclusion in the trials:

- Trial 4373, 4375, and 4376 (without T2D): eGFR $\geq$ 15 mL/min/1.73 m²
- Trial 4374 (with T2D): eGFR $\geq$ 30 mL/min/1.73 m²; eGFR $\geq$ 60 mL/min/1.73 m² for those also treated with an SGLT2i

At baseline, 66% of subjects had normal renal function, 31% had mild, 2.5% had moderate, and <0.1% had severe renal insufficiency. No subject had end-stage renal disease in-line with the eligibility criteria.

The risk of acute renal failure in the phase 3 program was evaluated based on a predefined MedDRA search for acute renal failure⁸⁵ in the on-treatment period. There was a similar rate of events among treatment groups in the phase 3 pool (0.3 events per 100 PYE in both groups).

Table 137: Acute Renal Failure, MedDRA Predefined Search, Phase 3 Pool and By Trial, On-Treatment

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Phase 3 pool	N=2650		N=1529
Acute renal failure AEs	8 (0.4)		5 (0.3)
<i>PTs:</i>			
<i>Acute kidney injury</i>	6 (0.3)		4 (0.2)
<i>Renal impairment</i>	3 (0.1)		1 (<0.1)
Trial 4373	N=1306		N=655
Acute renal failure AEs	3 (0.2)		2 (0.3)
Trial 4374	N=403	N=402	N=402
Acute renal failure AEs	4 (1.0)	2 (0.5)	2 (0.5)
SAEs	2 (0.5)	2 (0.5)	1 (0.2)
Trial 4375	N=407		N=204
Acute renal failure AEs	0		0
Trial 4376	N=535		N=268
Acute renal failure AEs	1 (0.2)		1 (0.4)

Source: ISS, Table 7.3.16; Study 4373 CSR, Table 14.3.1.45; Study 4374 CSR, Table 14.3.1.45; Study 4375 CSR, Table 14.3.1.45; Study 4376 CSR, Table 14.3.1.59

⁸⁵ SMQ Acute renal failure, narrow terms only

None of the events led to permanent treatment discontinuation. Six of the events were reported as SAEs (3 in 2 subjects on semaglutide 2.4 mg, 2 in 2 subjects on semaglutide 1 mg, and 1 event in 1 subject on placebo); all from the trial in subjects with T2D (4374; Table 137). Brief narratives for the 2 semaglutide 2.4 mg subjects are as follows:

- Subject (b) (6) was a 58-year-old female with a BMI of 41.2 kg/m² and a medical history of T2D, diabetic neuropathy, hypertension, and hypercholesterolemia, who presented to the emergency room on study day 62 with nausea, vomiting, epigastric pain, and a serum creatinine of 2.6 mg/dL. The subject was diagnosed with chronic cholecystitis, gallstones, and acute renal failure. She underwent cholecystectomy during the hospitalization. Acute renal failure improved with hydration. Semaglutide was temporarily discontinued and reintroduced at a dose of 0.25 mg 2 weeks later.

Four months later, the subject was hospitalized with gastroenteritis (nausea, vomiting, syncope, diarrhea, decreased appetite, and fever) and acute renal insufficiency (creatinine 3.1 mg/dL). A CT of the abdomen and pelvis confirmed the diagnosis of gastroenteritis. Both SAEs of gastroenteritis and acute renal insufficiency were reported resolved approximately 1 week later. Semaglutide dosing was not changed.

- Subject (b) (6) was a 67-year-old male with BMI 37 kg/m² and a history of T2D, hyperlipidemia, obstructive sleep apnea, nephrolithiasis, hypertension, diabetic neuropathy, and diabetic nephropathy. Approximately 2 months after randomization, the subject presented with multiple complaints, including body aches. The symptoms worsened over the next 2 weeks and he was admitted to the hospital with acute kidney injury secondary to dehydration (creatinine 1.65 mg/dL), increased lipase, and acute cystitis. Of note, the subject had been receiving treatment with the following nephrotoxic agents within the past 3 months: aspirin, ibuprofen, naproxen, iohexol, lisinopril, and metformin. Lisinopril was switched to amlodipine, metformin was held, the subject received intravenous fluids and antibiotics, and his renal function improved. Final diagnoses were “myalgias etiology unclear” and “possible viral syndrome.”

In addition to the AEs above, in the run-in period in trial 4376, the MedDRA search for acute renal failure identified 2 AEs of acute kidney injury – associated with 1 SAE of dehydration – in 1 subject:

- Subject (b) (6) was a 74-year-old female with a BMI of 40 kg/m² and a medical history of asthma, hypertension (treated with triamterene), and nocturia who was treated for approximately 2 months with semaglutide when 2 non-serious acute renal failure AEs were reported secondary to an SAE of dehydration. [Verbatim terms: “acute renal failure (secondary to dehydration)” and “hypotension (secondary to acute renal failure)”]. The

subject was hospitalized due to the dehydration and had non-serious AEs of gastroenteritis, nausea, and vomiting prior and simultaneously to dehydration. The subject recovered after intravenous rehydration and remained in the trial (she was ultimately randomized to placebo).

Of the non-serious AEs of acute renal failure, 1 subject (b) (6) in trial 4373) reported an event of dehydration; this was in relation to an SAE of large intestine perforation.

With regards to renal laboratory parameters, in the phase 3 dose-escalation group, mean eGFR and serum creatinine were essentially unchanged in both groups during the trials. In addition, the proportion of subjects with serum creatinine > 1.5x ULN was low and similar among groups. No subjects in the dose-escalation group were observed to have serum creatinine > 3x ULN post-baseline. The categorical summaries for eGFR for the phase 3 dose-escalation group and trial 4376 are shown below.

Table 138: Categorical Summary of eGFR, Phase 3 Trials, On-Treatment

	Week -1		Week 20		Week 68	
	Sema 2.4	Placebo	Sema 2.4	Placebo	Sema 2.4	Placebo
Phase 3 Dose-Escalation Group*						
n	2116	1261	1922	1142	1735	996
Normal	67.9%	66.4%	57.2%	57.1%	55.8%	50.7%
Mild	29.9%	30.6%	31.1%	30.5%	24.4%	26.3%
Moderate	2.1%	3.0%	2.5%	2.9%	1.7%	2.0%
Severe	<0.1%	0	<0.1%	0	<0.1%	0
Missing			9.2%	9.5%	18.1%	21.0%
Trial 4376**						
n	803		535*	268*	494	233
Normal	71.7%		58.9%	64.2%	66.6%	72.5%
Mild	26.5%		37.6%	34.7%	31.4%	27.5%
Moderate	1.7%		3.4%	1.1%	1.8%	0
Severe	0		0.2%	0	0.2%	0
eGFR (mL/min/1.73 m ²): Normal ≥ 90, Mild 60-<90, Moderate 30-<60, Severe 15-<30						
*In the dose-escalation group, proportions were calculated based on the original n						
**In trial 4376, the week 20 values reflect 20 weeks of semaglutide 2.4 mg in both groups; proportions reflect available values at each visit						
Sema=semaglutide						

Source: ISS, Table 7.5.2; Study 4376 CSR, Table 14.3.5.41; reviewer added in % missing to the dose-escalation group (note there might be small rounding errors)

Across the phase 3 program, AEs related to abnormal renal parameters was seen more frequently in the semaglutide group (Table 139).

Table 139: Renal Investigations AEs, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650 n (adj. %)	Placebo N=1529 n (adj. %)
Renal and urinary tract investigations and urinalyses	20 (0.8)	4 (0.3)
Glomerular filtration rate decreased	11 (0.4)	3 (0.2)
Urine albumin/creatinine ratio decreased	2 (0.1)	0
Blood creatinine increased	2 (0.1)	0
Urine output decreased	2 (<0.1)	0
Urine albumin/creatinine ratio abnormal	1 (<0.1)	0
Glomerular filtration rate abnormal	1 (<0.1)	0
White blood cells urine	1 (<0.1)	0
Blood urine present	0	1 (<0.1)

Source: ISS, Table 7.2.2

An exploratory analysis to evaluate outliers in serum creatinine in the entire phase 3 program was undertaken by this reviewer. Four subjects, all randomized to semaglutide 2.4 mg, were observed to have serum creatinine > 2 mg/dL during the trial (1 subject had a baseline creatinine of 2.3 mg/dL).

Table 140: Serum Creatinine Outliers (>2 mg/dL), Phase 3 Program

Visit	Day	Serum creatinine (mg/dL)	Comment
NN9536-4375/	(b) (6)		
week -1	-9	2.3	
week 20	142	2.8	
week 52	365	2.4	
week 68	481	2.3	
week 68	526	2.2	
NN9536-4374/	(b) (6)		
week -1	-13	1.4	
week 8	84	1.8	AE of renal failure and d/c due to acute pancreatitis
unscheduled	91	2.1	
week 12	113	1.4	Off-treatment
week 20	140	1.5	Off-treatment
week 20	196	1.5	Off-treatment
week 52	366	1.7	Off-treatment
week 68	478	1.5	Off-treatment
NN9536-4376/	(b) (6)		
week -1	-8	1.3	
week 20	141	1.7	
week 52	365	2.0	AE of renal failure, no change to drug
week 52	372	2.9	
week 68	475	1.7	
NN9536-4374/	(b) (6)		
week -1	-14	1.8	

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

week 20	141	1.8	
week 20	147	1.8	
week 52	365	1.6	
week 68	481	2.0	

Source: Reviewer created from ISS datasets ADLB.xpt and ADAE.xpt

In a separate analysis of the T2D trial 4374, mean eGFR was essentially unchanged in the semaglutide groups versus placebo and urine albumin-to-creatinine ratio was not worsened. (The proportions of subjects on semaglutide 1 mg and 2.4 mg with micro- and macroalbuminuria decreased, whereas the proportions increased in the placebo group. Albuminuria was an exploratory efficacy endpoint in trial 4374; see Table 24 in Section 6.2.2.)

Finally, an exploratory search of the PT 'Dehydration' was undertaken. The cases shown in Table 141 are SAEs; most are from trial 4374 (the T2D trial). There were 2 semaglutide 2.4 mg events, 2 semaglutide 1 mg events, and 1 placebo event.

Table 141: 'Dehydration' SAEs

Study	Subj ID	Treat	Verbatim Term	Severity	Outcome	AE day	AE duration	Related	Action
4374	(b) (6) 48/B/M	Sema 1 mg	DEHYDRATION	Moderate	Recovered	89	3	Unlikely	Dose not changed
	(b) (6) 70/W/M	Sema 1 mg	DEHYDRATION	Severe	Recovered	3	4	Unlikely	Dose not changed
	(b) (6) 54/B/F	Placebo	DEHYDRATION, SEVERE	Moderate	Recovered	297	21	Unlikely	Dose not changed
	(b) (6) 67/W/M	Sema 2.4 mg	DEHYDRATION	Mild	Recovered	62	38	Possible	Temporary interruption of trial product
4376	(b) (6) 74/W/F	Sema 2.4 mg (run-in)	HOSPITALIZATION FOR DEHYDRATION	Severe	Recovered	68	4	Possible	Dose not changed

Sema=semaglutide

Source: Reviewer created from ISS dataset ADAE.xpt

To assess whether subjects with renal impairment at baseline might be more vulnerable to renal and related AEs, an assessment of selected AEs by renal function was conducted (Table 142).

Table 142: AEs by Baseline Renal Function, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg	Placebo
Normal (eGFR $\geq$ 90)	N=1752	N=1009
Mild renal impairment (RI) (eGFR 60-<90)	N=833	N=479
Moderate RI (30-<60)	N=63	N=41
Severe RI (15-<30)	N=2	N=0
<i>All AEs</i>		
Normal	1539 (87.6)	832 (83.0)
Mild RI	753 (90.6)	405 (84.8)
Moderate RI	54 (87.6)	35 (88.2)
Severe RI	2 (100)	0
<i>Renal and urinary disorders SOC</i>		
Normal	63 (3.6)	34 (3.3)
Mild RI	33 (4.6)	29 (5.6)
Moderate RI	9 (15.2)	3 (6.8)
Severe RI	1 (50.0)	0
<i>Electrolyte and fluid balance conditions HLG</i>		
Normal	17 (1.0)	10 (1.0)
Mild RI	13 (1.7)	8 (1.7)
Moderate RI	3 (6.6)	2 (6.7)
Severe RI	0	0

Source: ISS, Table 7.7.33

Reviewer comment: Subjects with moderate renal impairment (RI) had more kidney-related and electrolyte/fluid AEs than those with higher renal function (in both groups). In addition, in the moderate RI group, kidney-related AEs were more frequently reported in semaglutide-treated subjects than in placebo-treated subjects. This pattern was not observed for electrolyte and fluid AEs (which includes AEs such as dehydration). There were too few subjects with severe RI impairment to assess AEs.

In summary, semaglutide can lead to significant volume depletion in some individuals, potentially due to GI losses as well as some contribution of decreased intake, leading to acute renal failure. These events were infrequently observed in the clinical trials. Subjects with moderate renal impairment were more likely to have renal AEs on semaglutide versus placebo than subjects with normal renal function or mild renal impairment.

8.5.7. Hypoglycemia

Semaglutide lowers fasting and postprandial glycemia by stimulating insulin secretion in a glucose-dependent manner. In addition, weight loss can improve insulin sensitivity. The risk of

hypoglycemia with semaglutide in subjects not on concomitant antihyperglycemic medications (particularly insulin and sulfonylureas) is thought to be low.

In the Ozempic label, severe hypoglycemia⁸⁶ or blood glucose $\leq$ 56 mg/dL was not reported in subjects treated with semaglutide 0.5 mg or 1 mg as monotherapy in a 30-week trial. When administered as add-on to basal insulin with or without metformin, 10.7% of semaglutide 1 mg, 8.3% of semaglutide 0.5 mg, and 5.3% of placebo-treated subjects reported severe hypoglycemia or blood glucose $\leq$ 56 mg/dL.

Hypoglycemia in T2D

In the T2D study 4374, subjects were to be treated for their diabetes with either diet and exercise alone, or stable treatment with metformin, SU, SGLT2i, and/or glitazone (up to 3 oral antihyperglycemics were permitted). Subjects treated with SU were to reduce the SU dose by approximately 50% at the discretion of the investigator. At baseline, 22.7% of subjects were using SU across the 3 treatment groups.

Hypoglycemic episodes were reported in this trial using a specific hypoglycemic episode form. All cases of either plasma glucose $\leq$ 70 mg/dL or plasma glucose $>$ 70 mg/dL with concurrent hypoglycemic symptoms were to be reported as hypoglycemic episodes.

The evaluation of hypoglycemic episodes was based on the on-treatment period. Hypoglycemic episodes are summarized using the ADA 2018/IHSG 2017^{87,88} (Table 143) and the ADA 2013⁸⁹ (Figure 83) classifications.

Table 143: ADA 2018 and IHSG 2017 Classification of Hypoglycemia

Level	Glycemic Criteria	Description
Level 1: Hypoglycemia alert value	$\leq$ 70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Level 2: Clinically significant hypoglycemia	$<$ 54 mg/dL	Sufficiently low to indicate serious, clinically significant hypoglycemia
Level 3: Severe hypoglycemia	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

⁸⁶ "Severe hypoglycemia" is defined as hypoglycemia requiring the assistance of another person.

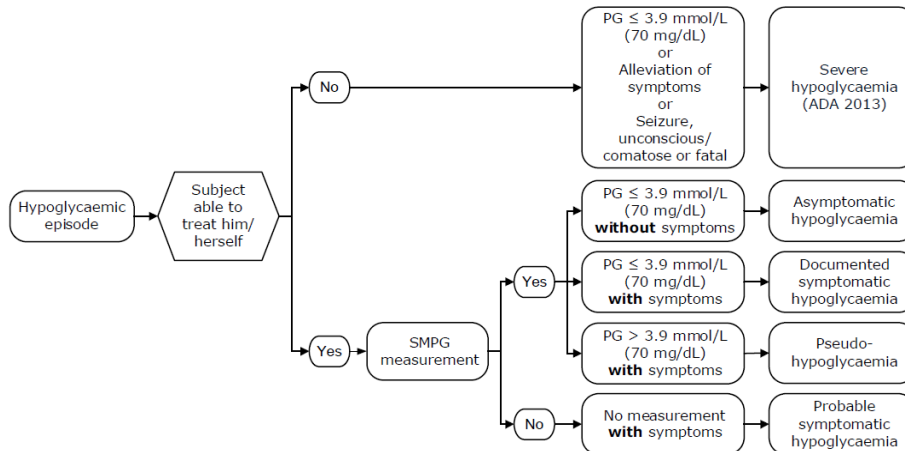
⁸⁷ American Diabetes A. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64.

⁸⁸ International Hypoglycaemia Study G. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7.

⁸⁹ Seaquist ER, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95.

Source: Study 4374 CSR, Table 9-6

Figure 83: ADA 2013 Classification of Hypoglycemia



Note: Glucose measurements are performed with capillary blood calibrated to plasma equivalent glucose values
 PG: plasma glucose SMPG: Self-measured plasma glucose

Source: Study 4374 Protocol, Appendix 8, Figure 11-2

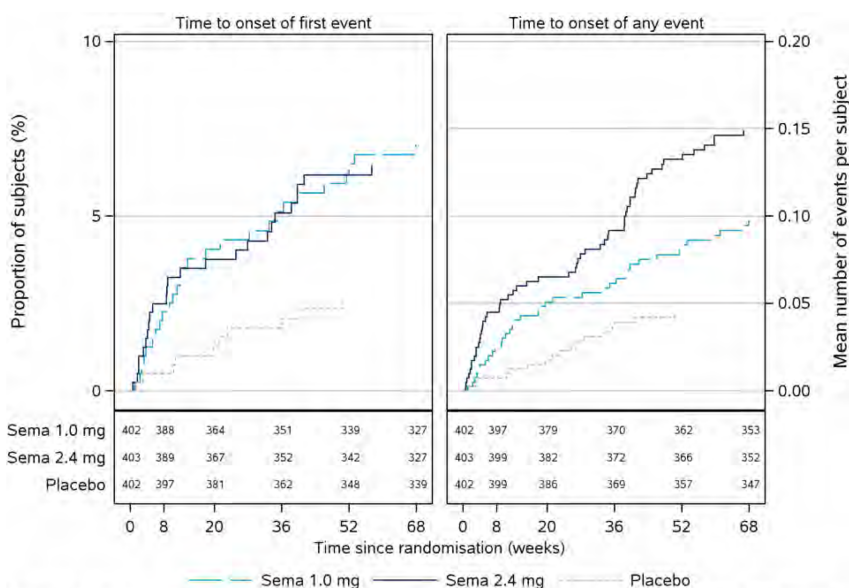
In trial 4374, subjects treated with semaglutide reported more hypoglycemia episodes than placebo, generally in a dose-dependent fashion. Table 144 summarizes the events by classification and level. Although similar proportions of subjects in the semaglutide 2.4 mg and 1 mg arms reported Level 2 or Level 3 (i.e., “clinically significant”) hypoglycemia, the table shows that there were more events in the semaglutide 2.4 mg arm than the semaglutide 1 mg arm. As noted by the applicant, increasing the dose of semaglutide did not lead to more subjects experiencing a clinically significant hypoglycemic episode, but for subjects who had already experienced an episode, more episodes were seen with the semaglutide 2.4 mg than with the semaglutide 1 mg dose. This is also demonstrated in Figure 84; time to first event is similar among dose levels and increases over time during the trial (left panel). Time to any event continues to increase in the semaglutide 2.4 mg arm, particularly after 36 weeks. This could be at a time in the trial when the weight loss in the 2.4 mg arm could be contributing to events of hypoglycemia. In addition, documented symptomatic events of hypoglycemia (ADA 2013) was observed more frequently with semaglutide in a dose dependent manner (Table 144).

Table 144: Hypoglycemic Episodes by Classification, Trial 4374, On-Treatment

	Semaglutide 2.4 mg		Semaglutide 1 mg		Placebo	
	N=403	PYE=533.0	N=402	PYE=529.8	N=402	PYE=528.3
ADA 2018						
Level 3 – Severe	1 (0.2)	1 (0.2)	0	0	0	0
Level 2 – Clinically significant	25 (6.2)	57 (10.7)	27 (6.7)	38 (7.2)	10 (2.5)	17 (3.2)
Level 1 – Alert value	82 (20.3)	258 (48.4)	63 (15.7)	205 (38.7)	31 (7.7)	70 (13.2)
Not hypoglycemia	35 (8.7)	64 (12.0)	35 (8.7)	49 (9.2)	24 (6.0)	31 (5.9)
Level 2 or 3 hypoglycemia	26 (6.5)	58 (10.9)	27 (6.7)	38 (7.2)	10 (2.5)	17 (3.2)
ADA 2013						
Severe	1 (0.2)	1 (0.2)	0	0	0	0
Documented symptomatic	61 (15.1)	178 (33.4)	51 (12.7)	99 (18.7)	29 (7.2)	70 (13.2)
Asymptomatic	58 (14.4)	168 (31.5)	44 (10.9)	173 (32.7)	14 (3.5)	21 (4.0)
Pseudohypoglycemia	8 (2.0)	15 (2.8)	11 (2.7)	12 (2.3)	12 (3.0)	15 (2.8)
Probable symptomatic	11 (2.7)	16 (3.0)	7 (1.7)	8 (1.5)	9 (2.2)	11 (2.1)
Unclassifiable	2 (0.5)	2 (0.4)	0	0	1 (0.2)	1 (0.2)
Severe or BG confirmed symptomatic hypoglycemia	23 (5.7)	51 (9.6)	22 (5.5)	29 (5.5)	12 (3.0)	18 (3.4)

Source: Study 4374 CSR, Table 14.3.1.64

Figure 84: Hypoglycemic Episodes (ADA 2018, Level 2 or 3), Plot Over Time, Trial 4374



Episodes with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. PYE: The duration of the on-treatment period in years. Lower panels: At risk tables. %: proportion of subjects with at least one episode. E: number of episodes. R: episodes per 100 years of exposure. ADA: American Diabetes Association.

Source: Study 4374 CSR, Figure 14.3.1.65

Reviewer comment: The risk of hypoglycemia events in subjects with T2D, including the continued risk over time with semaglutide 2.4 mg, should be described in labeling.

