Semaglutide Tablets (RYBELSUS)
National Drug Monograph
January 2020
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action
Semaglutide is a once daily oral glucagon-like peptide 1 (GLP-1) agonist used in the treatment of type2 diabetes. Semaglutide increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.

Indication(s) Under Review in This Document
- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of use:
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise
- Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy.
- Not indicated for use in type 1 diabetes mellitus or treatment of diabetic ketoacidosis

Dosage Form(s) Under Review
3mg, 7mg, and 14mg tablets supplied in blister packs to protect tablets from moisture

Executive Summary

Efficacy
- Mean reduction in A1C ranged from 0.9% to 1.4% and weight from 2.2kg to 4.4kg across phase 3 clinical trials
- In patients with type 2 diabetes and at high cardiovascular (CV) risk, oral semaglutide was found to be noninferior to placebo for the primary composite outcome (risk of CV death, nonfatal MI, nonfatal stroke). (Hazard Ratio 0.79; 95% CI 0.57, 1.11 $p<0.001$ for noninferiority and $p=0.17$ for superiority).
- Two secondary outcomes, all-cause mortality and CV-related death showed reduced risk relative to placebo. Microvascular outcomes (retinopathy and nephropathy) were not assessed.

Safety
- The most common adverse reactions, reported in ≥5% of patients treated with oral semaglutide are: nausea, abdominal pain, diarrhea, decreased appetite, vomiting, and constipation.

Other Considerations
Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. It is recommended that oral semaglutide be discontinued in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Projected Place in Therapy

Until more information is available regarding cardiovascular outcomes, oral semaglutide is not recommended as a second-line option for those with established CV disease. Oral semaglutide might be considered a third-line option for those without CV disease, similar to the injectable GLP1-agonists provided eventual cost is lower or comparable.

Background

Purpose for Review

The purpose of this monograph is to evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating oral semaglutide for possible addition to the VA National Formulary.

Other Therapeutic Options

Alternative treatments at the same step in therapy for type 2 diabetes are listed in the table below.

Table 1 Treatment Alternatives

Drug	Formulary Status		Other Considerations
Alogliptin	F	• Second-line after metformin	Oral agent, once daily administration, relatively inexpensive, A1C lowering <1%, weight neutral, low risk of hypoglycemia, did not improve cardiovascular outcomes vs. placebo
Empagliflozin	PA	• Second-line after metformin for those with CVD/HF/CKD • Third-line for all others	Oral agent, once daily administration, less costly than GLP-1 agonists, A1C lowering ~1%, weight loss, low risk of hypoglycemia, cardiovascular and renal benefits
Insulin (NPH, glargine U100, detemir, regular, aspart)	F	• Insulin can be used anytime	Injectable, titratable, risk of hypoglycemia, weight gain, low to moderate cost (excluding concentrated insulins)
Injectable GLP-1 agonists: liraglutide, dulaglutide, semaglutide, exenatide, exenatide extended-release (ER), lixisenatide,	NF/ CFU	• Second-line after metformin for those with CVD/CKD if not a good candidate for EMPA (LIRA, DULA, SEMA) • Third-line for all others	Injectable, A1C lowering 1-1.5%, weight loss, low risk of hypoglycemia, liraglutide, semaglutide, and dulaglutide shown to have CV and renal benefits, high cost

Dosing and Administration

See product labeling for complete dosing information including switching between semaglutide oral and injection and

- Take semaglutide tablet at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking semaglutide tablet with food, beverages (other than plain water) or other oral medications will lessen the effect of semaglutide by decreasing its absorption. Waiting more than 30 minutes to eat may increase the absorption semaglutide.
- Swallow tablets whole. Do not split, crush, or chew tablets.

- Start with 3 mg once daily for 30 days. The 3 mg dose is intended for treatment initiation and is not effective for glycemic control.
- After 30 days on the 3 mg dose, increase the dose to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 31, 2019) using the search term semaglutide and oral semaglutide. The search was limited to studies performed in humans and published in the English language.