Overall, there was 1 subject (semaglutide 2.4 mg) who experienced an event of severe hypoglycemia during a hospital admission for other SAEs, as described in the following narrative:

- Subject (b) (6) was a 58-year-old female with a history of T2D treated with metformin at baseline, diabetic neuropathy, hypertension, and hypercholesterolemia, who presented to the emergency room on study day 62 with nausea, vomiting, epigastric pain, and a serum creatinine of 2.6 mg/dL. The subject was diagnosed with chronic cholecystitis, gallstones, and acute renal failure (this case is also discussed under Section 8.5.6, acute renal failure). It was noted during the hospitalization that the subject was hypoglycemic (not reported as a serious event). The hypoglycemic episode was found on admission to the hospital and resolved once the subject was hydrated and given D50. Blood sugars were checked until they returned to normal. The first blood glucose reported was 56 (no units or reference ranges provided); subsequent values were 62 at approximately 20 minutes, 64 at 40 minutes, and 208 at 1 hour. The hypoglycemia episode was reported as resolved.

No hypoglycemia episodes were reported as SAEs in trial 4374.

Subject characteristics that could be potential risk factors for Level 2 or 3 hypoglycemia episodes are shown in Table 145. Subjects with hypoglycemia episodes were older and had a longer duration of diabetes on average, than those without. They also had a slightly lower HbA1c at week 68. A substantial number and proportion of subjects (50%) with hypoglycemia events while on semaglutide 2.4 mg occurred while *not* on a SU.

Table 145: Hypoglycemia Episodes (ADA 2018, Level 2 or 3), Subject Characteristics, Trial 4374

	Subjects with Episodes			Subjects without Episodes		
	Sema 2.4	Sema 1	Placebo	Sema 2.4	Sema 1	Placebo
Number of subjects	26	27	10	377	375	392
<i>Age (yrs)</i>						
Mean (SD)	57 (12)	58 (8)	65 (5)	55 (11)	55 (10)	55 (10)
Median	60	59	65	55	56	55
Min, Max	30, 73	41, 71	60, 73	19, 84	20, 81	20, 82
<i>Diabetes duration (yrs)</i>						
Mean (SD)	9.2 (5.5)	9.7 (7.6)	11.6 (5.0)	8.2 (6.2)	7.6 (5.8)	8.0 (6.2)
Median	9.6	9.7	12.3	6.7	6.3	6.7
Min, Max	1.6, 21.5	0.5, 34.4	2.8, 17.6	0.5, 37.7	0.5, 34.7	0.6, 29.9

<i>HbA1c at baseline (%)</i>						
Mean (SD)	8.3 (0.8)	8.1 (0.9)	8.0 (0.7)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Median	8.3	8.0	7.7	7.9	8.0	8.0
Min, Max	7.2, 9.9	6.3, 10.1	7.2, 9.2	6.7, 10.6	5.8, 10.2	5.7, 10.3
<i>HbA1c at week 68 (%)</i>						
N	25	26	8	325	324	329
Mean (SD)	6.0 (0.6)	6.2 (0.7)	7.3 (0.8)	6.3 (1.1)	6.5 (1.0)	7.8 (1.3)
Median	5.9	6.0	7.1	6.0	6.3	7.6
Min, Max	5.2, 7.6	5.2, 8.0	6.4, 9.0	4.8, 13.4	5.0, 10.9	5.1, 11.8
<i>SU at time of event(s)</i>						
Yes, n (%) / E	16 (61.5) / 32	15 (55.6) / 23	7 (70.0) / 11			
No, n (%) / E	13 (50.0) / 26	13 (48.1) / 15	4 (40.0) / 6			
Sema=semaglutide; SU=sulfonylurea For 'SU at time of event(s)' subjects are able to contribute to both depending on their SU status at time of event.						

Source: Study 4374 CSR, Table 14.3.1.66

In summary, the risk for clinically significant hypoglycemia in subjects with T2D is greater in those treated with semaglutide versus placebo. Whereas there does not appear to be a dose-response (2.4 mg vs. 1 mg) for the first episode, subjects who experienced 1 event on semaglutide appear to have been at greater risk for additional episodes at the higher (2.4 mg) dose. Subjects treated with semaglutide at risk of clinically significant hypoglycemia had a longer history of T2D and were slightly older than those without episodes. Subjects with and without significant hypoglycemia had substantial reductions in HbA1c with semaglutide. A substantial proportion of events of significant hypoglycemia occurred in subjects *not* on SUs at the time of the event. Subjects on insulin were not studied.

Hypoglycemia in Subjects without T2D

Trial 4153

In the phase 2 trial 4153, hypoglycemic episodes were collected on a separate hypoglycemia form, and were classified according to the ADA 2013 classification system (Figure 83).

In total, 86 hypoglycemic episodes were reported in 53 subjects (including comparators). The frequencies of hypoglycemic episodes increased slightly with increasing doses of semaglutide. No severe hypoglycemic episodes were reported. The majority of events were classified as "probable symptomatic". There were only 2 episodes of "documented symptomatic" hypoglycemia; 1 in a subject in the semaglutide 0.3 mg fast escalation arm and 1 in a subject in the semaglutide 0.4 mg fast escalation arm (Table 146).

Table 146: Hypoglycemic Episodes, Trial 4153, On-Treatment

	Semaglutide							Lira N=103	Pbo N=136
	0.5 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
Subjects with episodes	1 (1.0)	4 (3.9)	4 (3.9)	5 (4.9)	9 (8.8)	8 (7.8)	10 (9.7)	4 (3.9)	8 (5.9)
Numbers of episodes	1	5	4	8	10	20	16	4	8
ADA 2013									
Severe	0	0	0	0	0	0	0	0	0
Documented symptomatic	0	0	0	0	0	1 (1.0)	1 (1.0)	0	0
Asymptomatic	0	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	4 (3.9)	2 (1.9)	1 (0.7)
Pseudo-hypoglycemia	0	0	0	0	0	1 (1.0)	0	0	0
Probable symptomatic	1 (1.0)	3 (2.9)	3 (2.9)	4 (3.9)	8 (7.8)	7 (6.9)	5 (4.9)	2 (1.9)	7 (5.1)
Lira=liraglutide; Pbo=placebo									

Source: Study 4153 CSR, Table 12-39

Phase 3 Trials (Non-T2DM)

Hypoglycemia in the phase 3 without T2D pool (trials 4373, 4375, and 4376) was evaluated based on a MedDRA search of AE data⁹⁰ (i.e., there was not a separate hypoglycemic form). AEs were generally based on symptoms rather than glucose measurements, as subjects were not routinely provided glucometers. No events were reported as serious or severe in the trials in subjects without T2D.

Because of the differences in study design of the phase 3 trials, hypoglycemia AEs are presented in Table 147 separately by study – for example, it is of interest to evaluate whether there was more reported hypoglycemia in semaglutide-treated subjects on concomitant very low-calorie diets in trial 4375 (there were only 2 hypoglycemia events reported in this trial in semaglutide subjects, and the rate was not higher than in other trials).

Table 147: Hypoglycemia AEs, Phase 3 Trials in Subjects without Type 2 Diabetes, On-Treatment

	Semaglutide 2.4		Placebo	
	N=2650	PYE=2776.4	N=1529	PYE=1357.0
Phase 3 pool				
AEs	13 (0.6)	20 (0.7)	8 (0.7)	10 (0.8)
Trial 4373	N=1306	PYE=1706.1	N=655	PYE=829.6
AEs	8 (0.6)	15 (0.9)	5 (0.8)	7 (0.8)
PTs:				
Hypoglycemia	7 (0.5)	13 (0.8)	5 (0.8)	7 (0.8)
Postprandial hypoglycemia	1 (<0.1)	2 (0.1)	0	0
Trial 4375	N=407	PYE=526.1	N=204	PYE=261.4
AEs	2 (0.5)	2 (0.4)	0	0
PT:				
Hypoglycemia	2 (0.5)	2 (0.4)	0	0
Trial 4376	N=535	PYE=544.3	N=268	PYE=266.1
AEs	3 (0.6)	3 (0.6)	3 (1.1)	3 (1.1)
PT:				
Hypoglycemia	3 (0.6)	3 (0.6)	3 (1.1)	3 (1.1)
4376 semaglutide run-in:	1/902 (0.1)			

Source: SCS, Table 2-55; Study 4373 CSR, Table 14.3.1.59; Study 4375 CSR, Table 12-26; Study 4376 CSR, Table 14.3.1.73 and text

One subject on semaglutide 2.4 mg in trial 4373 (ID: (b) (6), 26-year-old male) reported 6 non-serious AEs of hypoglycemia, severity reported as mild, all exactly 7 days apart between days

⁹⁰ SMQ Hypoglycemia, narrow terms only

264 to 299, all reported as leading to dose reduction of trial product. Blood glucose values are not available in the study database for that time period. Baseline fasting plasma glucose for this subject was 102 mg/dL and ranged between 75-81 mg/dL during the trial.

Hypoglycemia AEs were also evaluated based on baseline glycemic status (normoglycemia vs. pre-diabetes). There was no clear evidence that semaglutide resulted in more hypoglycemia events in 1 group over another based on baseline glycemic status.

Table 148: Hypoglycemia AEs by Glycemic Status at Baseline, Phase 3 Trials in Subjects without Type 2 Diabetes, On-Treatment

	Semaglutide 2.4		Placebo	
	N=1196	PYE=1475.2	N=642	PYE=769.1
Normoglycemia	N=1196	PYE=1475.2	N=642	PYE=769.1
Pre-diabetes	N=1051	PYE=1301.2	N=485	PYE=588.0
<i>Hypoglycemia AEs</i>				
Normoglycemia	7 (0.6)	7 (0.5)	6 (0.9)	7 (0.9)
Pre-diabetes	5 (0.5)	11 (0.8)	2 (0.4)	3 (0.5)

Source: ISS, Table 7.7.38

Finally, an exploratory search was conducted of fasting plasma glucose (FPG) in routine trial blood work in subjects without T2D. Only 2 subjects had FPG less than 54 mg/dL; both were randomized to placebo in trial 4373.

In summary, the risk of significant hypoglycemia in subjects with obesity but without T2D treated with semaglutide 2.4 mg appears low; however, hypoglycemia was not collected or reported in a systematic manner in the phase 3 program. More episodes were likely identified in the phase 2 trial due to a specific form in which potential cases were formally collected (mostly “probable symptomatic” and “asymptomatic”) versus the phase 3 program in which they were collected as AEs only.

8.5.8. Retinal Disorders

In a 2-year CVOT with Ozempic in subjects with T2D and high CV risk, more events of diabetic retinopathy complications occurred in Ozempic (3.0%) versus placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (Ozempic 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (Ozempic 0.7%, placebo 0.4%). While it has been

established that chronic hyperglycemia is a major cause of diabetic retinopathy,^{91,92} rapid improvement in glucose control in patients with longstanding poor glucose control has been associated with a temporary worsening of diabetic retinopathy.⁹³

A randomized clinical trial (NN9535-4352) is currently being conducted to evaluate the long-term effects of semaglutide versus placebo on diabetic retinopathy development and progression when added to standard-of-care in subjects with T2D. The trial enrolled its first subject May of 2019 and has a 5-year treatment duration.

The focus of retinal disorders in this NDA is in trial 4374, the phase 3 weight management trial in subjects with T2D. In addition, the applicant compiled an updated integrated review of diabetic retinopathy from all the completed trials in subjects with diabetes (i.e., from all semaglutide programs). These results are presented separately in this section.

Trial 4374

In study 4374, the proportion of subjects at baseline with a history of diabetic retinopathy was 10.2% overall.

Retinal disorders in trial 4374 were considered AEs of special interest and an evaluation was conducted by a pre-defined MedDRA search.⁹⁴ In addition, eye examinations (fundus photography or a dilated funduscopy) were performed at baseline, at week 52, and at end of treatment (week 68). Eye examination results were summarized by category: normal, abnormal not clinically significant, and abnormal clinically significant, for left and right eye, respectively, and presented for semaglutide and placebo at screening, at 1 year of treatment, and at end-of-treatment. The data are supported by shift tables by left eye and right eye for subjects who have changed category after 1 year of treatment and at end-of-treatment.

A total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search during the in-trial period. These events were reported by a larger proportion of subjects with semaglutide versus placebo (6.9% semaglutide 2.4 mg, 6.2% semaglutide 1 mg, and 4.2%

⁹¹ Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977.

⁹² UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837.

⁹³ Bain SC, et al. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. *Diabetes Obes Metab.* 2019 Mar;21(3):454-466.

⁹⁴ Custom query (NNMQ Retinal disorders and visual impairment): SMQ Retinal disorders, narrow terms only; HLT Visual impairment and blindness (excl color blindness), primary terms only

placebo). The majority of events were reported as ‘Diabetic retinopathy’ (4.0%, 2.7%, and 2.7%, respectively) and ‘Non-proliferative retinopathy’ (0.7%, 0%, and 0%, respectively). No SAEs of retinal disorders were reported in any of the treatment arms.

In 45 events, the investigator considered the AE a new-onset or worsening of diabetic retinopathy and collected additional data as per protocol. Of these 45 events, 20 events occurred in 19 subjects treated with semaglutide 2.4 mg, 12 events in 12 subjects treated with semaglutide 1 mg, and 13 events in 12 subjects treated with placebo. In all events reported in subjects treated with semaglutide 2.4 mg, the AE was identified by routine or protocol-scheduled examination. Treatment was only administered to 1 event identified in the semaglutide 2.4 mg subjects; the other 19 events were managed with observation.

Characteristics of subjects with and without diabetic retinopathy events that could suggest risk factors are shown in Table 149, below. The proportion of subjects with a history of diabetic retinopathy at baseline was higher in subjects with events compared to those without events; this was especially evident in the semaglutide 1 mg arm. Subjects on semaglutide 2.4 mg with a retinopathy event were more likely to have been diagnosed with diabetes for a shorter duration and have a greater decrease in HbA1c than subjects without a retinopathy event, in contrast to subjects on semaglutide 1 mg and placebo.

Table 149: Characteristics in Subjects with and without Diabetic Retinopathy Events, Trial 4374, In-Trial Period

	Subjects with Events			Subjects without Events		
	Sema 2.4	Sema 1	Placebo	Sema 2.4	Sema 1	Placebo
Number of subjects	19	12	11	384	390	391
<i>History of diabetic retinopathy</i>						
No, n (%)	14 (73.7)	5 (41.7)	8 (72.7)	344 (89.6)	356 (91.3)	357 (91.3)
Yes, n (%)	5 (26.3)	7 (58.3)	3 (27.3)	40 (10.4)	34 (8.7)	34 (8.7)
<i>Age (yrs)</i>						
Mean (SD)	55 (11)	53 (12)	57 (7)	55 (11)	56 (10)	55 (11)
Median	55	53	54	56	56	56
Min, Max	32, 74	35, 71	50, 72	19, 84	20, 81	20, 82
<i>Diabetes duration (yrs)</i>						
Mean (SD)	7.1 (5.6)	8.8 (5.7)	10.3 (7.8)	8.3 (6.2)	7.7 (5.9)	8.1 (6.1)
Median	4.6	7.6	8.8	6.9	6.5	6.7
Min, Max	0.5, 17.6	1.9, 23.4	0.6, 29.9	0.5, 37.7	0.5, 34.7	0.6, 29.6
<i>HbA1c at baseline (%)</i>						
Mean (SD)	8.3 (1.0)	8.4 (0.8)	8.2 (1.0)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Median	7.7	8.5	8.4	8.0	8.0	8.0

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Min, Max	7.2, 10.4	7.2, 9.4	6.6, 9.7	6.7, 10.6	5.8, 10.2	5.7, 10.3
<i>HbA1c change at week 68 (%)</i>						
N	19	12	10	362	363	363
Mean (SD)	-2.0 (1.2)	-1.3 (1.8)	-0.2 (1.3)	-1.7 (1.2)	-1.6 (1.1)	-0.3 (1.3)
Median	-2.0	-1.6	-0.2	-1.7	-1.7	-0.3
Min, Max	-4.5, +1.1	-3.7, +3.5	-2.1, +1.6	-4.9, +5.4	-4.7, +2.8	-3.8, +6.1
Sema=semaglutide						

Source: Study 4374 CSR, Table 12-43

Summaries of the eye examination findings during the trial are shown in the tables below. Of note, in subjects randomized to semaglutide 2.4 mg, at baseline, 22 subjects (5.5%) had clinically significant (CS) findings on right eye or left eye funduscopy, which was slightly more than those on semaglutide 1 mg (3.2% left eye, 3.5% right eye) and placebo (3.7% left eye, 4.0% right eye).

Table 150: Eye Examinations at Baseline and End-of-Treatment, Trial 4374, In-Trial Period

	Sema 1.0 mg N (%)	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	402	403	402
Left-eye funduscopy			
Visit 1 (week -1)			
N	402 (100)	403 (100)	402 (100)
Normal	290 (72.1)	296 (73.4)	296 (73.6)
Abnormal, NCS	99 (24.6)	85 (21.1)	91 (22.6)
Abnormal, CS	13 (3.2)	22 (5.5)	15 (3.7)
Visit 24 (week 68)			
N	355 (88.3)	374 (92.8)	361 (89.8)
Normal	247 (69.6)	262 (70.1)	270 (74.8)
Abnormal, NCS	99 (27.9)	96 (25.7)	75 (20.8)
Abnormal, CS	9 (2.5)	16 (4.3)	16 (4.4)
Right-eye funduscopy			
Visit 1 (week -1)			
N	402 (100)	403 (100)	400 (99.5)
Normal	277 (68.9)	296 (73.4)	296 (74.0)
Abnormal, NCS	111 (27.6)	85 (21.1)	88 (22.0)
Abnormal, CS	14 (3.5)	22 (5.5)	16 (4.0)
Visit 24 (week 68)			
N	355 (88.3)	374 (92.8)	359 (89.3)
Normal	250 (70.4)	260 (69.5)	263 (73.3)
Abnormal, NCS	97 (27.3)	96 (25.7)	81 (22.6)
Abnormal, CS	8 (2.3)	18 (4.8)	15 (4.2)

N: Number of subjects, %: Percentages are based on subjects with an observation at the visit, NCS: Abnormal not clinically significant, CS: Abnormal clinically significant.
Observed data from in-trial period.

NCS=not clinically significant, CS=clinically significant

Source: Study 4374 CSR, Table 14.3.6.8

Table 151: Eye Examinations by Week, Shift Table, Trial 4374, In-Trial Period

Left eye	N	Normal at Baseline			NCS at Baseline			CS at Baseline		
		Normal N (%)	NCS N (%)	CS N (%)	Normal N (%)	NCS N (%)	CS N (%)	Normal N (%)	NCS N (%)	CS N (%)
Week 52										
Sema 2.4	376	343 (88.4)	29 (10.5)	3 (1.1)	22 (27.8)	54 (68.4)	3 (3.8)	5 (22.7)	3 (13.6)	14 (63.6)
Sema 1	363	233 (90.0)	24 (9.3)	2 (0.8)	21 (22.8)	69 (75.0)	2 (2.2)	3 (25.0)	5 (41.7)	4 (33.3)
Placebo	355	340 (92.3)	17 (6.5)	3 (1.2)	24 (29.6)	56 (69.1)	1 (1.2)	2 (14.3)	0	12 (85.7)
Week 68										
Sema 2.4	374	240 (87.3)	32 (11.6)	3 (1.1)	18 (23.1)	58 (74.4)	2 (2.6)	4 (19.0)	6 (28.6)	11 (52.4)
Sema 1	355	228 (89.8)	24 (9.4)	2 (0.8)	17 (19.1)	71 (79.8)	1 (1.1)	2 (16.7)	4 (33.3)	6 (50.0)
Placebo	361	244 (92.4)	16 (6.1)	4 (1.5)	24 (29.3)	57 (69.5)	1 (1.2)	2 (13.3)	2 (13.3)	11 (73.3)
Right eye										
Week 52										
Sema 2.4	376	246 (89.1)	25 (9.1)	5 (1.8)	24 (30.4)	53 (67.1)	2 (2.5)	2 (9.5)	3 (14.3)	16 (76.2)
Sema 1	363	227 (91.5)	20 (8.1)	1 (0.4)	28 (27.5)	72 (70.6)	2 (2.0)	5 (38.5)	4 (30.8)	4 (30.8)
Placebo	354	241 (92.7)	16 (6.2)	3 (1.2)	20 (25.3)	58 (73.4)	1 (1.3)	2 (13.3)	1 (6.7)	12 (80.0)
Week 68										
Sema 2.4	374	238 (86.9)	33 (12.0)	3 (1.1)	20 (25.3)	57 (72.2)	2 (2.5)	2 (9.5)	6 (28.6)	13 (61.9)
Sema 1	355	222 (91.4)	19 (7.8)	2 (0.8)	25 (25.3)	74 (74.7)	0	3 (23.1)	4 (30.8)	6 (46.2)
Placebo	359	238 (90.2)	23 (8.7)	3 (1.1)	22 (28.2)	55 (70.5)	1 (1.3)	2 (12.5)	3 (18.8)	11 (68.8)

Source: Study 4374 CSR, Table 14.3.6.9

Reviewer comment: Few subjects were considered to have CS findings overall. Most subjects who were normal or NCS at baseline remained in that category during the trial for each eye. An imbalance was seen for the semaglutide 2.4 mg arm in shifts from normal to NCS in both eyes. There was also an imbalance in shifts from NCS to CS in the semaglutide 2.4 mg arm, but the numbers were small. These examination findings are consistent with the small imbalances seen for retinal disorder AEs.

Retinopathy Report

The applicant provided a report that summarized the available clinical trial data to assess retinal disorders in patients with T2D treated with semaglutide. The SUSTAIN program supports the safety and efficacy of Ozempic (semaglutide 0.5 mg and 1 mg SC once-weekly) and the PIONEER program supports the safety and efficacy of Rybelsus (3 mg, 7 mg, and 14 mg oral once-daily). STEP 2, also referred to as trial 4374, is the T2D trial to support the weight management NDA. Differences in eligibility criteria and trial assessments are shown in Table 152.

Table 152: Overview of Semaglutide T2D Trial Design Features Relevant for the Evaluation of Diabetic Retinopathy

Parameter	SUSTAIN 6	SUSTAIN 1-5 and 7	SUSTAIN JP	SUSTAIN 8-10 + China	PIONEER 1-10	STEP 2
Proliferative retinopathy or maculopathy requiring acute treatment as exclusion criterion	no	yes	yes	yes	yes	yes*
Detailed diabetic retinopathy history form	yes	no	no	yes	yes	yes
MedDRA search among investigator reported AEs	yes	yes	yes	yes	yes	yes
Additional data collection on a dedicated diabetic retinopathy form	no	no	no	yes	yes	yes
Adjudicated composite endpoint related to diabetic retinopathy complications	yes	no	no	no	no	no
Fundoscopy or fundus photography						
Fundoscopy required dilation of both pupils	no	no	no	yes	yes	yes
Baseline examination	yes	yes	yes	yes	yes	yes
1 year of treatment	yes	NA	NA	NA	yes [#]	yes
End-of-treatment/end-of-trial examination	yes	no	yes	yes	yes	yes

*For STEP 2, the wording for the exclusion criterion was 'uncontrolled and potentially unstable diabetic retinopathy or maculopathy'

[#]Yes: for the PIONEER 3 and PIONEER 6 trials that had treatment durations greater than 1 year

NA: not applicable (as the treatment duration was shorter than 1 year)

SUSTAIN 1=monotherapy

SUSTAIN 2-5 and 7-10=combination therapy

SUSTAIN JP and China=designed to meet country requirements of Japan and China, respectively

SUSTAIN 6=CVOT

PIONEER 1=monotherapy

PIONEER 2-5 and 7-9=combination therapy

PIONEER 9 & 10=designed to meet country requirements of Japan

PIONEER 6=CVOT

Source: Diabetic retinopathy report, Table 2-1

Note that the SUSTAIN 6 CVOT was the only trial investigating semaglutide treatment that did not include an exclusion criterion related to diabetic retinopathy. In addition, there was no upper limit in HbA1c for the subjects upon trial entry. The CVOT population studied had long-standing T2D, were older and at high cardiovascular risk. Furthermore, SUSTAIN 6 included an independently adjudicated composite efficacy endpoint related to diabetic retinopathy complications: vitreous hemorrhage, onset of diabetes-related blindness, need for treatment with intravitreal agents, or need for treatment with photocoagulation. The result of this adjudicated endpoint was presented in the introduction to this section: 3.0% semaglutide versus 1.8% placebo. The reader should refer to the EMDAC advisory committee meeting for Ozempic where this result was discussed in detail,⁹⁵ the clinical review of this trial, and the Ozempic label, for additional information.

A summary of the AEs of retinal disorders across development programs and trials based on a MedDRA search (i.e., events were reported by the investigator but *not* adjudicated) are

⁹⁵ Endocrinologic and Metabolic Drugs Advisory Committee Meeting for NDA 209637, 18 October 2017.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

presented in Figure 85. Most events of diabetic retinopathy were identified by the eye examinations scheduled in the trial.

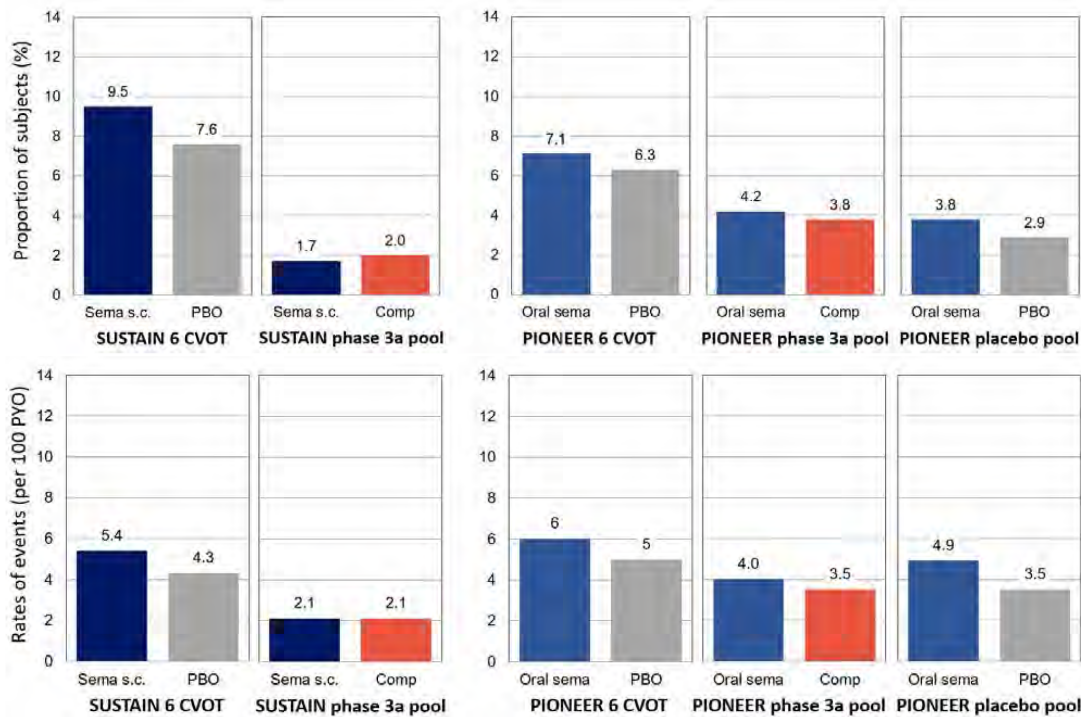
In most presentations of trials and pools, semaglutide was associated with a greater proportion of events versus placebo or comparator.

The CVOTs SUSTAIN 6 and PIONEER 6 had the highest incidence of events, likely due to the patient populations studied (e.g., longer duration of diabetes) as well as the longer duration of the trials. SUSTAIN 6 may have had more events than PIONEER 6 due to the lack of a diabetic retinopathy exclusion criterion as noted above.

As 5 out of 7 trials in the SUSTAIN phase 3a pool did not do a follow-up eye examination at end of treatment, the number of AEs in the SUSTAIN phase 3a pool is possibly underestimated.

A total of 30 diabetic retinopathy/retinal disorder events were reported as SAEs across the clinical development programs; most in SUSTAIN 6 (0.7% semaglutide vs. 0.5% placebo). Across the remaining trials and programs, 4 SAEs in semaglutide-treated subjects versus 5 SAEs in comparator/placebo subjects were reported.

Figure 85: AEs of Diabetic Retinopathy, MedDRA Search, SUSTAIN and PIONEER Programs



Adverse events of diabetic retinopathy (SUSTAIN/PIONEER MedDRA search) are presented in relevant trials and pools across clinical development programmes with semaglutide: the SUSTAIN 6 CVOT, the SUSTAIN phase 3a pool, the PIONEER 6 CVOT, the PIONEER phase 3a pool and the PIONEER placebo pool. Proportions of subjects (%) are presented in the top panel and rates of events (per 100 patient years of observation) are presented in the bottom panel. Comparators included sitagliptin, exenatide ER, insulin, OADs (one of the following: sulphonylurea, glinide, α -glucosidase inhibitors or thiazolidinedione) and placebo for the SUSTAIN phase 3a pool, and empagliflozin, sitagliptin, dulaglutide and placebo for the PIONEER phase 3a pool.

Sema: semaglutide; Comp: comparator; CVOT: cardiovascular outcomes trial; PBO: placebo; PYO: patient years of observation; s.c.: subcutaneous

Source: Diabetic retinopathy report, Figure 3-1

The applicant notes that the currently available data may be too limited to assess a dose response. This is of interest as the semaglutide 2.4 mg dose would be the highest dose approved for treatment of a T2D population. There is a suggestion that the incidence of retinal disorders was slightly increased in the semaglutide 2.4 mg arm as compared with the semaglutide 1 mg arm in the weight management trial 4374 in T2D (see the discussion above); trial 4374 utilized a different (broader) MedDRA search than the SUSTAIN and PIONEER programs and therefore cannot be directly compared.

- In the SUSTAIN 6 CVOT, the proportions of events were 9.0% for semaglutide 0.5 mg and 10.0% for semaglutide 1 mg (5.0 and 5.8 events per 100 PYO, respectively).
- In the SUSTAIN phase 3a pool, the proportions of events were 2.1% for semaglutide 0.5 mg and 1.5% for semaglutide 1 mg (2.6 and 1.9 events per 100 PYO, respectively).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

- The 72-week safety trial PIONEER 3 the proportions of subjects with events were 6.7%, 6.0%, and 5.6% and event rates were 4.8, 4.6, and 3.8 events per 100 PYO, for oral semaglutide doses 3 mg, 7 mg, and 14 mg, respectively.
- In the PIONEER placebo dose pool, proportions of subjects with events were 3.3%, 5.6%, and 4.2% and event rates were 3.5, 7.2, and 4.9 events per 100 PYO, for oral semaglutide doses 3 mg, 7 mg, and 14 mg, respectively.

In summary, these trials and programs do not provide clear evidence of a dose-response for retinal disorders/diabetic retinopathy events. Semaglutide does appear to be associated with diabetic retinopathy events in these relatively short time periods of the clinical trials.

8.5.9. Psychiatric Disorders

Suicidality and depression are safety issues of concern for all the centrally acting obesity drugs.^{96,97,98,99} For example (and particularly relevant to this review of semaglutide given it is in the same drug class), suicidal behavior and ideation are labeled in the Warnings and Precautions section of the Saxenda label due to an imbalance reported in the phase 3 trials.⁵⁹

There was no evidence to suggest an increased risk of psychiatric adverse events or suicidal behavior or ideation with semaglutide in the weight management program.

In the phase 2 and 3 trials in the weight management program, subjects with severe past or present psychiatric disorders were not eligible for enrollment. Specific exclusions were as follows: history of major depressive disorder within 2 years, history of other severe psychiatric disorders, Patient Health Questionnaire-9 (PHQ-9) score of ≥ 15 , any lifetime history of a suicidal attempt, any suicidal behavior within 30 days, any suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). The PHQ-9 and C-SSRS are standard questionnaires used in screening and monitoring of weight management phase 2 and 3 trials, and are described further below.

At screening, the proportion of subjects in the phase 2 trial 4153 with history of any psychiatric disorder was 10.9%. These were most commonly reported as depressed mood disorders (6.5%) and anxiety disorders and symptoms (2.8%).

In the phase 3 pool, a history of psychiatric disorder at screening was reported in 29.8% of subjects; specifically, depression or another mood disorder (17.2%) or anxiety (13.6%).

⁹⁶ Egan A. FDA Clinical Review of NDA 21888 (rimonabant), EMDAC 13 Jun 2007.

⁹⁷ Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 Sep 2010 and 10 May 2012.

⁹⁸ Roberts M. FDA Clinical Review of NDA 22580 (phentermine/topiramate), EMDAC 15 July 2010 and 22 Dec 2012.

⁹⁹ Craig E. FDA Clinical review of NDA 200063 (naltrexone/bupropion), EMDAC 7 Dec 2010.

In trial 4153, the review of psychiatric disorders AEs was undertaken by using the SOC 'Psychiatric disorders.' In addition, the 2 standard mental health questionnaires, C-SSRS and PHQ-9, were conducted during the trial.

The evaluation for mental health disorders in the phase 3 weight management program was based on a pre-defined MedDRA search,¹⁰⁰ as well as the C-SSRS and the PHQ-9.

Adverse Events

Trial 4153

In the phase 2 trial 4153, 111 psychiatric disorders were reported in 92 subjects in the on-treatment period. None of the reported psychiatric disorders were serious. The most frequently reported events were insomnia, anxiety, and depression, with no clear pattern in dose or versus comparators. A summary of events is provided below:

Table 153: Psychiatric AEs, Trial 4153, On-Treatment

	Semaglutide							Lira N=103	Pbo N=136
	0.05 N=103	0.1 N=102	0.2 N=103	0.3 N=103	0.4 N=102	0.3F N=102	0.4F N=103		
Psychiatric disorders SOC	6 (5.8)	12 (11.8)	13 (12.6)	7 (6.8)	7 (6.9)	6 (5.9)	16 (15.5)	11 (10.7)	14 (10.3)
Led to premature discontinuation	1 (1.0)	1 (1.0)	0	0	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (0.7)
'Severe'	1 (1.0)	2 (2.0)	0	1 (1.0)	1 (1.0)	0	1 (1.0)	0	0

Lira=liraglutide; Pbo=placebo

Source: Study 4153 CSR, Tables 12-36, 14.3.1.50, and 14.3.1.20

One non-serious AE of suicidal ideation was reported in the trial:

- Subject (b) (6) (semaglutide 0.3 mg) was a 25-year-old male with a history of autism spectrum disorder and depression who reported a moderate AE of 'Suicidal ideation' on study day 217 (on-treatment). This event was considered unlikely due to treatment, the dose was not changed (the subject completed the trial), and the subject reportedly recovered in 5 days.

Phase 3 Trials

In the phase 3 pool, AEs of psychiatric disorders were reported in 9.3% of subjects in the semaglutide 2.4 mg arm (10.0 events per 100 PYE) and 10.7% of subjects in the placebo arm (12.1 events per 100 PYE).

¹⁰⁰ Custom query: SOC Psychiatric disorders, primary terms only

Table 154: Psychiatric Disorders ($\geq 0.2\%$ of Subjects in the Semaglutide Arm), Pre-Defined MedDRA Search, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650	Placebo N=1529
Psychiatric disorders AEs	254 (9.3)	157 (10.7)
Insomnia	63 (2.3)	39 (2.7)
Anxiety	64 (2.3)	40 (2.7)
Depression	41 (1.5)	30 (2.0)
Depressed mood	22 (0.8)	14 (1.0)
Stress	17 (0.6)	11 (0.8)
Sleep disorder	16 (0.6)	8 (0.6)
Irritability	12 (0.4)	4 (0.3)
Libido decreased	11 (0.4)	3 (0.2)
Suicidal ideation	5 (0.2)	2 (0.1)
Restlessness	4 (0.2)	0
SAEs	4 (0.1)	1 (<0.1)
Severe AEs	7 (0.2)	5 (0.3)
Leading to permanent treatment discontinuation	10 (0.4)	6 (0.4)
Suicidal ideation or behavior AEs ^a	5 (0.2) ^b	4 (0.3) ^c
a HLT: 'Suicidal and self-injurious behavior' b Semaglutide group includes 4 patients who did not change dose and 1 patient who temporarily interrupted trial product due to event c Placebo group includes 1 patient who had an event on day 1 and day 299 and 1 patient who was on semaglutide during the run-in period of 4376		

Source: SCS, Tables 2-65 and 2-66; reviewer created from ISS dataset ADAE.xpt (suicidal ideation and behavior AEs, proportions are unadjusted)

The SAEs were: in the semaglutide 2.4 mg arm, 1 subject each with 'Acute stress disorder' and 'Suicidal ideation,' and 2 subjects with 1 event each of 'Anxiety'; in the placebo arm (trial 4373), 1 subject with 'Suicide attempt.' Brief narratives for the SAEs of the semaglutide-treated subjects are below. There was an additional suicide attempt in the placebo group from trial 4376 that was reported as non-serious (the subject put pills in the mouth but did not swallow them). As this subject was exposed to semaglutide during the run-in period, a brief narrative is included for completeness. No psychiatric SAEs or AEs of suicide attempt or ideation were reported during the run-in period of trial 4376. In addition, there were no psychiatric SAEs or AEs of suicide attempt or ideation reported in the semaglutide 1 mg arm in trial 4374.

Semaglutide 2.4 mg:

- Subject NN9534-4373 (b) (6): Acute stress disorder

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

This was a 33-year-old female with BMI 33.2 kg/m² and a history of intermittent anxiety who was treated for approximately 3 months with semaglutide when she reported a left hemicranial headache with vomiting in the context of known intermittent anxiety, worsened by a recent job loss. She was hospitalized and received intravenous acetaminophen. The vomiting resolved the next day and she was discharged from the hospital. The headache was reported resolved 2 weeks later.

- Subject NN9534-4373 (b) (6): Anxiety

This was a 73-year-old female with BMI of 51.5 kg/m² and history of coronary artery disease, atrial fibrillation, and anxiety since 2015 who was treated with semaglutide for 2.5 months when she presented to the ER with chest pain. The subject was diagnosed with unstable angina, costochondritis, and worsening anxiety. She recovered from all events and was discharged from the hospital 2 days later.

- Subject NN9534-4373 (b) (6): Suicidal ideation

This was a 47-year-old male with BMI of 44.4 kg/m² and history of attention deficit hyperactivity disorder, anxiety, situational depression, and self-mutilation (cutting), on clonazepam and vortioxetine. The subject was treated with semaglutide for 2 to 3 months when it was reported that he had been dealing with worsening depression due to life-stressors. Around that period, he had onset of "suicidal ideations." However, this was not disclosed until a site visit approximately 6 months later when he answered positively on the C-SSRS (as suicidal behavior) and received a score of 16 on the PHQ-9. He reported that at the time (6 months previously) he had thoughts of shooting himself with a rifle, but his son walked in and convinced him not to commit suicide. At the time of the interview with the PI, he denied suicidal ideations. He was referred to a mental health provider but did not follow through. He reported his medications were being monitored by his PCP and he was managing his anxiety and depression with lifestyle changes and meditation.

- Subject NN9534-4375 (b) (6): Anxiety

This was a 62-year-old female with BMI of 33.7 kg/m² and history of migraine headaches, insomnia, and uterine cancer. After 7 months on semaglutide, the subject presented to the ER and was subsequently admitted for "palpitations due to anxiety of abuse by significant other." Per report, the subject was abused by her boyfriend and developed a fluttering heart, right-sided neck pain, and anxiety. Urine drug screening was positive for cocaine. It is unknown if she received any treatment. Three days later, she was discharged from the hospital to a women's shelter. The SAE was reported as resolved.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Placebo (after semaglutide run-in):

- Subject NN9534-4376/ (b) (6): Suicide attempt (non-serious)

This was a 46-year-old female with BMI of 35.4 kg/m² and history of anxiety disorder and depression on escitalopram. On study day 425 (i.e., approximately 285 days after the run-in period) she reported an AE of suicide attempt. The event was classified as non-serious as the subject took some pills in the mouth but did not swallow them.

Questionnaires

C-SSRS

The C-SSRS is a standardized assessment to quantify the severity of suicidal ideation and behavior.¹⁰¹ The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of the ideation, and 6 questions addressing suicidal behavior. The following categories were used in order to classify the events:

- Suicidal ideation:
 1. Wish to be dead (passive)
 2. Non-specific active suicidal thoughts (no method, intent, or plan)
 3. Active suicidal ideation with any methods (not plan) without intent to act
 4. Active suicidal ideation with some intent to act, without specific plan
 5. Active suicidal ideation with specific plan and intent
- Suicidal behavior:
 1. Completed suicide
 2. Actual suicide attempt
 3. Interrupted suicidal attempt
 4. Aborted suicide attempt
 5. Preparatory acts or behavior towards making a suicidal attempt
- Non-suicidal self-injurious behavior

In trial 4153, no suicidal behavior was reported on the C-SSRS in any of the treatment arms during post-baseline visits. A total of 7 subjects (4 with semaglutide, 2 with liraglutide, and 1 with placebo) reported suicidal ideation events post-baseline. One of these subjects also reported a non-serious AE of suicidal ideation (subject (b) (6); see AE narrative above).

¹⁰¹ Posner K, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Amer J Psych.* 2011; 168: 1266-77.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

In the phase 3 trials, 2 subjects reported post-baseline suicidal behavior on the C-SSRS; both subjects are described in the AE discussion above: subject NN9534-4373 (b) (6) (semaglutide 2.4 mg) had an AE of 'Suicidal ideation,' and subject NN9534-4376/ (b) (6) (placebo) had a AE of 'Suicide attempt.'

The C-SSRS summary results (suicidal ideation and/or behavior) for subjects in the 3 trials in the phase 3 dose-escalation group (4373, 4374, and 4375) are shown in Table 155.

Table 155: C-SSRS, Proportions of Subjects with Suicidal Ideation and/or Behavior,¹⁰² Dose-Escalation Group (Trials 4373, 4374, and 4375), In-Trial Period

	Sema 2.4 mg N (%)	Placebo N (%)
Number of subjects	2116	1261
Lifetime assessment		
Number of subjects answering the C-SSRS	2116	1260
Subjects with suicidal ideation and/or behaviour	30 (1.4)	28 (2.2)
Subjects with suicidal ideation	30 (100)	28 (100)
Subjects with suicidal behaviour	0	1 (3.6)
At baseline		
Number of subjects answering the C-SSRS	2104	1248
Subjects with suicidal ideation and/or behaviour	1 (0.0)	2 (0.2)
Subjects with suicidal ideation	1 (100)	2 (100)
Subjects with suicidal behaviour	0	0
Post-baseline		
Number of subjects answering the C-SSRS	2066	1228
Subjects with suicidal ideation and/or behaviour	8 (0.4)	7 (0.6)
Subjects with suicidal ideation	8 (100)	7 (100)
Subjects with suicidal behaviour	1 (12.5)	0

Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.

C-SSRS: Columbia suicidality severity rating scale, N: Number of subjects

Subjects with suicidal ideation and/or behaviour: %: Percentages are based on subjects with an observation at the visit.

Subjects with suicidal ideation and subjects with suicidal behaviour: %: Percentages are based on subjects with suicidal ideation and/or behaviour.

Lifetime assessment is at screening visit. Baseline assessment is at randomisation visit.

Post-baseline is the subject's worst assessment after randomisation visit.

Suicidal ideation is defined as a subject answering yes to either question 1: Wish to be dead or question 2: Non-Specific Active Suicidal Thoughts. Suicidal behaviour is defined as a subject answering yes to one of the following: actual attempt, interrupted attempt, aborted attempt or preparatory acts/behaviour.

Source: SCS, Table 2-67

¹⁰² The subject with post-baseline suicidal behavior in this table is NN9534-4373 (b) (6). This subject also had suicidal ideation type 4 (intent to act but no plan). Narrative for the AE suicidal ideation is presented above.

In addition to the results shown in the table above, 2 subjects (0.5%) in the semaglutide 1 mg arm of trial 4374 reported post-baseline suicidal ideation on the C-SSRS (none reported post-baseline suicidal behavior).¹⁰³

Because of the difference in trial design, including a run-in period, the C-SSRS data for trial 4376 were analyzed separately:¹⁰⁴

- At screening, the subjects made a lifetime assessment. Sixteen subjects (2.0%) had suicidal ideation prior to the start of the trial and none had suicidal behavior.
- At week 0, 3 subjects (0.4%) had suicidal ideation (none were type 4 or type 5) and no subjects had suicidal behavior.
- After the start of run-in period up to (but not including week 20), 1 subject had suicidal ideation (type 1) and no subjects had suicidal behavior.
- At week 20, no subjects had suicidal ideation or suicidal behavior.
- After randomization up to and including week 68, 1 subject (0.2%) in the semaglutide 2.4 mg group and 3 subjects (1.1%) in the placebo group had suicidal ideation. A subject in the placebo group had suicidal ideation of type 4 as well as suicidal behavior.¹⁰⁵

PHQ-9

The PHQ-9 is a 9-item depression subscale of the self-administered patient health questionnaire (mental disorder instrument for use in primary care).¹⁰⁶ The patient rates the frequency of the following nine items on the scale from 0 (not at all) to 3 (nearly every day) in the last 2 weeks:

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television

¹⁰³ Source: Study 4374, Table 14.3.6.10

¹⁰⁴ Source: Study 4376, Table 14.3.6.8

¹⁰⁵ The subject with post-baseline suicidal ideation type 4 and suicidal behavior is NN9534-4376/ (b) (6). Narrative for the non-serious AE of suicide attempt is presented above.