Review of Efficacy

Phase 2 trial

This trial was a 26-week dose-finding trial comparing 5 doses of oral semaglutide to subcutaneous (SC) once-weekly semaglutide. The doses used in this study are not the ones used in the Phase 3 trials and marketed doses (3mg, 7mg, 14mg). However, this trial will be briefly discussed because it is the only one comparing oral and subcutaneous semaglutide. There were nine treatment arms in total. Patients were randomized to 2.5, 5, 10, 20, or 40mg using standard dose escalation or 40mg using slow escalation or fast escalation. The comparators were 1mg semaglutide SC and placebo. Only the 5, 10, and 20mg doses will be presented as they are the ones closest to the marketed doses. Patients started at 2.5mg and the dose was escalated at 4-week intervals until the final randomized dose was reached.

Mean baseline A1C ranged between 7.8-8.0%, mean fasting plasma glucose (FPG) 170mg/dL, and mean weight 93kg; 85% were receiving metformin. Change in A1C, FPG, and weight decreased in a dose-dependent fashion, while adverse gastrointestinal effects increased. The outcomes were similar for oral 20mg and subcutaneous semaglutide (**Table 2**).

Table 2 Phase 2 Trial

Change from baseline	Oral SEM 5.0mg	Oral SEM 10mg	Oral SEM 20mg	SEM SC 1.0mg	Placebo
A1C (%)	-1.2	-1.5	-1.7	-1.9	-0.3
FPG (mg/dL)	-27.8	-42.1	-41.9	-56.3	-1.1
Weight (kg)	-2.7	-4.8	-6.1	-6.4	-1.2
All GI AEs (%)	31	54	56	54	28

Abbreviations: FPG=fasting plasma glucose; GI=gastrointestinal; SC=subcutaneous; SEM=semaglutide

Phase 3 trials

There are ten phase 3 randomized, placebo and/or active control trials; four were placebo-controlled only, five were active comparator only, and one was both placebo- and active- controlled. The active comparators were sitagliptin, empagliflozin, and liraglutide. Oral semaglutide was evaluated as monotherapy or combination with metformin, metformin with or without sulfonylurea, metformin with or without a SGLT2 inhibitor, insulin with or without metformin.

In the PIONEER clinical trials (excluding PIONEER 7), all patients randomized to oral semaglutide initiated treatment with 3 mg once daily and followed a fixed 4-week dose-escalation regimen until reaching the randomized dose of 7mg or 14mg. PIONEER 7 evaluated flexible adjustment of semaglutide whereby the dose

was increased or decreased depending on glycemic efficacy and GI tolerability. Dosing for semaglutide began at 3mg and could be adjusted to 7mg and 14mg at eight-week intervals based on A1C or GI tolerability.

All semaglutide doses were taken in the morning in the fasted state with 120mL of water at least 30 minutes before any food or other beverages and oral medications.

PIONEER 5 was conducted in patients with renal impairment (eGFR 30-59mL/min/1.73m^2). Patients with rapidly progressing renal disease or known nephrotic albuminuria were excluded. Forty-percent of patients were considered Stage 3b renal impairment (eGFR 30-44mL/min/1.73m^2). The urinary albumin to creatine ratio (UACR) was less than 30mg/g in 62% of patients, UACR 30 to ≤300mg/g in 21%, and UACR >300mg/g in 15%. Patients with rapidly progressing renal disease or nephrotic albuminuria were excluded. Those who were on basal insulin at baseline reduced their dose by 20% to minimize the risk of hypoglycemia. Once the maximum semaglutide dose was reached, the dose of basal insulin could be titrated up to the baseline dose if needed.

PIONEER 6 was a cardiovascular outcome study and is discussed separately.