¹⁰⁶ Kroenke K, et al. The PHQ-9 – validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606-13.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself in some way

The total score ranges from 0 to 27. Total scores of 0-4 represent no to minimal depression, total scores of 5-9 represent mild depression, total scores of 10-14 represent moderate depression, total scores of 15-19 represent moderately severe depression, and total scores of 20-27 represent severe depression.

Major depression is diagnosed if 5 or more of the 9 criteria have been present at least “more than half the days” in the past 2 weeks and 1 of the symptoms is depressed mood or anhedonia.

The symptom criterion in Question 9, “thoughts that you would be better off dead or hurting yourself in some way,” counts if present at all, regardless of duration.

Before making a final diagnosis, the clinician is expected to rule out physical causes of depression, normal bereavement, and history of a manic episode.¹⁰⁶

On the PHQ-9 in trial 4153, 16.5% to 28.4% of subjects depending on treatment arm worsened from baseline to the highest score, with no pattern for dose-response or versus comparator; the majority of shifts were in the none to mild category. Most subjects had no change from baseline in severity of score category. Three subjects (semaglutide 0.05 mg, semaglutide 0.2 mg, and semaglutide 0.3 mg) had a PHQ-9 total score $\geq$ 20 post-baseline. The number of subjects with at least 1 positive score (1, 2, or 3) to question 9 (“Thoughts that you would be better off dead or of hurting yourself in some way”) post-baseline was: 10 subjects with semaglutide (0 – 2.9%, no apparent dose-dependency), 2 subjects with liraglutide (1.9%), and 9 subjects with placebo (6.7%).

In the phase 3 dose-escalation group (trial 4373, 4374, and 4375), similar proportions of subjects in the semaglutide 2.4 mg and placebo treatment arms reported maximum PHQ-9 scores 10-14, 15-19, and $\geq$ 20, and positive responses to question 9 (“thoughts that you would be better off dead, or of hurting yourself in some way”).

Table 156: PHQ-9 Maximum Total Score, Phase 3 Dose-Escalation Group, In-Trial Period

	Sema 2.4 mg N (%)	Placebo N (%)	Total N (%)
Number of subjects	2116	1261	3377
Visit 2 (week 0)			
N	2104 (100)	1254 (100)	3358 (100)
0-4	1840 (87.5)	1116 (89.0)	2956 (88.0)
5-9	232 (11.0)	124 (9.9)	356 (10.6)
10-14	32 (1.5)	14 (1.1)	46 (1.4)
15-19	0	0	0
>=20	0	0	0
Maximum total score post baseline until week 68			
N	2115 (100)	1260 (100)	
0-4	1320 (62.4)	753 (59.8)	
5-9	581 (27.5)	357 (28.3)	
10-14	154 (7.3)	96 (7.6)	
15-19	44 (2.1)	37 (2.9)	
>=20	16 (0.8)	17 (1.3)	
Subjects with positive score for question 9 at any time post baseline until week 68			
N	2115 (100)	1260 (100)	
Yes	74 (3.5)	66 (5.2)	
No	2041 (96.5)	1194 (94.8)	

Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.

PHQ-9: 9-item patient health questionnaire, N: Number of subjects, %: Percentages are based on subjects with an observation at the visit

Question 9: Thoughts that you would be better off dead, or of hurting yourself in some way.

Source: SCS, Table 2-68

In the semaglutide 1 mg arm in trial 4374, the proportions of subjects with maximum post-baseline PHQ-9 total scores were: 10-14 = 6.9%, 15-19 = 2.5%, and ≥ 20 = 0.8%. The proportion of subjects with any positive question 9 score was 5.8%.¹⁰⁷

Because of the difference in trial design, including a run-in period, the PHQ-9 data for trial 4376 were analyzed separately:¹⁰⁸

- At week 0, 10 subjects (1.3%) had a score between 10-14 and no subjects had a score ≥ 15 .
- At week 20 (after run-in period), 10 subjects (1.2%) had a score of 10-14 and 6 subjects (0.7%) had a score of 15-19. From week 0 until week 20, 1 subject ((b) (6) discussed with AEs and the C-SSRS above) answered yes to question 9 'Thoughts that you would be better off dead or of hurting yourself in some way'.
- After randomization at week 20 until week 68, the proportion of subjects with maximum scores of 10-14 (semaglutide 2.3% vs. placebo 8.8%), 15-19 (0.4% vs. 3.1%), and ≥ 20 (0 vs. 1.5%) were not higher in the semaglutide 2.4 mg group compared to the placebo group. Of the 12 subjects in the placebo group with maximum scores of 15-19 and ≥ 20 at any visit

¹⁰⁷ Source: Study 4374 CSR, Table 14.3.6.11

¹⁰⁸ Source: Study 4376, Tables 14.3.6.9 and 12-30

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

during the randomized period, 11 had scores < 15 at week 20. Of these 11 subjects, the shifts to scores ≥ 15 appeared to mostly occur towards the end of the randomized period.

- Six subjects (1.1%) in the semaglutide 2.4 mg group answered yes to question 9 compared to 5 subjects (1.9%) in the placebo group.

In summary, patients in this population are at risk for psychiatric disorders, although based on the clinical trial data, there does not appear to be an increased risk with use of semaglutide.

Blinded Data

Blinded data as reported in the NDA and 120-day safety update identified 4 subjects in the SELECT CVOT with fatal events of suicide (1 suicide attempt and 3 completed suicides that were listed as fatal events). As the events are blinded, an assessment of suicide with semaglutide cannot be completed at this time.

8.5.10. Gastrointestinal Disorders

Gastrointestinal (GI) disorders with GLP-1 RAs are well-characterized adverse events and are known to be dose-/exposure-dependent and the primary cause for premature discontinuation. Most consequences of GI disorders are symptomatic (e.g., nausea, vomiting, and diarrhea), but particularly in vulnerable populations, can lead to volume depletion, dehydration, and renal insufficiency. Other potential risks could include electrolyte disturbances and orthostasis/syncope. These events are more commonly reported during the dose-escalation period; the 16-week dose-escalation paradigm is intended to mitigate some of the GI symptoms associated with dose-escalation. Additionally, constipation was prominent in this program and was a frequent AE in other GLP-1 programs.

Trial 4153

In the phase 2 dose-ranging trial, the proportions of subjects reporting AEs and the rate of AEs in the SOC 'Gastrointestinal disorders' increased with increasing doses in the semaglutide arms and were higher at all dose levels compared to placebo (Table 157). In particular, the incidence and rate of serious and severe AEs, and AEs leading to discontinuation increased to a greater extent at doses of semaglutide 0.4 mg SC once daily and the 2 fast dose-escalation arms. The rate of events with liraglutide 3 mg was similar to that of the semaglutide 0.2 mg or 0.3 mg arms.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 157: Gastrointestinal AEs, Study 4153, On-Treatment

	Semaglutide														Lira		Placebo	
	0.05		0.1		0.2		0.3		0.4		0.3F		0.4F		N	PYO	N	PYO
	N	PYO	N	PYO	N	PYO	N	PYO	N	PYO	N	PYO	N	PYO				
	103	99.6	102	106.3	103	105.4	103	105.5	102	103.1	102	96.7	103	107.6	103	105.5	136	131.9
n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	n (%)	E (R)	
GI AEs	64 (62.1)	152 (1.53)	72 (70.6)	249 (2.34)	72 (69.9)	311 (2.95)	72 (69.9)	263 (2.49)	84 (82.4)	343 (3.33)	84 (82.4)	335 (3.47)	78 (75.7)	335 (3.11)	77 (74.8)	256 (2.43)	52 (38.2)	107 (0.81)
SAEs	1 (1.0)	1 (0.01)	1 (1.0)	1 (0.01)	1 (1.0)	1 (0.01)	1 (1.0)	1 (0.01)	3 (2.9)	4 (0.04)	2 (2.0)	3 (0.03)	1 (1.0)	1 (0.01)	0	0	1 (0.7)	1 (0.01)
Severe	3 (2.9)	4 (0.04)	3 (2.9)	5 (0.05)	6 (5.8)	11 (0.10)	6 (5.8)	7 (0.07)	9 (8.8)	14 (0.14)	8 (7.8)	13 (0.13)	8 (7.8)	13 (0.12)	7 (6.8)	10 (0.09)	0	0
D/C	6 (5.8)	9 (0.09)	5 (4.9)	5 (0.05)	3 (2.9)	7 (0.07)	4 (3.9)	4 (0.04)	13 (12.7)	17 (0.16)	12 (11.8)	21 (0.22)	8 (7.8)	13 (0.12)	4 (3.9)	8 (0.08)	2 (1.5)	2 (0.02)

D/C = AEs leading to discontinuation
E=number of events
R=rate per patient-years
Lira=liraglutide

Source: Study 4153 CSR, Table 12-11

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Phase 3 Trials

This section reviews GI disorders identified in the pre-defined MedDRA search.¹⁰⁹ Table 158 presents a summary of GI AEs for the phase 3 trials individually, as well as for the dose-escalation group (trials 4373, 4374, and 4375; this group is being focused on in this section to evaluate GI AE frequency and timing).

¹⁰⁹ SOC Gastrointestinal disorders, primary terms only

Table 158: Gastrointestinal AEs in the Phase 3 Dose-Escalation Group and by Trial, On-Treatment Period

	Semaglutide 2.4 mg	Semaglutide 1 mg	Placebo
Phase 3 dose-escalation group	N=2116		N=1261
AEs	1562 (72.9)		581 (47.1)
SAEs	26 (1.3)		5 (0.4)
Severe	91 (4.1)		11 (0.9)
D/C	90 (4.3)		9 (0.7)
Trial 4373	N=1306		N=655
AEs	969 (74.2)		314 (47.9)
SAEs	18 (1.4)		0
Severe	58 (4.4)		4 (0.6)
D/C	59 (4.5)		5 (0.8)
Trial 4374	N=403	N=402	N=402
AEs	256 (63.5)	231 (57.5)	138 (34.3)
SAEs	6 (1.5)	3 (0.7)	3 (0.7)
Severe	9 (2.2)	7 (1.7)	4 (1.0)
D/C	17 (4.2)	14 (3.5)	4 (1.0)
Trial 4375	N=407		N=204
AEs	337 (82.8)		129 (63.2)
SAEs	2 (0.5)		2 (1.0)
Severe	24 (5.9)		3 (1.5)
D/C	14 (3.4)		0
Trial 4376 – run-in	N=902		
AEs	644 (71.4)		
SAEs	2 (0.2)		
Severe	15 (1.7)		
D/C	44 (4.9)		
Trial 4376 – randomized	N=535		N=268
AEs	224 (41.9)		70 (26.1)
SAEs	1 (0.2)		4 (1.5)
Severe	11 (2.1)		5 (1.9)
D/C	2 (0.4)		4 (1.5)
D/C = AEs leading to permanent treatment discontinuation			

Source: SCS, Table 2-15; Study 4373 CSR, Table 14.3.1.25; Study 4374 CSR, Table 14.3.1.25; Study 4375 CSR, Table 14.3.1.25; Trial 4376 CSR, Tables 14.3.1.33 and 14.3.1.34

In the phase 3 dose-escalation group, the GI AEs reported in the highest proportion of subjects in the semaglutide 2.4 mg arm were nausea (semaglutide 43.9% vs. placebo 16.1%), diarrhea (29.7% vs. 15.9%), vomiting (24.5% vs. 6.3%), constipation (24.2% vs. 11.1%), and abdominal

pain¹¹⁰ (19.7% vs. 10.0%). The proportion of subjects reporting gastritis¹¹¹ (sema 3.6% vs. placebo 1.3%) and hemorrhoids (2.1% vs. 0.4%) was also was also higher in the semaglutide 2.4 mg arm versus the placebo arm.

In the run-in period of trial 4376 (during dose-escalation), the GI AEs reported in the highest proportion of subjects were nausea (46.8%), diarrhea (23.5%), constipation (22.2%) and vomiting (15.5%). In the randomized portion of trial 4376, the most frequent GI AEs were diarrhea (semaglutide 14.4% vs. placebo 7.1%), nausea (14.0% vs. 4.9%), constipation (11.6% vs. 6.3%), and vomiting (10.3% vs. 3.0%).

Serious GI AEs were reviewed. ‘Vomiting’ and ‘Abdominal pain’ were the most frequently reported SAE by PT. Other SAEs of note, for which there was an imbalance not favoring (greater occurrence in) semaglutide-treated subjects include non-infectious inflammatory conditions such as colitis, as well as hiatus hernia. The numbers are small; however, a relationship to semaglutide is plausible. Although appendicitis is not included in the ‘Gastrointestinal disorders’ SOC, it is also plausibly related to semaglutide and an imbalance was noted. See Section 8.4.2, Serious Adverse Events. Acute pancreatitis is discussed separately in Section 8.5.2.

Table 159: Gastrointestinal SAEs, Dose-Escalation Group

	Semaglutide 2.4 mg N=2116 n (unadj. %)	Placebo N=1261 n (unadj. %)
GI SAEs	26 (1.3)	5 (0.4)
Gastrointestinal signs and symptoms (HLGT)	9 (0.4)	0
Vomiting (PT)	6 (0.3)	0
Abdominal pain (PT)	4 (0.2)	0
Gastrointestinal inflammatory conditions (HLGT)	5 (0.2)	0
Colitis (PT)	2 (0.1)	0
Colitis ischemic (PT)	1 (<0.1)	0
Enteritis (PT)	1 (<0.1)	0
Gastritis (PT)	1 (<0.1)	0
Gastrointestinal motility and defecation conditions (HLGT)	3 (0.1)	0
Constipation (PT)	1 (<0.1)	0
Diarrhea (PT)	1 (<0.1)	0
Esophageal achalasia (PT)	1 (<0.1)	0
Abdominal hernias and other abdominal wall conditions (HLGT)	3 (0.1)	2 (0.2)
Hiatus hernia (PT)	2 (0.1)	0
Abdominal hernia (PT)	1 (<0.1)	0

¹¹⁰ Grouped PTs: Abdominal pain, Abdominal pain upper, Abdominal pain lower, Gastrointestinal pain, Abdominal tenderness, Abdominal discomfort, Epigastric discomfort

¹¹¹ Grouped PTs: Gastritis, Chronic gastritis, Reflux gastritis, Gastritis erosive

	Semaglutide 2.4 mg N=2116 n (unadj. %)	Placebo N=1261 n (unadj. %)
Inguinal hernias (HLT)	0	2 (0.2)
Gastrointestinal conditions NEC (HLGT)	2 (0.1)	0
Exocrine pancreas conditions (HLGT)	2 (0.1)	1 (0.1)
Gastrointestinal stenosis and obstruction (HLGT)	2 (0.1)	1 (0.1)
Gastrointestinal ulceration and perforation (HLGT)	2 (0.1)	1 (0.1)
Gastrointestinal hemorrhages NEC (HLGT)	1 (<0.1)	0
Gastrointestinal vascular conditions (HLGT)	1 (<0.1)	0

Note: this is an exploratory analysis and percentages are unadjusted

Source: Reviewer created from ISS ADAE.xpt dataset

Narratives of selected SAEs were reviewed, including the following SAE of interest:

- NN9536-4373/ (b) (6) (semaglutide 2.4 mg): 'Large intestine perforation': This was a 48-year-old female subject with BMI of 29 kg/m² with a history of depression, dyslipidemia, and previous hysterectomy who presented to her PCP after approximately 11 months in the trial reporting right lower quadrant abdominal pain, nausea, and vomiting. She was diagnosed with a urinary tract infection and given unspecified antibiotics. She developed constipation and continued to feel worse over the next several days and presented to the ER, where an CT scan of the abdomen and pelvis showed free intraperitoneal air, free fluid, wall thickening of the sigmoid colon, mesenteric inflammatory changes, and small bowel distension. She was diagnosed with stercoral perforation due to impacted stool. The subject had a partial colectomy with colostomy performed and admission to the ICU semaglutide was discontinued. The subject was discharged from the hospital after 2 weeks and had the stoma closed 3 months later.

Reviewer comment: Although it was stated in the narrative that no AEs were reported for this subject in the 11 months prior to this event, given that semaglutide can be associated with GI AEs including constipation, the relationship to semaglutide cannot be completely dismissed. The unspecified antibiotic treatment for the urinary tract infection may have played a role as well.

As noted in Table 158, in trial 4376, 2 subjects in the run-in period and 1 subject treated with semaglutide in the randomized portion of the trial reported an SAE from the GI disorders SOC:

- The SAEs in the subjects in the run-in period were both reported as abdominal pain; neither SAE led to changes in dosing of trial product.
- In the randomized period, 3 events were reported in 1 subject (0.2%) in the semaglutide 2.4 mg group and 4 events in 4 subjects (1.5%) in the placebo group.

- The 3 events in the subject in the semaglutide group (abdominal pain, vomiting, nausea) were related to an event of cholelithiasis.
- In the placebo group, the 4 SAEs were: abdominal pain (appeared to be related to gallstone disease within 1 to 2 months after randomization to placebo), diverticular perforation (6 months after randomization to placebo), constipation (11 months after randomization to placebo), and intestinal obstruction (4 months after randomization, likely related to cancer; see narrative for fatal event for subject ID (b) (6), under Section 8.4.1).

A gastrointestinal issue that has been evaluated for other GLP-1 RAs, including liraglutide, is delayed gastric emptying/gastroparesis. GLP1 RAs are known to delay gastric emptying. An exploratory search was conducted of the phase 3 trial data with the PT: 'Impaired gastric emptying.' No SAEs were reported. In the phase 3 pool, 2 subjects randomized to semaglutide 2.4 mg and 1 subject randomized to placebo reported moderate AEs of impaired gastric emptying; both semaglutide subjects permanently discontinued treatment due to the AEs. None of the events were reported from subjects in trial 4374, the T2D trial. In addition, 3 subjects reported mild AEs of impaired gastric emptying in the semaglutide run-in period of trial 4376. In all these cases, dosing was not changed as a result of the events.

So far, this reviewer is aware of 2 subjects in the ongoing CVOT with gastroparesis reported as 15-day safety reports to IND 126360.¹¹²

- An 80-year-old male with BMI of 32.2 kg/m², sleep apnea syndrome, coronary heart disease, hypertension, and heart failure with preserved ejection fraction reported abdominal pain and constipation after 1 month in the trial. Three days later, he reported he was no longer constipated, but abdominal pain continued, and he was admitted to the hospital. CT scan showed distended stomach and abnormal thickening of the lower esophagus suggestive of gastric outlet obstruction (either mechanical or functional) and reflux esophagitis. The subject was subsequently transferred to another hospital and after an appropriate period of fasting, the subject underwent an upper endoscopy. This revealed that despite fasting, there was still a large amount of material in the stomach, which lead to aspiration of gastric contents into the lungs. The subject was diagnosed with severe gastroparesis as well as aspiration pneumonia requiring ventilation in the intensive care unit. Endoscopy biopsy showed esophagitis and gastritis with no evidence of gastric outlet obstruction. The study drug was discontinued.
- A 77-year-old female with a BMI of 29.3 kg/m², interstitial lung disease, hyperlipidemia, kidney stones, coronary heart disease, hypertension, and heart failure NYHA class I was also

¹¹² Randomization was unblinded: both patients were treated with semaglutide

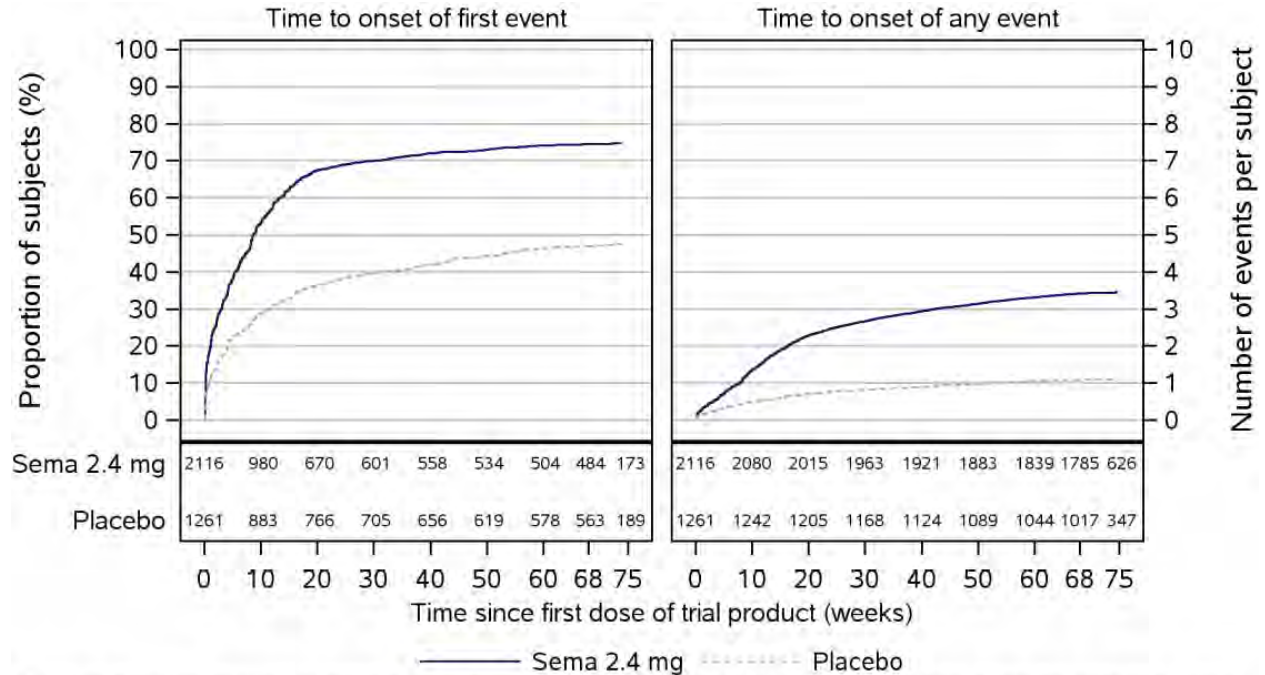
Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

reported to have a history of vomiting since 1995 and nausea since 2003 on and off. The investigator also reported that nausea and vomiting began 2 months prior to the start of the trial. After approximately 2 months in the trial the subject had an onset of gastroparesis, diagnosed after visiting the ER with complaints of nausea and vomiting for 3 weeks. She was hospitalized for evaluation of dehydration and temporarily discontinued drug for approximately 1 week. Approximately 1 month later a gastric study showed significant delay in gastric emptying. She was treated with metoclopramide. Drug was permanently discontinued approximately 1 month later.

Reviewer comment: Semaglutide may be associated with gastroparesis, particularly in vulnerable patients. However, this assessment is relying on single cases from an ongoing CVOT (for which a full assessment is not available at this time); significant gastroparesis was not reported in the weight management clinical program.

Figure 86 and Figure 87, below, illustrate the timing and prevalence of GI AEs during the trials in the phase 3 dose-escalation group. The left panel of Figure 86 suggests that the majority of first reported GI AEs occurred during the dose-escalation period (initial 20 weeks), and then after week 20 the reporting paralleled that of placebo. The right panel, which is the time to onset of any event, suggests that subjects treated with semaglutide reported more GI events than placebo throughout the trials.

Figure 86: Gastrointestinal AEs, Time-to-Onset, Phase 3 Dose-Escalation Group, On-Treatment



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.

Numbers shown in the lower panel are subjects at risk.

Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

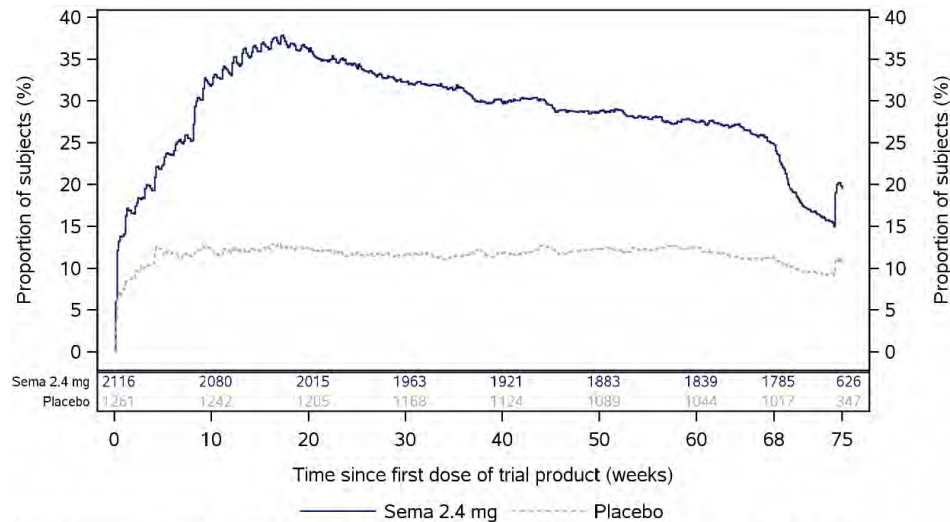
MedDRA version 22.1

nn9536/nn9536-summary/subm_iss_20201001_er
 255EP2020:10:29:18 - faetimeplot.sas/faegitimeplotot.png

Source: SCS, Figure 2-14

Figure 87 shows that the prevalence of GI AEs was higher with semaglutide than placebo throughout the trials in the phase 3 dose escalation group.

Figure 87: Gastrointestinal AEs, Prevalence Plot, Phase 3 Dose-Escalation Group



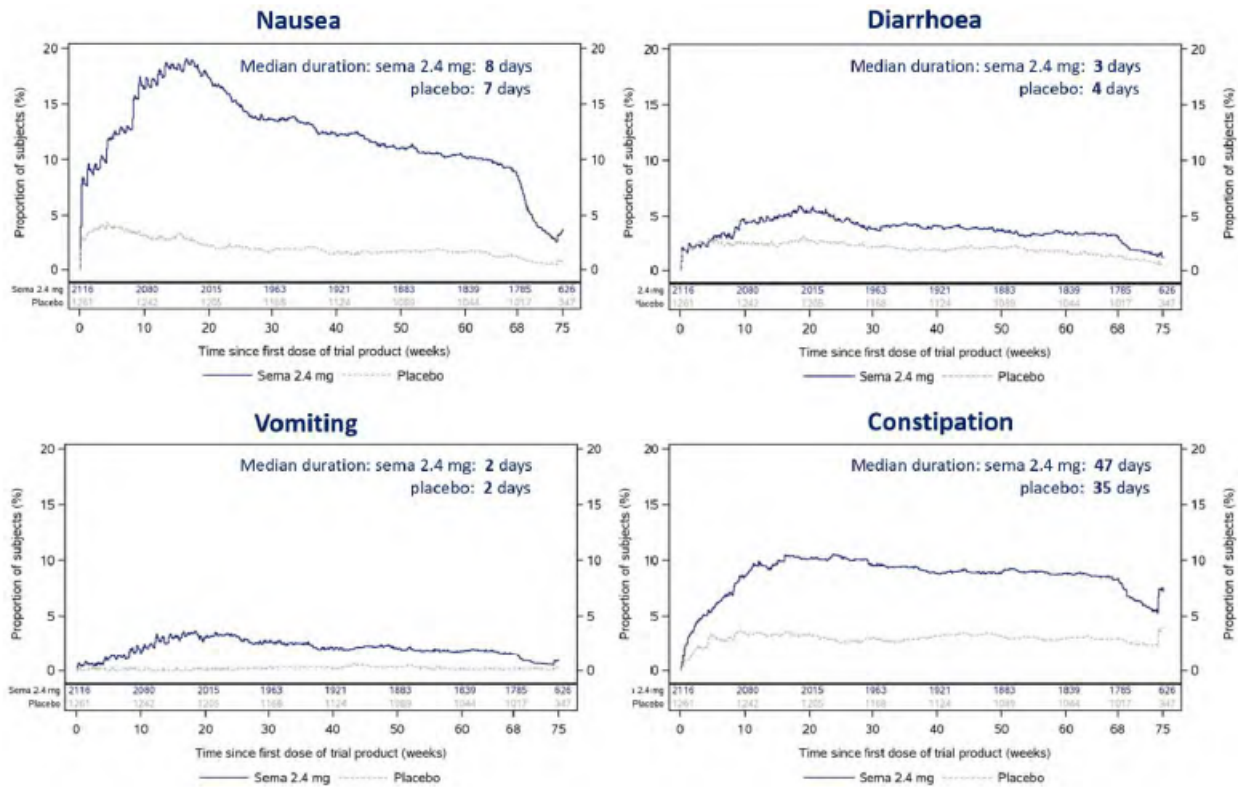
Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Numbers shown in the lower panel are subjects at risk.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
 MedDRA version 22.1

nn9536/nn9536-summary/summ_iss_20201001_er
 25SEP2020 10:28:09 - f5afprevalence.sas/faegjprevalencecot.png

Source: SCS, Figure 2-15

The prevalence of the most common GI AEs, with the median AE duration, is shown in Figure 88. Constipation was reported for the longest median duration of these GI AEs, with a median duration of 47 days in the semaglutide 2.4 mg arm and 35 days in the placebo arm.

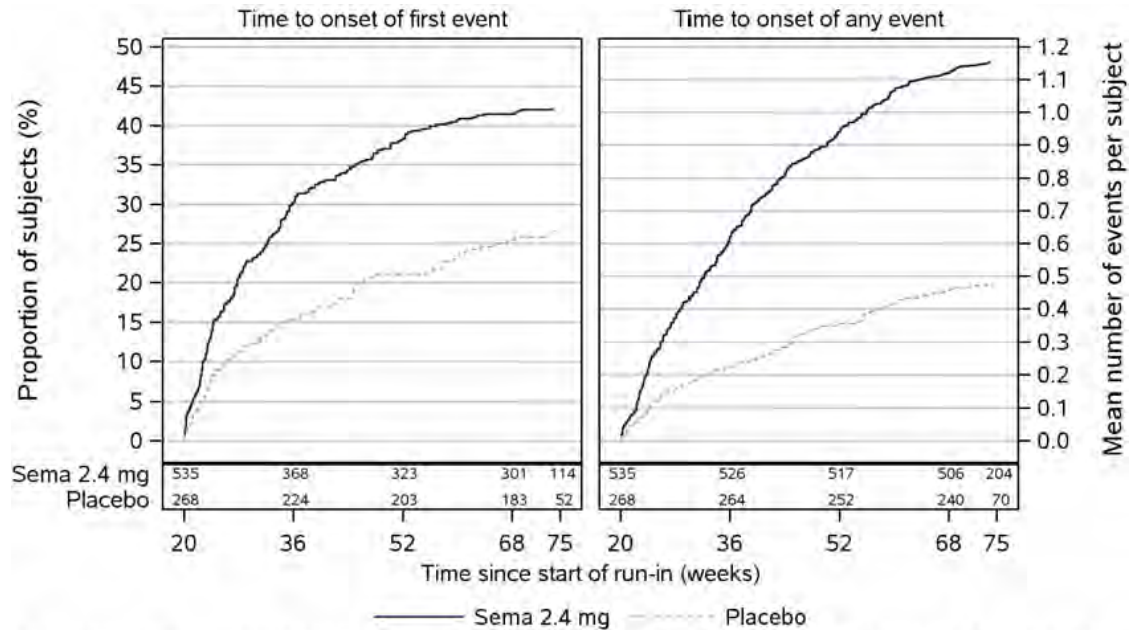
Figure 88: Timing and Duration of Common Gastrointestinal AEs, Phase 3 Dose-Escalation Group



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Semaglutide 2.4 mg or Placebo during the controlled periods of the trials. Numbers shown in the lower panels are subjects at risk. The event duration distribution was estimated using the Kaplan-Meier estimator. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days. MedDRA version 22.1.
 Source: SCS, Figure 2-16

In trial 4376, the proportion of subjects with GI AEs was higher with semaglutide 2.4 mg than with placebo after the semaglutide run-in period (Figure 89). Only AEs with onset during the randomized period were included. A prevalence plot by GI AE severity suggests that most of the imbalance of events in the randomized portion of trial 4376 were of mild severity (Figure 90).

Figure 89: Gastrointestinal AEs, Time-to-Onset, Randomized Period of Trial 4376, On-Treatment

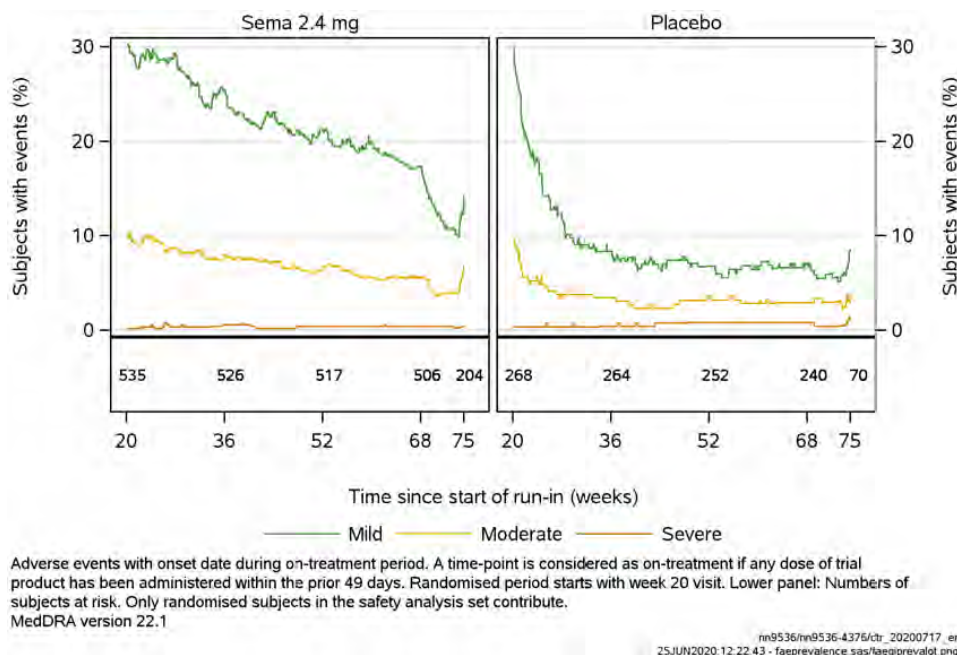


Adverse events with onset date during on-treatment period. A time-point is considered as on-treatment if any dose of trial product has been administered within the prior 49 days. Only AEs with onset in the randomised period included. Randomised period starts with week 20 visit. Lower panels: At risk tables. Only randomised subjects in the safety analysis set contribute. MedDRA version 22.1

nn9536/nn9536-4376/ctr_20200717_er
 25JUN2020.12:23:02 - faet/imeplot.sas/faegitimeplot.png

Source: Study 4376 CSR, Figure 14.3.1.36

Figure 90: Gastrointestinal AEs by Severity, Prevalence Plot, Randomized Period of Trial 4376, On-Treatment



Source: Study 4376 CSR, Figure 14.3.1.37

In summary, gastrointestinal AEs were the most commonly reported AEs in semaglutide-treated subjects, generally appear dose-dependent, and as discussed in Section 8.4.3, the most likely group of AEs to lead to drug discontinuation. However, most GI AEs were not serious, were of mild or moderate severity, and did not lead to study drug discontinuation. The most frequently reported AEs were nausea, diarrhea, vomiting, and constipation. There was a case of severe constipation associated with perforation but the link to semaglutide is somewhat unclear. Other infrequent serious or severe GI events can occur with semaglutide likely as a result of delays in gastric emptying or constipation. In previous sections of this review, rare cases of GI AEs potentially masking conditions such as cancer have been raised. Severe volume depletion and/or dehydration from vomiting and diarrhea can lead to renal impairment; this is discussed further in Section 8.5.6 and labeling should address this concern. Most symptomatic events appear to be self-limited.

8.5.11. Rare Events

The applicant has identified events that are potentially likely to be drug-related if identified but could also be obscured by their rarity; a number of MedDRA searches were employed to identify potential events of interest.¹¹³ The results of this search are shown in Table 160 below.

¹¹³ Custom query (NNMQ Rare events) excluding events that are included in other safety focus areas:

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Because the events as a group do not capture or suggest a single syndrome or safety concept, they are presented by SOC and PT, but not overall. (In particular, regarding congenital disorders, unless the AE occurred in the setting of a pregnancy, the likelihood that these are treatment-related seems low.)

SMQ Agranulocytosis, narrow terms only; SMQ Guillain-Barre syndrome, narrow terms only; SMQ Hematopoietic cytopenias affecting more than 1 type of blood cell, broad and narrow terms; SMQ Hematopoietic leukopenia, broad and narrow terms; SMQ Hematopoietic thrombocytopenia, narrow terms only; SMQ Interstitial lung disease, narrow terms only; SMQ Neuroleptic malignant syndrome, narrow terms only; SMQ Pseudomembranous colitis, narrow terms only; SMQ Retroperitoneal fibrosis, narrow terms only; SOC Congenital, familial and genetic disorders, (all terms are primary PTs); HLT Angioedemas, primary and secondary routed PTs; HLT Glomerulonephritis and nephrotic syndrome, primary and secondary routed PTs; HLT Nephritis NEC, primary and secondary routed PTs; Additional PTs: Disseminated intravascular coagulation, Hepatic lymphocytic infiltration, Multiple organ dysfunction syndrome

Table 160: "Rare Events" by Pre-Defined MedDRA Search, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg N=2650	Placebo N=1529
Blood and lymphatic system disorders	8 (0.3)	5 (0.3)
Thrombocytopenia	4 (0.1)	5 (0.3) ^a
Pancytopenia	2 (<0.1)	1 (<0.1)
Leukopenia	2 (<0.1)	0
Congenital, familial and genetic disorders	5 (0.2)	3 (0.2)
Type V hyperlipidemia	2 (<0.1)	0
Carpus curvus	1 (<0.1)	0
Gilbert's syndrome	1 (<0.1)	0
Arnold-chiari malformation	1 (<0.1)	0
Phimosis	0	1 (<0.1)
Urachal abnormality	0	1 (<0.1) ^a
Renal and urinary disorders	3 (0.1)	0
Hydronephrosis	3 (0.1)	0
Respiratory, thoracic and mediastinal disorders	2 (<0.1)	0
Idiopathic interstitial pneumonia	1 (<0.1)	0
Pulmonary fibrosis	1 (<0.1)	0
Investigations	2 (<0.1)	0
Platelet count decreased	2 (<0.1)	0
Infections and infestations	1 (<0.1)	0
Clostridium difficile colitis ^b	1 (<0.1)	0
Neutropenic sepsis	0	1 (<0.1)
a "Rare disorders" that occurred in the placebo arm in trial 4376 (and therefore were exposed to semaglutide during the run-in period) were 1 subject with thrombocytopenia and 1 subject with urachal abnormality. The thrombocytopenia event occurred in a 78-year-old female on trial day 477 (i.e., after last dosing, which was day 470); the platelet assessment was 122 x10⁹/L (normal range: 150-400 x10⁹/L). The urachal abnormality occurred in a 29-year-old woman on trial day 182 (approximately 42 days after randomization). She also had an AE of urogenital disorder on study day 134 (on semaglutide), as well as a second AE of urachal abnormality on day 524, occurring after last dosing and treated with flucloxacillin. b Note that there was also an event of C. diff colitis in a subject in the semaglutide 1 mg arm in trial 4374. The narrative is included below.		

Source: SCS, Table 2-69

Three events were serious; 1 event each of hydronephrosis and pancytopenia in subjects treated with semaglutide 2.4 mg, and 1 event of neutropenic sepsis in a subject randomized to placebo (in trial 4373).

Brief narratives for selected AEs in the semaglutide-treated subjects are below (note that non-serious AE narratives have limited information):

- NN9536-4373/ (b) (6) Pulmonary fibrosis: This was a 38-year-old female who had a non-serious AE of pulmonary fibrosis on day 264. A non-serious AE of granulomatous liver disease was also reported on the same day. The investigator judged the severity as mild. The event was not recovered. The subject did not have changes in dosing of trial product.

- NN9536-4374/ (b) (6) Idiopathic interstitial pneumonia: This was a 76-year-old woman who had a non-serious AE of idiopathic interstitial pneumonia on trial day 141. She had a history of treatment with atorvastatin. The investigator judged the severity as mild. The event was not recovered. The subject did not have changes in dosing of trial product.

Reviewer comment: Not enough information is available to assess causality for idiopathic interstitial pneumonia (an umbrella diagnosis that can include idiopathic pulmonary fibrosis) based on these 2 cases. Drugs have been associated with idiopathic interstitial pneumonia, including statins.¹¹⁴ To my knowledge, GLP-1 RAs, including semaglutide, have not to date been associated with idiopathic interstitial pneumonia.

- NN9536-4373/ (b) (6) Hydronephrosis: This was a 51-year-old male who had a non-serious AE of hydronephrosis in association with an SAE of nephrolithiasis and an AE of ureterolithiasis on trial day 46. The subject did not have changes in dosing of trial product.
- NN9536-4375 (b) (6) Hydronephrosis: This was a 49-year-old female with a history of uterine fibroids, who had SAEs of hydronephrosis and uterine leiomyoma after approximately 4 months on treatment (diagnosed on ultrasound). She received an elective hysterectomy approximately 5 months later. There was no change to trial drug administration, except for temporary pause in anticipation of surgical procedure. Approximately 1 year after the onset of hydronephrosis, the event was reported as recovering/resolving.
- NN9536-4376 (b) (6) Hydronephrosis: This was a 62-year-old female who had a non-serious event of hydronephrosis on day 360. Of note, an AE of nephrolithiasis was reported 3 days prior. After a duration of 18 days, the outcome was reported as recovered. The subject did not have changes in dosing of trial product.

Reviewer comment: These events of hydronephrosis were associated with other conditions and appear unlikely related to semaglutide.

- NN9536-4373 (b) (6) Thrombocytopenia: This was a 51-year-old male who had a non-serious AE of thrombocytopenia in association with an SAE of bacterial colitis on trial day 117. Platelet count at the time of the AE is not available, but platelet counts at other times in the trial were: screening=163 x10⁹/L, week 20=147 x10⁹/L, additional assessment (day 169)=118 x10⁹/L, week 52=148 x10⁹/L, week 68=171 x10⁹/L (normal range: 150-400 x10⁹/L). The subject did not have changes in dosing of trial product.

¹¹⁴ www.uptodate.com Causes, clinical manifestations, evaluation, and diagnosis on nonspecific interstitial pneumonia. Accessed 16 Mar 2021.

- NN9536-4374/ (b) (6) Platelet count decreased: This was a 57-year-old male who had a non-serious AE of platelet count decreased on trial day 371 ($73 \times 10^9/L$, normal range: $150-400 \times 10^9/L$). Values during the trial were as follows: screening= $150 \times 10^9/L$, week 20= $196 \times 10^9/L$, week 52 (day 367)= $73 \times 10^9/L$, week 68= $221 \times 10^9/L$. The subject did not have changes in dosing of trial product. Of note, the subject did have a single episode of positive ADAs reported ~10 months prior to the platelet count of $73 \times 10^9/L$. He was ADA negative at the time of this decreased platelet count.
- NN9536-4374/ (b) (6) Pancytopenia: This was a 73-year-old male with a history of hemolytic anemia, who had a non-serious AE of pancytopenia on trial day 435. Of note, the subject had an SAE of myeloid leukemia with onset on day 371, which led to permanent discontinuation of trial product on day 442. The last available laboratory values in the trial were from week 52: neutrophils $1.19 \times 10^9/L$ (ref: 1.80-7.00), lymphocytes $0.54 \times 10^9/L$ (ref: 1.20-4.00), hemoglobin 10.6 g/dL (ref: 13.2-17.0), and platelets $131 \times 10^9/L$ (ref: 150-400).
- NN9536-4375/ (b) (6) Platelet count decreased: This was a 33-year-old woman who had a non-serious AE of platelet count decreased. Prior to the AE (trial day 308), the subject had sinusitis and pharyngitis streptococcal. Values during the trial were as follows: screening= $227 \times 10^9/L$, week 20= $217 \times 10^9/L$, week 52 (day 368)= $80 \times 10^9/L$, additional assessment (day 403)= $209 \times 10^9/L$, week 68= $221 \times 10^9/L$ (ref: 150-400). The subject did not have changes in dosing of trial product and the event resolved after 36 days.
- NN9536-4375/ (b) (6) Leukopenia: This was a 46-year-old female who had 2 non-serious events of leukopenia reported, 1 on day 143 (moderate severity, recovered) and 1 on day 367 (mild severity, not recovered). The subject had AEs of anemia and leukopenia reported during the screening period. Values during the trial were as follows: screening= $3 \times 10^9/L$, week 20= $3 \times 10^9/L$, additional assessment (day 143)= $5 \times 10^9/L$, week 52 (day 365)= $4 \times 10^9/L$, additional assessment (day 395)= $4 \times 10^9/L$ (ref: 4-11). The subject's last day of trial dosing was day 449 and she was lost to follow-up on day 476.
- NN9536-4376/ (b) (6) Thrombocytopenia: This was a 25-year-old male who had a non-serious AE of thrombocytopenia on the last day of dosing, day 475 (week 68). After a duration of 15 days, the outcome was reported as recovered. Platelet count on day 475 was $70 \times 10^9/L$ (normal range: $150-400 \times 10^9/L$). The subject reported an AE of influenza, approximately 1 month before the onset of thrombocytopenia.
- NN9536-4376/ (b) (6) Thrombocytopenia: This was a 39-year-old female who had a non-serious AE of thrombocytopenia on day 139. The platelet count on day 139 was $138 \times 10^9/L$ (ref: 150-400). Values during the trial were as follows: screening= $151 \times 10^9/L$, week 20 (day

139)=138 x10⁹/L, additional assessment (day 202)=145 x10⁹/L, week 52 (day 368)=137 x10⁹/L, week 68=122 x10⁹/L. The subject did not have changes in dosing of trial product.