PIONEER 8 was an add-on to insulin study. The mean baseline total daily insulin dose 58 units; 42% on basal, 39% basal-bolus, 18% premixed. At randomization a 20% reduction in insulin dose was recommended and maintained for 8 weeks unless increase was needed to avoid acute metabolic deterioration. Between weeks 8-26, the dose of insulin could be increased up to the pre-randomization dose. During weeks 26-52, the dose could be adjusted at the investigator's discretion. At any time, the dose of insulin could be reduced as needed. At week 26, the mean change in insulin dose was -8, -9, and -1 unit for semaglutide 7mg, 14, and placebo respectively. At week 52, the change in insulin dose was -6, -7, and +10 units respectively.

The PIONEER trials used two estimands for presenting outcomes. The first was the "treatment policy" estimand evaluated the treatment effect for all randomized patients regardless of trial product discontinuation or use of rescue medication. The second was the "trial product" estimand which evaluated the treatment effect for all randomized patients with the assumption that all patients continued taking the trial treatment for the duration of the trial and did not use rescue medications. In this review, the "treatment policy" estimand will be presented. This estimand is the currently known method of data reporting (intent-to-treat) and was the one used to determine sample size and whose results were displayed in the product package insert.

Key Inclusion Criteria

Age greater than or equal to 18 years (PIONEER 6 greater than or equal to 50 years)
A1C 7.0% to 9.5% (PIONEER 2 and 3 were 7.0% to 10.5%; no baseline A1C requirement in PIONEER 6)

Key Exclusion Criteria

Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; history of pancreatitis; history of major surgical procedures involving the stomach potentially affecting absorption of trial product; New York Heart Association Class IV heart failure; planned coronary, carotid, or peripheral artery revascularization known on the day of screening; proliferative retinopathy or maculopathy requiring acute treatment verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomization; myocardial infarction, stroke or hospitalization for unstable angina or transient ischemic attack within the past 180 days prior to the day of screening (for PIONEER 6 it was within past 60 days); eGFR <60 (excludes PIONEER 5; for PIONEER 6 it was eGFR <30); history of DKA (PIONEER 2, 4, 6, 7), alanine aminotransferase > 2.5 times upper normal limit, malignant neoplasms in last 5 years (excluding basal and squamous skin and carcinoma in situ)

Glycemic Efficacy Outcomes

The mean decrease in A1C among the three trials with a 7mg treatment arm was -0.9%, -1.0%, and -1.2%. The mean change in A1C with the 14mg dose ranged from -1.0% to -1.4%. In the flexible adjustment trial, 30.2% and 59.4% were on 7mg and 14mg respectively at the end of the trial and the mean change in A1C was -1.3%.

Treatment with semaglutide resulted in significantly greater decrease in A1C than placebo and active comparators.

Two trials of interest will be discussed separately. PIONEER 2 compared semaglutide 14mg to empagliflozin 25mg as add-on to metformin. The mean change in A1C was -1.3% with semaglutide and -0.9% with empagliflozin both at week 26 and 52.

PIONEER 4 compared oral semaglutide 14mg to liraglutide 1.8mg, and placebo as add-on to metformin ± a SGLT2 inhibitor. The mean change in A1C with semaglutide was -1.2% at weeks 26 and 52 and -1.1% and -0.9% with liraglutide at weeks 26 and 52 respectively.

Refer to **Table 4** for other outcomes such as percentage of patients with A1C less than 7%, change in fasting blood glucose, 7-point self-monitoring of blood glucose, and need for rescue therapy.

Renal outcomes

In PIONEER 5, the moderate renal impairment (eGFR 30-59) study, renal outcomes such as change in eGFR or albuminuria were measured as safety outcomes. Renal function was unchanged in both oral semaglutide and placebo groups. The geometric mean of the urinary albumin to creatinine ratio (ratio of week 26 to baseline) was 0.86 (range 0.04-56.71) in the oral semaglutide group and 1.19 (range 0.01-79.59) in the placebo group.

In PIONEER 6, the CV outcome trial, those with an eGFR <30 were excluded and in the remaining PIONEER trials, those with an eGFR <60 were excluded. Estimated GFR was measured as a laboratory safety assessment. There was no change in the eGFR ratio from baseline to end of treatment in the oral semaglutide and placebo/active comparator groups. Urinary albumin-to-creatine ratio was not assessed.

Table 3 Glycemic Outcomes (Results shown as week 26/endpoint week where applicable)

Study	Weeks	Patients	Baseline Medications	Treatment arms	n	BL A1C (%)	A1C (%)	A1C < 7% (%pts)	BL FPG (mg/dL)	FPG (mg/dL)	7-point SMBG (mg/dL)	Add med (%) ¶	Rescue (%) †
Aroda PIONEER 1	26	Diet and exercise alone	None	SEMA (esc to 7mg) SEMA (es to 14mg) PBO	175 175 178	8.0 8.0 7.9	-1.2* -1.4* -0.3	69* 77* 31	162 158 160	-28* -33* -3	-36* -40* -8	4.6 4.0 19.7	2.3 1.1 15.2
Robard PIONEER 2	26/52	Add-on to MET		SEMA (esc to 14mg) EMPA 25mg	412 410	8.1 8.1	-1.3*/-1.3* -0.9/-0.9	67*/66* 40/43	172 174	-36/-36 -36/-38	-40*/-41* -35/-36	4/13 3/14	2/8 1/11
Rosenstock PIONEER 3	26/78	Add-on to MET ± SU	SU (47%)	SEMA (esc to 7mg) SEMA (esc to 14mg) SITA 100mg	465 465 467	8.4 8.3 8.3	-1.0*/-0.8 -1.3*/-1.1* -0.8-0.7	42*/37* 55*/44* 32/29	170 168 172	-21*/-18 -31*/-31* -15/-15	-27*/-25 -29*/-30* -21/-23	4/26 3/16 4/32	2/22 1/10 3/28
Pratley PIONEER 4	26/52	Add-on to MET±SGLT2	SGLT2 (26%)	SEMA (esc to 14mg) LIRA (esc to 1.8mg) PBO	285 284 142	8.0 8.0 7.9	-1.2/-1.2* -1.1/-0.9 -0.2/-0.2	68/61 62/55 14/15	167 167 166	-36/-34* -34/-26 -6/-13	-40*/-38* -34/-29 -25/-18	7/14 6/10 9/32	4/7 3/6 8/30
Mosenzon PIONEER 5 **Renal impairment**	26	Add-on to MET ± SU or BI ± MET	MET (75%) SU (40%) Insulin (35%)	SEMA (esc to 14mg) PBO	163 161	8.0 7.9	-1.0* -0.2	58* 23	164 164	-27* -7	Not assessed	7.4 13	4.3 9.9
Husain PIONEER 6 **CV safety**	f/u 15.9 mos.	Add-on to usual care	MET (77%) Insulin (60%) SU (32%) SGLT2 (10%)	SEMA (esc to 14mg) PBO	1591 1592	8.2 8.2	-1.0* -0.3	NA	155 157	Not assessed	Not assessed		
Pieber PIONEER 7	52	Add-on to 1-2 OADs	Monotx (40%) 2-drug tx (60%) Majority MET or MET+SU	SEMA flex dose adjustment** SITA 100mg	253 252	8.3 8.3	-1.3* -0.8	58* 25	176 176	-40* -26	Not assessed	8.7 18.7	3.2 15.9
Zinman PIONEER 8	26/52	Add-on to insulin± MET	Mean insulin dose 58U MET (67%)	SEMA (esc to 7mg) SEMA (esc to 14mg) PBO	182 181 184	8.2 8.2 8.2	-0.9*/-0.8* -1.3*/-1.2%* -0.1/-0.2	43*/40* 58*/54* 7/9	153 149 149	-19*/-18* -24/-28* 5/-2	-13*/-11 -16*/-7 -2/-4	4/25 4/24 6/41	1/18 2/17 5/36