- NN9536-4376 (b) (6) Thrombocytopenia: This was a 41-year-old male who had a non-serious AE of thrombocytopenia on trial day 483 (i.e., after last day of dosing, day 478). The platelet count at week 68 was 97 x10⁹/L (ref: 150-400). After a duration of 24 days, the event was reported as recovered. On day 506, the platelet count was 276 x10⁹/L. The subject reported a traumatic hematoma 5 days before the onset of thrombocytopenia.
- NN9536-4376 (b) (6) Leukopenia: This was a 60-year-old female who had a non-serious event of leukopenia on trial day 369 (3 x10⁹/L; ref: 4-11). At screening and at week 68, leukocyte count was 4 x10⁹/L. Values were 3 x10⁹/L at other visits and assessments. The subject had no changes to dosing of trial product.
- NN9536-4376 (b) (6) Pancytopenia: This was a 66-year-old female who had an SAE of pancytopenia after 1 year on treatment. Drug was discontinued as a result of the event. Laboratory values were as follows:

CMV (Test Name: Cytomegalovirus test), Comments: Positive finding.
Ferritin (Test Name: Serum ferritin), Results: 4.0 ng/mL, Norm High: 291, Norm Low: 10.
HCT (Test Name: Haematocrit), Results: 26.7 %, Norm High: 46.0, Norm Low: 35.0.
HGB (Test Name: Haemoglobin), Results: 8.7 g/dL, Norm High: 15.0, Norm Low: 11.7.
Iron (Test Name: Blood iron), Results: 24.0 µg/dL, Norm High: 145, Norm Low: 42.
MCV (Test Name: Mean cell volume), Results: 73.1 femtoliter, Norm High: 98.0, Norm Low: 80.0.
Non-acute Epstein-Barr (Test Name: Epstein-Barr virus test), Comments: Positive finding.
Parvo B19 (Test Name: Parvovirus B19 test), Comments: Positive finding.
Platelet count (Test Name: Platelet count), 116.0 K/uL, Norm High: 400, Norm Low: 150.
WBC (Test Name: White blood cell count), 2.1 K/uL, Norm High: 11.0, Norm Low: 3.5.

It was unknown when the subject was exposed to EBV, CMV, or Parvo B19.

Bone marrow biopsy was negative for aplastic anemia or myelodysplasia. Bone marrow was described as normocellular to hypercellular. Abdominal ultrasound to assess liver and spleen was reportedly negative.

The etiology was not apparent. The marked decrease to absence of stainable iron indicated a component of iron deficiency. The differential diagnosis included immune/autoimmune disorders, infections, vitamin/nutritional deficiencies, and drugs/toxins.

The subject continued to be monitored without resolution at the date of last visit (approximately 6 months after drug discontinuation).

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Reviewer comment: Most of the reported AEs of hematological disorders were associated with confounding factors and/or were resolved while the subject was still on drug. There is no clear association with semaglutide. See Section 8.4.6 for additional hematology discussion.

NN9536-4374 (b) (6) Clostridium difficile colitis: This was a 73-year-old male randomized to semaglutide 1 mg who had a non-serious AE of clostridium difficile colitis on trial day 311. It appears he had an AE of diverticulitis on day 290, and was treated on day 291 with ciprofloxacin and metronidazole. After a duration of 15 days the outcome was reported as recovered. The subject did not have changes in dosing of trial product.

NN9536-4376 (b) (6) Clostridium difficile colitis: This was a 52-year-old female who had a non-serious AE of clostridium difficile colitis on trial day 252. After a duration of 26 days and treatment with vancomycin, the outcome was reported as recovered. The subject did not have changes in dosing of trial product.

Reviewer comment: Subject (b) (6) was not reported to have been treated with antibiotics prior to this event. Changes to diet and the gastrointestinal AEs could change intestinal flora, so a potential contribution of the drug is unclear. The cause of the event in subject (b) (6) was likely antibiotic treatment for diverticulitis.

8.6. Safety Analyses by Demographic Subgroups

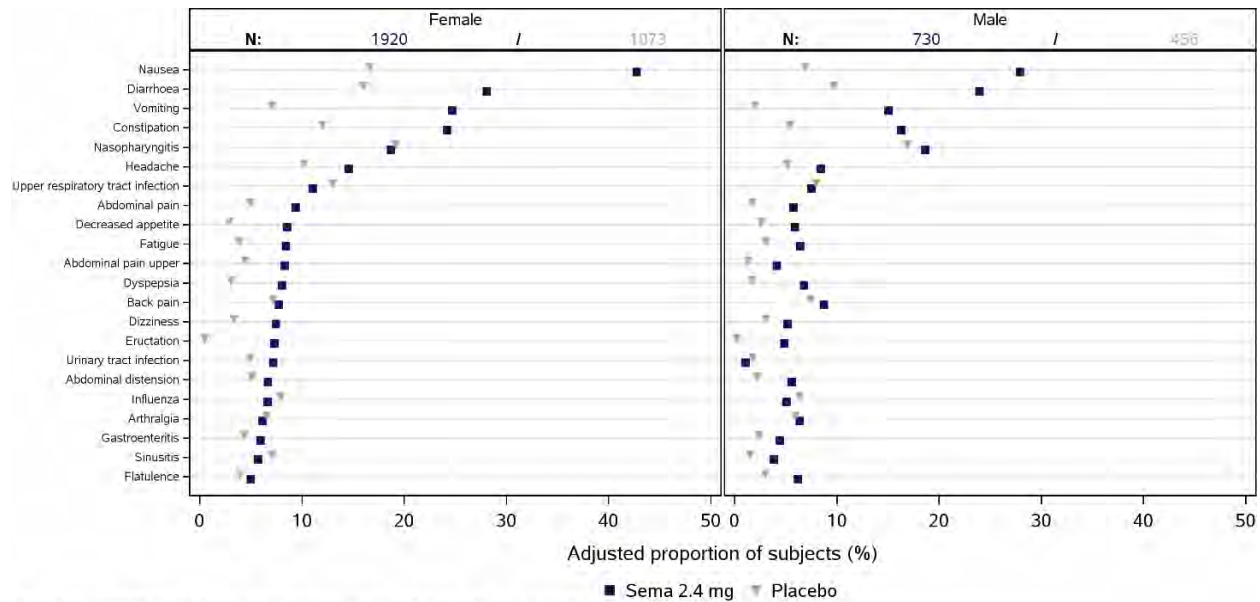
This section summarizes AEs by sex, baseline age, race, and ethnic origin (Hispanic/Latino or not Hispanic/Latino).

Sex

Overall, females were slightly more likely to experience AEs than males, in both treatment groups. The treatment difference in the proportions of subjects reporting AEs, SAEs, severe AEs, and AEs leading to permanent trial product discontinuation appeared comparable in males and females except for SAEs where the treatment difference (semaglutide – placebo) was larger in females than in males, partly due to a lower reporting of SAEs among females in the placebo group.

Greater treatment differences (semaglutide – placebo) of AEs for females versus males were seen for PTs such as nausea, vomiting, diarrhea, and constipation, decreased appetite, and headache and dizziness (Figure 91). The applicant postulates that these treatment differences are related to the lower body weight of females, which results in a higher semaglutide exposure. However, in a separate analysis of AEs by body weight, more pronounced treatment differences in gastrointestinal effects were not observed among subjects with the lowest body weight subgroup (< 90 kg); see Section 8.8.

Figure 91: Most Frequent AEs by Sex and PT, Phase 3 Pool, On-Treatment



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Adverse events with onset prior to randomisation are not included.
 Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms and if the preferred terms have been reported by 5 or more subjects.
 Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
 N: Number of subjects
 The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

nn9536/nn9536-summary/submit_iss_20201001_er
 25SEP2020 10:27:15 - faesummarygrp.sas/faesummary5pctsexot.png

Source: SCS, Figure 5-2

Baseline Age

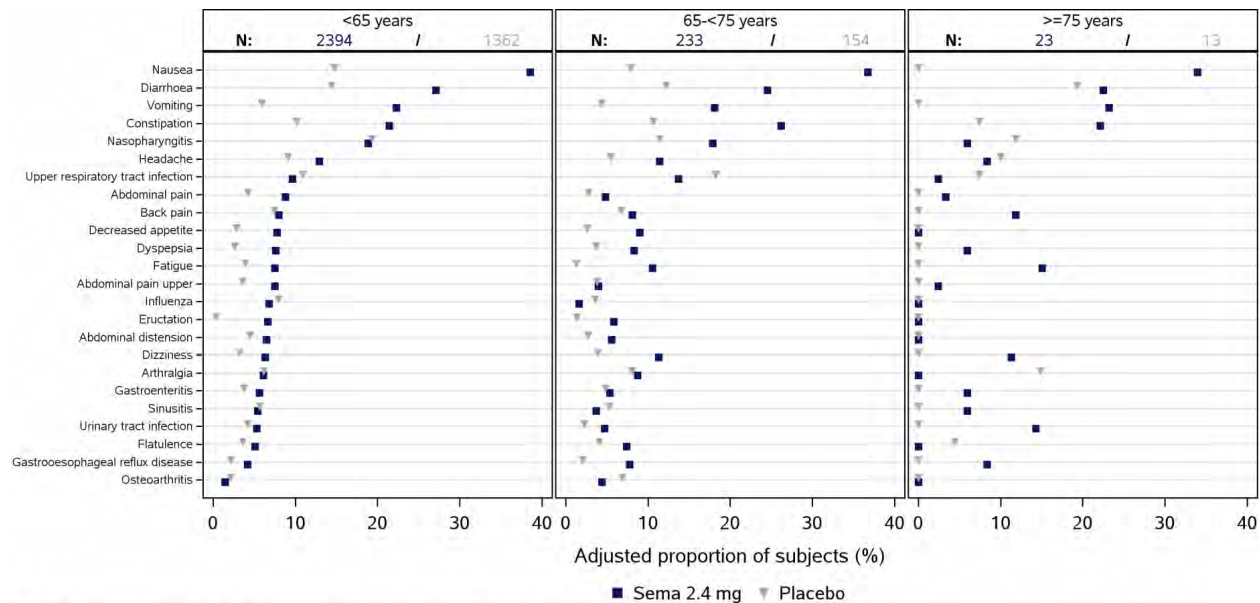
The majority of the phase 3 population was < 65 years, and only 23 subjects treated with semaglutide and 13 subjects treated with placebo were 75 years or older. In addition, half of the subjects with age ≥ 75 years were from trial 4374 (T2D trial). Nevertheless, the applicant evaluated the age groups in the categories of: < 65, 65 to < 75, and ≥ 75 years.

In both treatment groups, the proportions of subjects with AEs, SAEs, severe AEs, and AEs leading to permanent trial product discontinuation were higher in subjects with age 65 to < 75 years compared to subjects with age < 65 years. The treatment differences (semaglutide – placebo) were comparable except for AEs leading to permanent discontinuation of trial product where the treatment difference was larger in subjects with age 65 to < 75 years than in subjects with age < 65 years.

In subjects with age ≥ 75 years, fewer SAEs and severe AEs were reported with semaglutide 2.4 mg than with placebo. AEs leading to permanent discontinuation of trial product were only reported in the semaglutide 2.4 mg group (3 AEs in 3 subjects).

Treatment differences (semaglutide – placebo) of specific AEs by PT that were observed in the older age groups versus younger age groups included: nausea, vomiting, constipation, GERD, dizziness, and fatigue (Figure 92). Higher age groups reported fewer gastrointestinal AEs than the younger age group in the placebo group only. Subjects in the ≥ 75 years subgroup reported more urinary tract infection in the semaglutide group.

Figure 92: Most Frequent AEs by Baseline Age and PT, Phase 3 Pool, On-Treatment



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Adverse events with onset prior to randomisation are not included.
 Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms and if the preferred terms have been reported by 5 or more subjects.
 Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
 N: Number of subjects
 The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

nn9536/mn9536-summary/summ_iss_20201001_er
 25SEP2020 10:27:28 - faesummarygrp.sas/faesummary5pctageot.png

Source: SCS, Figure 5-4

Race

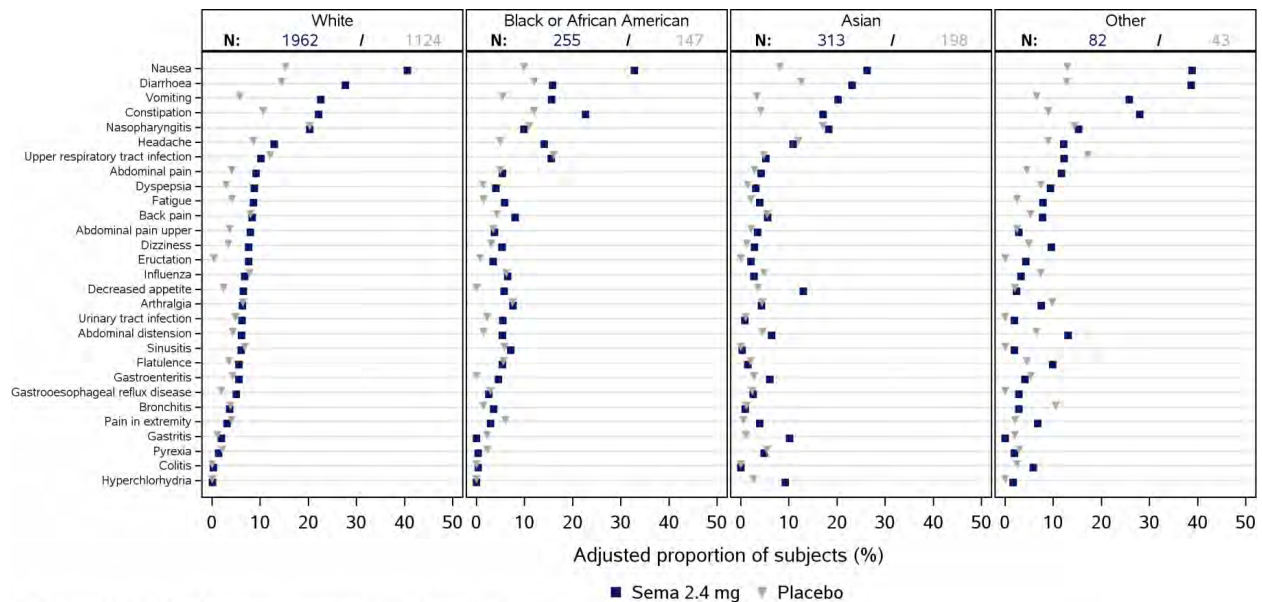
AEs by race were evaluated with the following categories: White, Black/African American, Asian, Other.¹¹⁵ Of note, Asian subjects were most frequently represented in trial 4374 (T2D), while Black/African American subjects were most frequently represented in trial 4375 (100% US). White subjects made up the largest proportion of the total population.

¹¹⁵ Including American Indian, Alaska Native, Native Hawaiian, Pacific Islander. For 55 subjects in France where the law prohibits the collection of information about race, race was reported as no applicable; data from this subgroup were not discussed in this analysis.

Treatment differences (semaglutide – placebo) appeared generally similar across the subgroups by race for AEs, SAEs, severe AEs, and AEs leading to permanent trial product discontinuation, although treatment differences observed for SAEs and severe AEs were not present among Asian subjects, and the treatment difference observed for AEs leading to permanent treatment discontinuation was not present among Blacks/African American subjects.

The most frequently reported AEs by PT are shown in Figure 93. Compared to other race subgroups, Asian subjects had more decreased appetite, gastritis, and hyperchlorhydria (semaglutide – placebo) and no treatment difference in headache, and Black/African American subjects had more headache and fewer gastrointestinal disorders (semaglutide – placebo), mostly due to lower reporting of AEs of diarrhea and vomiting in the semaglutide group.

Figure 93: Most Frequent AEs by Race, Phase 3 Pool, On-Treatment



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Adverse events with onset prior to randomisation are not included.
 Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms and if the preferred terms have been reported by 5 or more subjects.
 Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
 N: Number of subjects
 The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

m9536/mn9536-summary/submit_iss_20201001_er
 25SEP2020.10:27:39 - faesummarygrp.sas/faesummary5pctraceot.png

Source: SCS, Figure 5-6

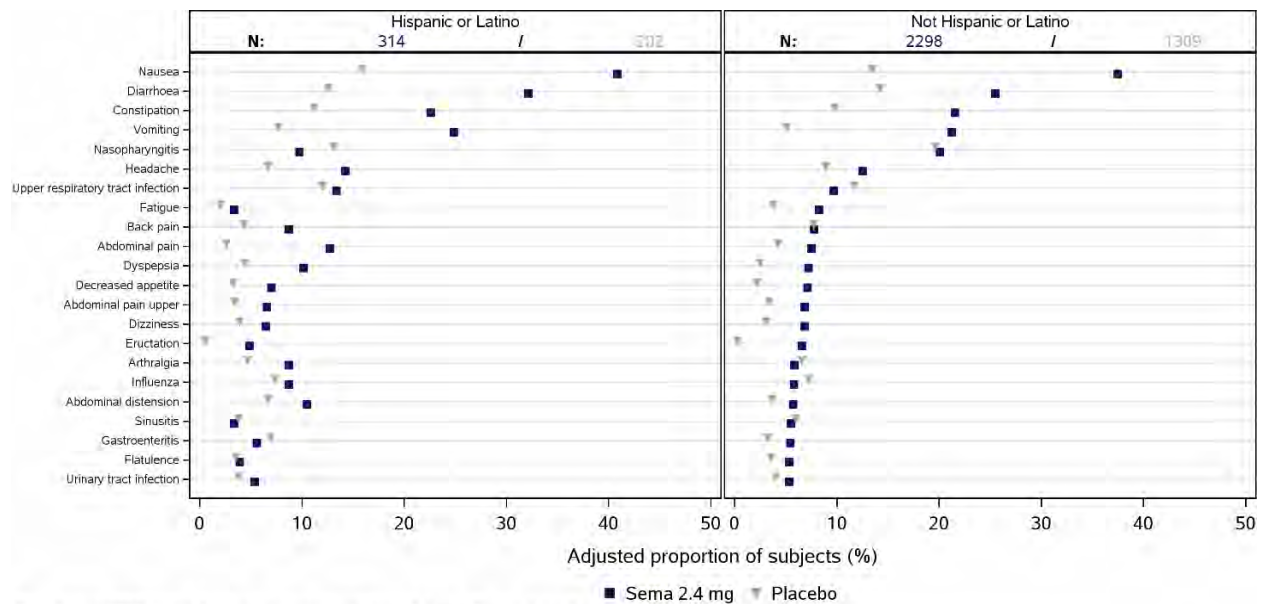
Ethnicity

This analysis evaluated AEs by ethnic origin: Hispanic or Latino and Not Hispanic or Latino.¹¹⁶ Of note, Hispanic or Latino subjects were most frequently represented in trial 4375 (100% US). Subjects not of Hispanic or Latino origin made up the larger proportion of the total population.

Treatment differences (semaglutide – placebo) for AEs, SAEs, and severe AEs appeared comparable across subgroups by ethnic origin. SAEs and severe AEs were reported somewhat less frequently overall (both treatment groups) in subjects of Hispanic or Latino origin versus subjects not of Hispanic or Latino origin. No treatment difference (semaglutide – placebo) was observed in permanent discontinuation of trial product in subjects of Hispanic or Latino origin.

Greater treatment differences (semaglutide – placebo) were observed in subjects of Hispanic or Latino origin versus subjects not of Hispanic or Latino origin for AEs of diarrhea, abdominal pain, and headache (Figure 94).

Figure 94: Most Frequent AEs by Ethnic Origin, Phase 3 Pool, On-Treatment



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Adverse events with onset prior to randomisation are not included.
 Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms and if the preferred terms have been reported by 5 or more subjects.
 Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
 N: Number of subjects
 The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

nm0536/n0536-summary/submit_iss_20201001_er
 25SEP2020:10:27:49 - faesummarygrp.sas/faesummarySectethnot.png

Source: SCS, Figure 5-8

¹¹⁶ For 55 subjects in France where the law prohibits the collection of information about ethnic origin, ethnicity was reported as no applicable; data from this subgroup were not discussed in this analysis. In addition, 1 subject was adopted and therefore not aware of ethnic origin; data from this subject were excluded.

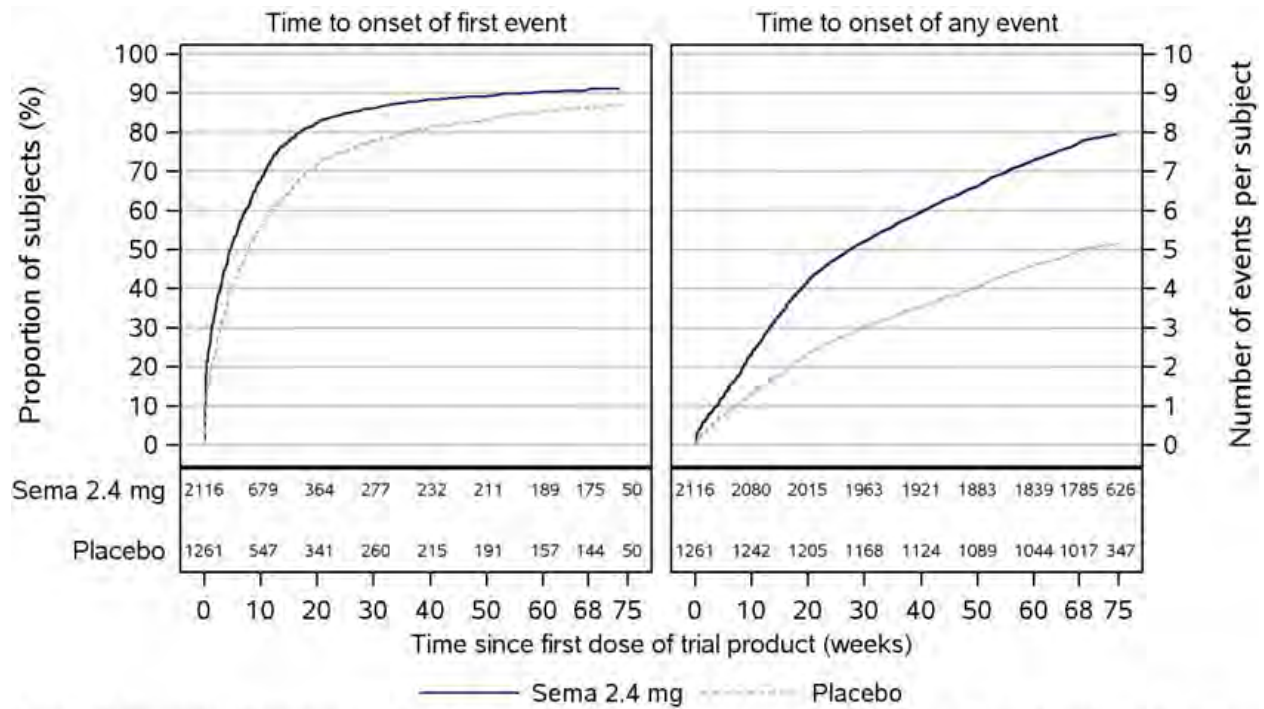
8.7. Specific Safety Studies/Clinical Trials

Not applicable to this application.

8.8. Additional Safety Explorations

Adverse events were explored for time-dependency, utilizing the phase 3 dose-escalation group (Figure 95). For both dose groups, the reporting of the first AE mainly occurred during the first 20 weeks of treatment, with the slope being steeper for the semaglutide 2.4 mg group (left panel). According to the figure, ~50% of semaglutide-treated subjects reported their first event in the first 5 weeks of treatment, versus ~50% placebo-treated subjects who reported their first event in the first 10 weeks of treatment. After the 20-week dose-escalation period, the time to onset of any AE was similar for semaglutide and placebo based on the similar slope of the curves (right panel).

Figure 95: Adverse Events Over Time, Phase 3 Dose Escalation Group



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
 Numbers shown in the lower panel are subjects at risk.
 Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

nn9536/nn9536-summary/subin_iss_20201001_er
 25SEP2020:10 28:26 - faetimeplot.sas/faetimeplotot.png

Source: ISS, Appendix 7.2, Figure 7.2.7

Because body weight is a covariate for semaglutide exposure (lower weights are associated with higher exposure⁶⁰), AEs were evaluated by baseline weight subgroups. In addition, semaglutide exposure could change over the course of the trial as subjects lose large amounts of body weight. Large amounts of weight loss in and of itself could be associated with safety concerns as well.¹¹⁷ Therefore, an exploratory assessment of AEs by baseline body weight and body weight loss are presented below (specific AEs associated with large and/or rapid weight loss – i.e., gallbladder AEs – are discussed further in Section 8.5.1). Because weight loss is a post-randomization factor, in particular this analysis should be interpreted with caution.

Overall, the treatment differences (semaglutide – placebo) for all AEs, SAEs, severe AEs, and AEs leading to permanent discontinuation of trial product were similar across subgroups of baseline body weight. However, there appeared to be a slightly more pronounced treatment difference in the reporting of all AEs in the lowest baseline body weight category, mainly due to fewer events in the placebo arm. Specific AEs that were reported with a greater treatment difference in the lowest body weight subgroup included decreased appetite and fatigue, as well as AEs within the ‘Infections and infestations’ SOC (across many different PTs).

Table 161: AEs by Body Weight at Baseline, Phase 3 Pool, On-Treatment

	Semaglutide 2.4 mg	Placebo
< 90 kg	N=819	N=490
90 - < 100 kg	N=540	N=328
100 - < 115 kg	N=625	N=353
≥ 115 kg	N=666	N=358
<i>AEs</i>		
< 90 kg	734 (89.7)	389 (79.6)
90 - < 100 kg	473 (87.4)	272 (83.1)
100 - < 115 kg	552 (88.6)	309 (88.1)
≥ 115 kg	589 (88.0)	302 (84.9)
<i>SAEs</i>		
< 90 kg	75 (9.2)	30 (6.1)
90 - < 100 kg	52 (9.6)	19 (5.6)
100 - < 115 kg	48 (7.6)	22 (6.1)
≥ 115 kg	71 (10.9)	29 (7.7)
<i>Severe</i>		
< 90 kg	72 (8.5)	34 (7.0)
90 - < 100 kg	58 (10.6)	19 (5.8)
100 - < 115 kg	57 (8.8)	26 (7.6)
≥ 115 kg	82 (12.1)	26 (6.8)
<i>Fatal outcome</i>		
< 90 kg	0	2 (0.4)

¹¹⁷ Tsai AG and Wadden TA. The evolution of very-low-calorie diets: an update and meta-analysis. *Obesity* (2006); 14: 1283-93.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

90 - < 100 kg	0	0
100 - < 115 kg	1 (0.1)	1 (0.3)
≥ 115 kg	1 (0.2)	0
<i>Leading to permanent discontinuation</i>		
< 90 kg	52 (6.2)	21 (4.2)
90 - < 100 kg	28 (5.4)	8 (2.4)
100 - < 115 kg	38 (6.4)	8 (2.4)
≥ 115 kg	31 (4.6)	10 (2.7)

Source: ISS, Table 7.7.21

A summary of AEs by weight loss ($\geq 20\%$ vs. $< 20\%$) are shown in Table 162. Note that only 23 subjects on placebo lost $\geq 20\%$ of baseline body weight, limiting the conclusions. There does not appear to be a substantial interaction between semaglutide and large weight loss for AE reporting. In both treatment groups, subjects with large weight loss were less likely to have discontinued treatment due to an AE than those with lesser degrees of weight loss.

Table 162: AEs by Weight Loss at Week 68, Phase 3 Dose-Escalation Group, On-Treatment

	Semaglutide 2.4 mg	Placebo
≥ 20%	N=572	N=23
< 20%	N=1401	N=1118
Missing	N=143	N=120
<i>AEs</i>		
≥ 20%	524 (91.8)	23 (100)
< 20%	1271 (90.6)	960 (86.3)
Missing	119 (82.9)	88 (75.3)
<i>SAEs</i>		
≥ 20%	53 (9.2)	4 (16.7)
< 20%	140 (10.0)	72 (6.3)
Missing	12 (8.9)	9 (6.9)
<i>Severe</i>		
≥ 20%	61 (10.0)	2 (8.6)
< 20%	155 (10.8)	70 (6.3)
Missing	16 (11.3)	12 (9.0)
<i>Fatal outcome</i>		
≥ 20%	0	0
< 20%	0	0
Missing	1 (1.0)	2 (1.4)
<i>Leading to permanent discontinuation</i>		
≥ 20%	11 (1.5)	0
< 20%	106 (7.5)	29 (2.6)
Missing	24 (17.8)	11 (8.6)

Source: ISS, Table 7.7.51

8.8.1. Human Carcinogenicity or Tumor Development

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Refer to Section 8.5.4, Neoplasms.

8.8.2. Human Reproduction and Pregnancy

In the weight management program, there were 37 pregnancies across the 5 phase 2 and 3 trials (29 semaglutide and 8 placebo¹¹⁸). (No new pregnancies were reported from the completed trials in the 120-day safety update.) Pregnancies from the weight management program are listed in Table 163 and Table 164, below. The narrative for pregnancy with outcome "child with malformation" is included below the tables.

¹¹⁸ In addition, there was a pregnancy in a subject randomized to placebo (but exposed to semaglutide during the run-in period) in trial 4376 reported after the data lock. Pregnancy was confirmed approximately 1 year after the run-in period and 7 months after treatment in the randomized period with placebo. Outcome was a healthy live birth at 41 weeks.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Table 163: Pregnancies Reported in Phase 3 Trials

Treatment	Total pregnancies	Outcome of pregnancy	Subjects	Maternal exposure during pregnancy ^a	Comment
Semaglutide 2.4 mg OW	24	Healthy child	10	~ 0–17 weeks	Birth in gestational week 32–41. Birth weight of 2265–4160 g.
		Child with malformation	1	~ 14 weeks	Birth in gestational week 38. Birth weight 2640 g.
		Ongoing pregnancy ^b	1	~ 11 weeks	
		Spontaneous abortion	4	~ 0–10 weeks	In gestational week 3, 6, 8 and 12. One subject had 3 previous spontaneous abortions
		Elective abortion	6	~ 0–7 weeks	In gestational week 6–7. None were known to be due to congenital anomalies
		Ectopic pregnancy	1	~ 3 weeks and 4 days	Termination in gestational week 5 due to ectopic pregnancy.
		Lost to follow-up	1	~ 4 weeks	
Placebo	8	Healthy child	3	~ 8–14 weeks	Birth in gestational week 38–41. Birth weight 3312-3575g.
		Child with malformation	1	~ 9 weeks	Birth in gestational week 37. Neonate with imperforate anus and recto-vaginal fistula
		Spontaneous abortion	1	~ 8 weeks	Before week 20
		Stillbirth	1	~11 weeks	Week 24
		Elective abortion	1	~ 8 weeks ^c	In gestational week 12. Not due to congenital anomalies.
		Lost to follow-up	1	~ 17 weeks	

^a Approximate period of exposure to trial product includes a washout period of 7 weeks. ^bOngoing as per (b) (6)
^{(b) (6)} ^cThis pregnancy occurred in STEP 4 and the subject had been exposed to semaglutide before start of pregnancy, but not during pregnancy. OW: once weekly.

Source: SCS, Table 5-15

Table 164: Pregnancies Reported in Phase 2 Trial 4153

Treatment	Total pregnancies	Outcome of pregnancy	Subjects	Maternal exposure during pregnancy ^a	Comment
Semaglutide 0.4 mg OD	1	Healthy child	1	~ 5 weeks	Birth in gestational week 36 + 4 days. Birth weight 2640 g. APGAR score at 1 minute: 9
Semaglutide 0.4 mg OD F	1	Spontaneous abortion	1	None	Spontaneous abortion in week 5. Withdrew from trial due to wish of becoming pregnant
Semaglutide 0.2 mg OD	1	Healthy child	1	~ 10 weeks + 4 days	Birth in gestational week 37. Birth weight 2810 g. APGAR score at 1 minute: 9
Semaglutide 0.05 mg OD	2	Healthy child	1	~ 2 weeks + 2 days	Healthy twins. Birth in gestational week 35+5. Birth weights 2180 g and 2280 g. APGAR score at 1 min 8 for both children.
		Spontaneous abortion	1	6 weeks + 0 days	Spontaneous abortion in week 8. One previous live birth

^a Approximate period of exposure to trial product includes a washout period of 7 weeks.

F: fast dose escalation; OD: once daily.

Source: SCS, Table 5-16

The pregnancy with “malformation” outcome is described as follows:

- Subject NN9536-4373/ (b) (6) was a 38-year-old female with BMI of 44.1 kg/m² and history of high cholesterol, hypertension, HIV, and anemia, on HAART and lisinopril. The subject had an intrauterine device for birth control. She was treated with semaglutide in the trial from (b) (6). On an unknown date, the subject took a home pregnancy test which was positive. The subject came to site on the same day and a pregnancy test was done onsite which was also positive. The subject went to the emergency room to verify if it was a normal pregnancy due to the intrauterine device. The subject noted she did not have a period for 1 month, but she did not notify the site. On (b) (6) (last office visit), the urine pregnancy test was negative. Per subject, an ultrasound was done in the ER, which showed no IUD and that she was approximately 6

weeks pregnant.¹¹⁹ Investigational product was stopped. At gestational age 38 weeks 4 days the subject gave birth to 1 live male, length 48 cm and weight 2640 g, by elective caesarean section. No complications were observed during the delivery. APGAR scores were 8 and 9. At delivery and from birth until 1 month of age, the newborn was diagnosed with a congenital anomaly of small left ear fold and positive for sickle cell trait. The infant was given AZT and had 2 negative HIV RNA PCRs at birth and at 1-2 months of age. According to the subject, at approximately 4 months of age, the ear fold resolved.

In addition, there was 1 report of paternal exposure to semaglutide; the partner's pregnancy resulted in a healthy live birth by report.

In summary, pregnancy outcomes appear consistent with the relatively higher risk patient population (obese) studied in these trials; there was not a clear safety signal, but this will need to be continued to be monitored in the post-marketing setting. Refer to the review from Dr. Carrie Ceresa, Division of Pediatric and Maternal Health (DPMH) for additional details.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable; this submission only included studies in adults.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Although semaglutide is not known to be associated with abuse or dependence potential, it partially acts on satiety centers of the brain. Therefore, drug abuse potential was evaluated in the semaglutide weight management program in several different ways. Three predefined MedDRA searches¹²⁰ were utilized with the phase 3 pool to evaluate AEs of medication errors (including accidental overdose), drug abuse or misuse (including intentional overdose), and overdose (accidental and intentional).

In addition, potential withdrawal and rebound effects were evaluated as follows: (1) in trial 4376, which utilized a randomized withdrawal design; the evaluation of withdrawal effects were based on AEs reported within 7 weeks after randomization, and (2) in the phase 3 pool,

¹¹⁹ Note that because of the semaglutide half-life, the applicant calculated pregnancy exposure in Table 163 as ~14 weeks.

¹²⁰ (1) Medication errors: SMQ Medication errors (2) Abuse and Misuse: Custom query (NNMQ Abuse and Misuse): SMQ Drug abuse and dependence, narrow terms only; HLT 'Intentional product misuses'; Additional PTs: 'Poisoning deliberate,' 'Intentional dose omission,' 'Performance enhancing product use,' 'Completed suicide,' 'Intentional self-injury,' 'Suicide attempt,' 'Assisted suicide,' 'Suspected suicide attempt,' 'Suspected suicide' (3) Overdose: Custom query (NNMQ Overdose): HLT 'Overdoses NEC'; Additional PTs: 'Accidental overdose,' 'Completed suicide,' 'Suicide attempt,' 'Suspected suicide attempt,' 'Suspected suicide'

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

which evaluated AEs reported within 7 weeks of treatment discontinuation; planned and premature discontinuations were evaluated separately.

Medication Error

In the phase 3 pool, 24 subjects (0.9%) on semaglutide 2.4 mg versus 10 subjects (0.7%) on placebo reported a medication error. One of these events was reported as an SAE in a subject in the semaglutide group; this was an unintentional overdose of bupropion and the subject recovered. There were no medication error AEs in the run-in period of trial 4376 and 5 subjects on the semaglutide 1 mg arm of trial 4374 had non-serious medication error AEs.

Most of the medication error events occurred during the first 20 weeks of treatment (dose-escalation).

Drug Abuse or Misuse

In the phase 3 pool, no subjects in the semaglutide 2.4 mg group and 2 subjects in the placebo group reported AEs related to drug abuse or misuse according to the MedDRA search. Both events in the placebo group were AEs of 'Suicide attempt'; see Section 8.5.9 for more details. In addition, 1 AE of intentional overdose of the drug product was reported for a subject in the semaglutide 1 mg group in trial 4374. This AE was non-serious, mild, and reported as recovered. There were no AEs of abuse or misuse in the run-in period of trial 4376.

Overdose

In the phase 3 pool, 19 subjects (0.7%) on semaglutide 2.4 mg versus 9 subjects (0.6%) on placebo reported an overdose event. One event in each group was reported as an SAE: the semaglutide subject had an unintentional bupropion overdose and the placebo subject had a suicide attempt; both events were noted above (medication error and drug misuse, respectively). Another non-serious AE of intentional overdose (suicide attempt) was reported in the placebo group, as discussed under drug misuse above.

There were no overdose AEs in the run-in period of trial 4376 and 4 subjects with non-serious overdose AEs in the semaglutide 1 mg arm of trial 4374 (3 subjects reported accidental overdose and 1 subject reported intentional overdose, also noted under drug misuse above).

The most common reasons for overdose AEs were distraction or misunderstanding the dosing schedule.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

The applicant notes that AEs reported within 14 days of an overdose event were primarily gastrointestinal in nature; however, as these were also the most common AEs overall, it is unclear if the GI AEs were related to the medication errors.

No AEs of hypoglycemia were reported in the trials in subjects without T2D (4373, 4375, 4376) within 14 days of an overdose AE. In the trial in subjects with T2D (4374), the applicant reports that no hypoglycemic episodes were co-reported in relation to an overdose.

Withdrawal

Trial 4376

In trial 4376, in which subjects were randomized to semaglutide 2.4 mg or placebo after a 20-week semaglutide run-in period, the first 7 weeks after randomization were assessed to evaluate potential withdrawal symptoms.

Notable AEs that were reported more frequently in the placebo arm versus the semaglutide arm in the first 7 weeks after randomization included 'Increased appetite' PT (semaglutide 0.2% vs. placebo 1.9%), 'Psychiatric disorders' SOC (1.5% vs. 3.7%), and 'Hepatobiliary disorders' SOC (0.7% vs. 1.5%, see Section 8.5.1). The imbalance in psychiatric disorders among randomized groups in part was driven by anxiety (semaglutide 0.2% vs. placebo 1.5%).¹²¹ The absolute numbers however are small.

Phase 3 Pool

Reports of psychiatric AEs after discontinuation of randomized treatment in the phase 3 pool were also evaluated (although these results are not considered as reliable as the randomized withdrawal evaluation):

- AEs in the 'Psychiatric disorders' SOC reported within 7 weeks of premature treatment discontinuation were 2.5% for semaglutide and 1.5% for placebo. Anxiety was reported in 0.8% and 0.4%, respectively.¹²²
- AEs in the 'Psychiatric disorders' SOC reported within 7 weeks of planned treatment discontinuation were 0.6% for semaglutide and 0.4% for placebo. Anxiety was reported in 0.2% and <0.1%, respectively.¹²³

In summary, semaglutide does not appear to be associated with substantial abuse potential. Overdose was reported infrequently and therefore the risk evaluation is limited.

¹²¹ Source: ISS, Table 7.3.65

¹²² Source: ISS, Table 7.3.63

¹²³ Source: ISS, Table 7.3.64

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Gastrointestinal effects are the likeliest outcome of a semaglutide overdose, but the risk of more significant effects (hypoglycemia, acute renal failure due to volume losses) cannot be ruled out. In the first 7 weeks after discontinuing semaglutide, individuals may be at risk for anxiety.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Drug-Induced Liver Injury (DILI)

DILI was first raised as a post-marketing signal with Rybelsus (oral semaglutide for T2D). A subsequent preliminary review by DPV identified a number of cases across the GLP-1 RA class and is now being evaluated under NISS 1004209. See Section 8.5.5, Hepatic Disorders, for further discussion, as well as an assessment of relevant AEs and laboratory data from the weight management program and blinded data from ongoing weight management trials. This section specifically reviews the response to the 74-day letter regarding hepatic safety of semaglutide from post-marketing experience (i.e., Ozempic and Rybelsus).

According to this 74-day letter response, patient exposure is estimated to be as of the data lock of 31 Jan 2021, for Ozempic: 1,061,487 PYE in the US and 1,971,740 PYE worldwide, and for Rybelsus: 70,492 PYE in the US and 82,886 PYE worldwide.

To look for cases of potential DILI, cases captured by MedDRA search terms requested by the FDA, *Selected hepatic events*,¹²⁴ as well as the applicant's custom search, *Potential liver injury*,¹²⁵ were evaluated by 2 Novo Nordisk hepatologists according to the FDA guidance on drug-induced liver injury.¹²⁶ The following numbers of post-marketing events were identified for Ozempic and Rybelsus:

¹²⁴ MedDRA SMQ Cholestasis and jaundice of hepatic origin (broad scope) and SMQ Drug related hepatic disorders – severe events only (broad scope)

¹²⁵ Since the MedDRA SMQ searches are broad and include event types not specifically related to liver injury (e.g., neoplasms), NN hepatologists identified events from these searches indicating acute and subacute liver injury (or clinical signs thereof)

¹²⁶ Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. July 2009.

Table 165: Post-Marketing Hepatic-Related Adverse Drug Reactions Identified for Semaglutide Products

MedDRA search	Ozempic			Rybelsus		
	No. of cases	ADRs	Event rate/1000 PYE	No. of cases	ADRs	Event rate/1000 PYE
<i>Selected hepatic events</i>	58	62	0.031	5	5	0.060
<i>Potential liver injury</i>	30	33	0.017	4	4	0.048
ADRs=adverse drug reactions Case (b) (6) is included for both Ozempic and Rybelsus – patient was exposed to both products						

Source: Response to 74-day letter, Table 3-10

One case was considered by Novo Nordisk hepatologists to be “probably” related to semaglutide:

- Case (b) (6): A 46-year-old woman treated with Ozempic started experiencing acute right upper quadrant abdominal pain 30 minutes after fatty meals, with nausea and dizziness (time of onset was unknown). Medical history included T2D, cholecystectomy, hypothyroidism, pernicious anemia, and probable primary hyperparathyroidism. Concomitant medication included sitagliptin and empagliflozin. Approximately 2 months later, the patient was admitted to the hospital with pain, and was found to have elevated liver parameters [AST 417 U/L (ref: 14-50), ALT 222 U/L (ref: 11-60), total bilirubin 17.7 μmol/L (ref: 0-21), LDH 417 U/L (ref: 135-225), and GGT 100 U/L (ref: 10-71)]. The event was reported as “acute drug-induced hepatitis” (PT: ‘Drug-induced liver injury’, hepatotoxicity grade 1 - mild). No information on biopsy is available. Ultrasound showed no abnormalities, but information on timing of the ultrasound in relation to the symptoms is missing. After discontinuation of Ozempic, the liver enzymes improved and pain resolved, and the event was reported as recovering/resolving.

Reviewer comment: Semaglutide is known to be associated with gallstone formation and given the symptoms and history of cholecystectomy, as well as rapid recovery, gallstones and bile duct obstruction seem plausible, even with a negative ultrasound.

No publications were identified that are relevant to semaglutide and DILI.

Reviewer comment: This NISS and the information provided in response to an information request is currently under review. The preliminary evidence suggests that the cases suggestive of DILI in the ongoing and clinical trials are associated with confounding factors and/or negative rechallenge, and therefore, there is no clear causal relationship established at this time for a hepatotoxic effect of semaglutide. Nevertheless, as the applicant notes, an idiosyncratic and rare immune-mediated reaction to semaglutide or other GLP-1 RAs cannot be ruled out.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Severe and Serious Hypersensitivity Reactions

A DPV review was conducted in January 2021 to evaluate severe and serious hypersensitivity reactions with a focus on angioedema, anaphylaxis, and severe cutaneous adverse reactions (SCAR) reported with lixisenatide and semaglutide products from FAERS and the medical literature. The semaglutide sponsor also submitted a prior approval labeling supplement to add rash and urticaria to the Adverse Reactions Postmarketing Experience section of the Ozempic product label.

DPV identified cases of angioedema and anaphylaxis with evidence to support a possible association with use of insulin glargine/lixisenatide and semaglutide products, and these were recommended to be added to Warnings and Precautions of product labeling.

DPV identified some serious reports of rash and urticaria associated with semaglutide, and DPV agreed with including these to the Postmarketing Experience section of Ozempic labeling.

There was insufficient evidence from FAERS and medical literature to conclude there is an association with SCAR for either lixisenatide or semaglutide.

Severe Hypoglycemia

A DPV review was conducted in October 2020 to evaluate post-marketing events of severe hypoglycemia with use of GLP-1 RAs.¹²⁷ An association between GLP-1 RA and severe hypoglycemia in patients on GLP-1 RA monotherapy or with a non-secretagogue antidiabetic agent was not established in patients with T2D. Furthermore, there was insufficient evidence to establish an association between the GLP-1 RA class and severe hypoglycemia following an overdose in non-diabetic patients; however, one medical literature case report reported severe hypoglycemia following an overdose of liraglutide. Strengthened language in labeling information about dose adjustment and hypoglycemia with insulin and insulin secretagogues was recommended for all GLP-1 RA labels.

Acute Kidney Injury

In order to accurately describe acute kidney injury (AKI) from post-marketing reports in the semaglutide for weight management label, the applicant was asked to provide a summary of AKI with semaglutide. They stated that as of March 31, 2021, 170 post-marketing cases of

¹²⁷ Safety evaluator: Christine Chamberlain, SSID: 1004065

acute renal failure have been reported with Ozempic (s.c. semaglutide) and 15 cases with Rybelsus (oral semaglutide).

A literature search also identified a recent article with 2 case reports of worsening of kidney function in patients with diabetes and chronic kidney disease.¹²⁸

- Case 1: This was a woman in her early 80s with diabetes, hypertension, and chronic kidney disease (CKD), who was seen for increasing leg edema. Medications included amlodipine, insulin, metoprolol, and valsartan/hydrochlorothiazide. Semaglutide was started 5 months before presentation, when serum creatinine was 1.59 mg/dL. The patient reported nausea and vomiting after dose escalation from 0.25 mg to 0.5 mg weekly, so she returned to the 0.25 mg dose. Approximately 1 month before presentation, she attempted escalation again to 0.5 mg and again had nausea and vomiting and stopped the injection. She denied illness or NSAID use. Peripheral edema was noted and serum creatinine was 3.50 mg/dL with proteinuria. Kidney biopsy showed advanced diffuse and nodular glomerulosclerosis accompanied by interstitial lymphoplasmacytic and eosinophilic infiltrate and evidence of acute tubular injury. There has been no recovery of kidney function since semaglutide was discontinued.
- Case 2: This was a man in his 60s with diabetes, hypertension, and CKD. Medications included lisinopril/hydrochlorothiazide, carvedilol, and amlodipine. He was started on semaglutide 4 months prior to presentation. He was dose-escalated to 0.5 mg/week and then took only 1 dose of 0.75 mg before returning to the 0.5 mg dose. The reason was not given for returning to the 0.5 mg dose, but it was noted that he reported decreased appetite, fatigue, and a 15-pound weight loss. EGFR decreased from the 30 to 35 mL/min/1.73 m² range to 24 mL/min/1.73 m² then 22 mL/min/1.73 m² with proteinuria 1 week later after lisinopril/ hydrochlorothiazide was stopped. Semaglutide was stopped with resolution of symptoms, but no improvement in kidney function or proteinuria.

Reviewer comment: There was temporal correlation in these cases to semaglutide use and rapid worsening of kidney function during dose escalation, suggesting that patients with CKD might be particularly at risk of AKI (in these cases, without recovery) when developing adverse symptoms associated with semaglutide use.

Acute Pancreatitis

In order to accurately describe acute pancreatitis from post-marketing reports in the semaglutide for weight management label, the applicant was asked to provide a summary of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis with

¹²⁸ Leehey DJ, et al. Acute kidney injury associated with semaglutide. *Kidney Med*, 2021. 3(2): 282-5.

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

semaglutide. As of April 30, 2021, the following cases have been reported for Ozempic and Rybelsus, respectively.

Table 166: Acute Pancreatitis Post-Marketing Reports, Ozempic

Cases	Events	Exposure	Rate/1000 PYE	
506	510	2,489,238 PYE	0.20	
Serious event		Medically confirmed cases	Valid cases	
510		433	453	
Reported outcome				
Recovered/ recovering	Recovered with sequelae	Not recovered	Fatal	Unknown/Not reported
243	3	43	4	217
Preferred Term				
Pancreatitis		400		
Pancreatitis Acute		90		
Obstructive pancreatitis		8		
Pancreatitis chronic		5		
Alcoholic pancreatitis		2		
Pancreatic pseudocyst		2		
Pancreatitis necrotising		2		
Pancreatitis relapsing		1		

NNMQ pancreatitis narrow terms, data until 30-Apr-2021

Source: Response to FDA Request dated May 20, 2021, Table 2

Table 167: Acute Pancreatitis Post-Marketing Reports, Rybelsus

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Cases		Events		Exposure	Rate/1000 PYE
50		50		120,505 PYE	0.41
Serious		Medically confirmed		Valid	
50		47		41	
Reported outcome					
Recovered/ recovering	Recovered with sequelae	Not recovered		Fatal	Unknown/Not reported
23	0	6		0	21
Preferred Term					
Pancreatitis				45	
Pancreatitis acute				4	
Obstructive pancreatitis				1	

NNMQ pancreatitis narrow terms, data until 30-Apr-2021

Source: Response to FDA Request dated May 20, 2021, Table 3

Additional information on fatal, necrotizing, and hemorrhagic pancreatitis were presented:

Ozempic

Cases of pancreatitis with fatal outcome:

Cumulatively, 4 cases of pancreatitis with fatal outcome have been reported. The cases were reported as pancreatitis (2 cases) and pancreatitis acute (2 cases). All 4 cases were medically confirmed. None of the cases had information to confirm a diagnosis of pancreatitis according to the Atlanta criteria, and only 2 of the fatal cases had information to establish the timing of the events in relation to the use of Ozempic. Three cases had co-reported events: sepsis (1 case), cardiorespiratory arrest and respiratory distress (1 case), and gastrointestinal bleed (1 case). Two of the cases reported concomitant medications considered to be risk factors for development of acute pancreatitis. In general, limited information was provided.

Fatal cases of pancreatitis for which a timely association could be established included:

- A 75-year old patient was hospitalized for pancreatitis 2 days after starting Ozempic. Treatment included intravenous prednisone and nothing per mouth. It was reported that the pancreatitis was getting better, but the patient developed a gastrointestinal bleed and died a few days later. The patient was on concomitant medication linagliptin (associated with pancreatitis) and prednisolone (associated with GI bleed).
- A 77-year old patient was hospitalized for acute pancreatitis 5 months after starting Ozempic and died the next day due to respiratory distress, cardiorespiratory arrest, and acute pancreatitis. The patient was on concomitant amlodipine and furosemide (associated with pancreatitis).

Cases of necrotizing pancreatitis:

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

Cumulatively, 2 events in 2 cases were reported as necrotizing pancreatitis:

- The first case was medically confirmed. The case did not include diagnostic criteria to fulfill the Atlanta criteria and the exact timing of the event in relation to the use of Ozempic was not known. The case was co-reported with cholelithiasis.
- The second case included diagnostic criteria to support the diagnosis of pancreatitis [lipase 3000 U/L (ref. 14–63 U/L), and severe abdominal pain] with reference to the Atlanta criteria. The event happened 12 months after starting Ozempic. The case was co-reported with a gallbladder disorder. Both patients discontinued Ozempic due to the events. The outcome of the events of necrotizing pancreatitis was not reported in either of the cases, but both patients were discharged from the hospital.

Cases of hemorrhagic pancreatitis:

There were no events of hemorrhagic pancreatitis reported.

Rybelsus

No post-marketing events of fatal pancreatitis or non-fatal hemorrhagic or necrotizing pancreatitis have been reported with Rybelsus.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety of semaglutide is well-characterized at lower doses in patients with T2D (Ozempic, Rybelsus) and there is considerable experience with this class of drugs, including for weight management (Saxenda, liraglutide).

Given the better weight loss achieved with this product, an exaggerated safety profile might be expected. For example, it is possible that early treatment with semaglutide will lead to perturbations in volume status, and adverse events of hypotension, syncope, and acute kidney injury in susceptible patients. Cholelithiasis with adverse sequelae, pancreatitis, and hypoglycemia are possible. Gastrointestinal adverse events will be common and may be serious or severe in some patients. The ongoing long-term CVOT will be useful in assessing safety in a higher-risk, more vulnerable population.

8.9.3. Additional Safety Issues From Other Disciplines

All safety issues from other disciplines are discussed in other sections of this review.

8.10. Integrated Assessment of Safety

The safety of semaglutide 2.4 mg for weight management was primarily evaluated in 4 phase 3 trials, in which 2650 subjects were exposed to at least 1 dose. The safety profile of semaglutide in the weight management program is generally consistent with the safety profile characterized in the T2D semaglutide program (at lower doses) as well as other GLP-1 receptor agonists,

Clinical Review
Golden, J
NDA 215256
Wegovy (semaglutide)

including liraglutide for chronic weight management.

There were 3 deaths in the semaglutide 2.4 mg group, all were classified as cardiovascular deaths, and 3 deaths in the placebo group, all were classified as death due to malignancy. One of the placebo subjects had been exposed for 20 weeks to semaglutide in a run-in period.

More SAEs were reported with semaglutide 2.4 mg versus placebo, driven by GI AEs and gallbladder-related disorders.

More AEs leading to discontinuation were reported with semaglutide 2.4 mg versus placebo, primarily due to GI AEs (nausea, vomiting, diarrhea, upper abdominal pain, and constipation).

More AEs were reported overall with semaglutide 2.4 mg versus placebo; the imbalance was primarily due to GI AEs, as expected.

Safety issues of special interest are summarized as follows:

- Gallbladder disorders: Overall, 2.5% semaglutide- versus 1.6% placebo-treated subjects reported gallbladder events; the imbalance was more pronounced in the trial with intensive dietary and behavioral therapy (4375). In addition, more events were reported as SAEs in semaglutide-treated subjects. In general, gallbladder disorders were associated with larger weight loss in both treatment groups. However, the incidence of acute gallbladder disease was greater in semaglutide-treated patients than in placebo-treated patients even after accounting for weight loss, suggesting at least in part, a weight-independent effect.
- Pancreatitis: Acute pancreatitis was reported infrequently in the semaglutide program. Four subjects (0.2%) had 5 episodes of adjudicator-confirmed pancreatitis versus 1 patient on placebo (<0.1%) with 1 event. Adjudicator-confirmed pancreatitis events were associated with gallstones in 2 of the 4 semaglutide subjects and the 1 placebo subject with acute pancreatitis events. Semaglutide also appears to be associated with elevations in pancreatic enzymes, but these elevations were infrequently captured as pancreatitis events.
- Hypotension and syncope: Hypotension and orthostatic hypotension were reported with semaglutide. Use of antihypertensive medication at baseline appears to be a risk factor. Subjects with AEs of hypotension or orthostatic hypotension also on occasion reported AEs of syncope or fall. There were more events of syncope reported in the semaglutide-treated group versus placebo (0.8% vs. 0.4%, respectively).
- Volume losses and renal impairment: Semaglutide can lead to significant volume depletion in some individuals, potentially due to GI losses as well as some contribution of decreased intake, leading to acute renal failure. These events were infrequently observed in the

clinical trials. Overall, the incidence of acute renal failure AEs was infrequent. Mean eGFR and serum creatinine were essentially unchanged in both groups during the trials. In addition, the proportion of subjects with serum creatinine > 1.5x ULN was low and similar among groups. No subjects in the dose-escalation group were observed to have serum creatinine > 3x ULN post-baseline. Subjects with moderate renal impairment were more likely to have renal AEs on semaglutide versus placebo than subjects with normal renal function or mild renal impairment.

- Major adverse cardiovascular events (MACE): Adjudicated 3-component MACE, composed of cardiovascular death (including undetermined cause of death as per the EAC), non-fatal myocardial infarction, and non-fatal stroke was analyzed in the randomized phase 3 pool. Twenty MACE were confirmed by the EAC; 0.5% in each treatment group, with a hazard ratio of 0.991 (95% CI 0.400, 2.456).
- Heart rate (HR) increases: A treatment difference in HR of approximately 1-4 bpm greater than placebo was observed in the phase 3 trials. A maximum HR change from baseline $\geq$ 20 bpm were observed in 26% of semaglutide- versus 16% of placebo-treated subjects. There did not appear to be a dose-dependent HR effect. HR increases with semaglutide that could contribute to atrial arrhythmias cannot be ruled out as a theoretical concern.
- Neoplasms: The incidence of neoplasms and of malignancies were similar among groups. There was no medullary thyroid cancer or pancreatic cancer reported in any of the weight management trials. No subject had a post-baseline calcitonin $\geq$ 50 ng/L.
- Liver safety: The proportions of liver AEs were similar among groups, and rare serious AEs were associated with confounders. Mean transaminase values decreased with semaglutide, although mean total bilirubin increased with semaglutide. There were no reports of biochemical Hy's law (ALT/AST > 3x ULN concurrent with total bilirubin > 2x ULN) in the weight management program observed in the central laboratory through routine monitoring. (Events identified in local laboratory monitoring in AE narratives were associated with alternative etiologies in which liver enzyme abnormalities can be expected as part of the clinical course. The majority of cases were attributed to gallbladder disease.) There was only 1 subject on semaglutide with ALT > 5x ULN observed in the trial; this event was associated with a positive rechallenge and the subject was permanently discontinued. At this time there is not a clear signal for DILI with semaglutide. Nevertheless, DILI can be a rare and idiosyncratic event, and the review of post-marketing and trial data being undertaken by OSE as part of a NISS will help clarify the potential for a causal relationship for DILI with semaglutide and other GLP-1 RAs.

- Hypoglycemia:
 - With T2D: The risk for clinically significant hypoglycemia (severe hypoglycemia or blood glucose less than 54 mg/dL with or without symptoms) in subjects with T2D is greater in those treated with semaglutide versus placebo. Whereas there does not appear to be a dose-response (2.4 mg vs. 1 mg) for the first episode, subjects who experienced 1 event on semaglutide appear to have been at greater risk for additional episodes at the higher (2.4 mg) dose. Subjects treated with semaglutide at risk of clinically significant hypoglycemia had a longer history of T2D and were slightly older than those without episodes. Subjects with and without significant hypoglycemia had reductions in HbA1c with semaglutide. A substantial proportion of events of significant hypoglycemia occurred in subjects *not* on SUs at the time of the event. Subjects on insulin were not studied.
 - Without T2D: The risk of significant hypoglycemia in subjects with obesity but without T2D treated with semaglutide 2.4 mg appears low; however, hypoglycemia was not collected or reported in a systematic manner in the phase 3 program. More episodes were likely identified in the phase 2 trial due to a specific form in which potential cases were formally collected (mostly “probable symptomatic” and “asymptomatic”) versus the phase 3 program in which they were collected as AEs only.
- Retinopathy in T2D: A total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search during the in-trial period. These events were reported by a larger proportion of subjects with semaglutide versus placebo (6.9% semaglutide 2.4 mg, 6.2% semaglutide 1 mg, and 4.2% placebo). The majority of events were reported as ‘Diabetic retinopathy’ (4.0%, 2.7%, and 2.7%, respectively) and ‘Non-proliferative retinopathy’ (0.7%, 0%, and 0%, respectively). No SAEs of retinal disorders were reported in any of the treatment arms. With respect to the eye examinations, few subjects were considered to have clinically significant (CS) findings overall. Most subjects who were normal or not clinically significant (NCS) at baseline remained in that category during the trial for each eye. An imbalance was seen for the semaglutide 2.4 mg arm in shifts from normal to NCS in both eyes. There was also an imbalance in shifts from NCS to CS in the semaglutide 2.4 mg arm, but the numbers were small.
- Psychiatric disorders: Patients in this population are at risk for psychiatric disorders, although based on the clinical trial data, there does not appear to be an increased risk with use of semaglutide.
- Immunogenicity, allergy and injection site reactions: A total of 50 (2.9%) of semaglutide-treated subjects had positive ADAs during the trial, and 58% of these

subjects had “persistent” ADAs. A total of 56% of these subjects had ADAs that were cross-reacting with endogenous GLP-1 (5 were transient). No ADAs had neutralizing activity. No serious allergy AEs were reported, and few subjects reported AEs consistent with potential angioedema (1.0% semaglutide vs. 0.7% placebo). Injection site reactions were infrequent. Patients with ADAs tended to have more allergy and multiple injection site reactions than those without, but as the number of patients were small and these are not randomized groups, these associations should be interpreted with caution.

- Gastrointestinal (GI) disorders: GI AEs were the most commonly reported AEs in semaglutide-treated subjects, generally appear dose-dependent, and were the most likely group of AEs to lead to drug discontinuation. However, most GI AEs were not serious, were of mild or moderate severity, and did not lead to study drug discontinuation. The most frequently reported AEs were nausea, diarrhea, vomiting, and constipation. Most consequences of GI disorders are symptomatic, but particularly in vulnerable populations, can lead to volume depletion, dehydration, and acute kidney injury. Other potential risks could include electrolyte disturbances and orthostasis/syncope. Events are more commonly reported during the dose-escalation period; the 16-week dose-escalation paradigm is intended to mitigate some of the GI symptoms associated with dose-escalation.
- Pregnancy: In the weight management program, there were 37 pregnancies across 5 phase 2 and 3 trials (29 semaglutide and 8 placebo). Pregnancy outcomes appear consistent with the relatively higher risk patient population (obese) studied in these trials. There was not a clear safety signal, but this will need to be continued to be monitored in the post-marketing setting. Women who undergo significant weight loss might experience improved fertility, and therefore, prevention of unwanted pregnancy should be part of counseling when starting a weight loss program with semaglutide.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information (PI), medguide, and instructions for use have been made directly in those documents. The major PI edits are summarized as follows:

- The indication will mirror that of Saxenda and other chronic weight management drugs
-  (b) (4) An assessment of drug tolerability after dose-escalation and ensuring subjects tolerate the 2.4 mg dose will support the benefit-risk profile of the drug.
-  (b) (4) Sections 4 and 8 were updated accordingly.
-  (b) (4)
- Acute gallbladder disease and heart rate increases are expected events and could result in serious adverse sequelae. These were added to warnings and precautions (Section 5).
- Although suicidality was not reported frequently in the semaglutide program, the population is considered higher risk and suicidal ideation and behavior have been reported with other weight management products. Given that risk mitigation language was proposed by the applicant (for Section 6), Section 5 was considered the appropriate placement of this warning.
- For injection site reactions, the pre-defined MedDRA search included a number of PTs that describe trauma at the injection site (bruising, hematoma, etc.) that seem to add noise to the evaluation of immunological- or irritant-based injection site reactions. More pertinent terms are related to injection site reaction, erythema, pruritus, etc.
- Clinical data summaries were updated in Section 6.1.
- Hypoglycemia in patients without T2D, hypotension and syncope, and appendicitis were added to Section 6.1.
- Post-marketing reports of acute kidney injury and fatal and non-fatal acute pancreatitis and necrotizing pancreatitis were added to Section 6.3.
-  (b) (4)

- In the clinical studies section (Section 14):
 - The description of the trials was presented more succinctly
 - Proportions of subjects who discontinued study drug was added
 - Weight loss tables were limited to the weight parameters in the testing hierarchy
 - (b) (4) removed from the anthropometry and cardiometabolic tables to streamline results and limit over-interpretation of efficacy
 - Heart rate was added to the tables to be consistent with other weight management products

(b) (4)

- Section 17 was updated with information from relevant sections

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not considered necessary for this application.

12. Postmarketing Requirements and Commitments

The following are the 7 postmarketing requirements (PMRs); no postmarketing commitments (PMCs) are recommended for this application:

- 1) Conduct a 68-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of semaglutide for the treatment of obesity in pediatric patients ages 12 to 17 (inclusive).
- 2) Conduct a 68-week randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of semaglutide for the treatment of obesity in pediatric patients (b) (4) (b) (4). The trial may not be initiated until results from the semaglutide adolescent trial have been submitted to and reviewed by the Agency.

- 4) Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to semaglutide during pregnancy to an unexposed reference population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
- 5) Conduct an additional pregnancy study that uses a different observational design from the Pregnancy Exposure Registry, using claims or electronic medical record data, to assess the associations between semaglutide exposure during pregnancy with pregnancy outcomes and infant outcomes, including but not limited to major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age, preterm birth and postnatal growth and development; .
- 6) Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of semaglutide for the treatment of obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of semaglutide for the treatment of obesity.
- 7) Complete the ongoing randomized, double-blind, parallel-group, placebo-controlled trial in approximately 17,500 patients with established CV disease and overweight or obesity (randomized 1:1 to semaglutide 2.4 mg and placebo) to evaluate the long-term effects of semaglutide 2.4 mg on pancreatitis, gallbladder disorders, renal safety, serious hepatic events, malignant neoplasms, serious hypoglycemia, and serious gastrointestinal disorders.

13. Appendices

13.1. References

References are listed as footnotes throughout the document.

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

13.2. Financial Disclosure

The potential for bias in the phase 3 program was minimized through the design of adequate and well-controlled clinical trials which were randomized and double-blinded. The primary endpoints were based on body weight, which is easy to measure and objective. The trials were conducted at multiple sites. Of the total number of investigators, the majority of investigators did not have disclosable financial interests. Of those that had disclosable financial interests, these investigators contributed only a small proportion of the total subjects for the trial.

Covered Clinical Study (Name and/or Number): NN9535-4588

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>12</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Covered Clinical Study (Name and/or Number): NN9536-4590

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>12</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN9536-4455

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>19</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN953-4153

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>327</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Significant payments of other sorts: <u>1</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN9536-4373

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>614</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>17^a</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>0</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

minimize potential bias provided:		from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)
a: note that for 2 non-US sites, 8 sub-investigators disclosed financial interests; however, in the summary table provided by the applicant, the financial interest was only accounted for under the principal investigator		

Covered Clinical Study (Name and/or Number): NN9536-4374

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>677</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>14</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>14</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN9536-4375

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>293</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>12</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>12</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): NN9536-4376

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>359</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

Clinical Review
 Golden, J
 NDA 215256
 Wegovy (semaglutide)

<u>8</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>8</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>1^a</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>1</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)
a \$20,000 in shares		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE K GOLDEN
06/03/2021 01:34:09 PM

JOHN M SHARRETT
06/03/2021 10:09:57 PM
I concur with the findings and conclusions in this review.