Abbreviations: BI=basal insulin; BL=baseline; DM=diabetes mellitus; DULA=dulaglutide; EMPA=empagliflozin; GLA=glargine; FPG=fasting plasma glucose; LIRA=liraglutide; MET=metformin; NA=not applicable; OAD=oral antidiabetic agent; PBO=placebo; SGLT2=sodium-glucose cotransporter 2 inhibitor; SITA=sitagliptin; SEMA=oral semaglutide; SMBG=self-monitoring of blood glucose; SU=sulfonylurea

*Significant vs. comparator (placebo or active)

**At week 52, 9%, 30.2%, and 59.4% of patients were receiving semaglutide 3mg, 7mg, and 14mg respectively

¶ Additional glucose-lowering medication included an increase in current dose of ≥20% of that at randomization or use of rescue medication

†Rescue medication defined as additional medication initiated

Body Weight

Across studies, mean weight change ranged from -2.2 to -4.4kg. There was significantly greater weight loss with oral semaglutide than placebo, sitagliptin, and liraglutide. Weight loss was similar between oral semaglutide and empagliflozin; however, more patients had 10% or greater weight loss with semaglutide.

Table 4 Change in Weight (Results shown as week 26/endpoint week where applicable)

Study	Weeks	Treatments	Weight (kg)	Weight change (kg)	≥5% wt. loss (%)	≥10% wt. loss (%)	↓in A1C≥1% with ≥3%weight loss
PIONEER 1	26	SEMA (esc to 7mg)	89.0	-2.3	27*	8*	37*
		SEMA (es to 14mg)	88.1	-3.7*	41*	14*	51*
		PBO	88.6	-1.4	15	1	11
PIONEER 2	26/52	SEMA 14mg	91.9	-3.8/-3.8	41/40	13*/15*	45*/43*
		EMPA 25mg	91.3	-3.7/-3.6	36/39	7/8	28/26
PIONEER 3	26/78	SEMA (esc to 7mg)	91.3	-2.2*/-2.8*	19*/27*	5*/10*	26*/26*
		SEMA (esc to 14mg)	91.2	-3.1*/-3.4*	30*/33*	7*/11*	37*/34*
		SITA 100mg	90.9	-0.6/-1.0	10/14	2/4	9/14
PIONEER 4	26/52	SEMA (esc to 14mg)	92.9	-4.4*/-4.3*	44*/45*	14*/16*	47*/44*
		LIRA (esc to 1.8mg)	95.5	-3.1/-3.0	28/25	6/7	34/29
		PBO	93.2	-0.5/-1.0	8/12	0/3	4/7
PIONEER 5 Renal impairment	26	SEMA (esc to 14mg)	91.3	-3.4*	36*	8*	39*
		PBO	90.4	-0.9	10	0	8
PIONEER 6 CV trial	f/u 15.9 mos.	SEMA (esc to 14mg)	91.0	-4.2	Not assessed	Not assessed	Not assessed
		PBO	90.8	-0.8			
PIONEER 7	52	SEMA flex dose adjustment**	88.9	-2.6*	27*	6*	35*
		SITA 100mg	88.4	-0.7	12	2	11
PIONEER 8	26/52	SEMA 7mg	87.1	-2.4*/-2.0*	31*/28*	7*/10*	29*/22*
		SEMA 14mg	84.6	-3.7*/-3.7*	39*/39*	11*/12*	44*/38*
		PBO	86.0	-0.4/0.5	3/5	1/1	4/3

Abbreviations: BI=basal insulin; BL=baseline; EMPA=empagliflozin; GLA=glargine; LIRA=liraglutide; MET=metformin; NA=not applicable; OAD=oral antidiabetic agent; PBO=placebo; SEM=semaglutide; SU=sulfonylurea; TZD=thiazolidinedione

*Significant vs. placebo or active comparator

¶26-week data shown for change in weight

Cardiovascular Outcomes

PIONEER 6 evaluated the addition of oral semaglutide or placebo to usual care in 3183 patients with type 2 diabetes. There was no specific requirement for baseline A1C (mean was 8.2%). Eligibility included those who were ≥50 years old with established CV disease or chronic kidney disease OR ≥60 years old with CV risk factors only. The primary endpoint was the composite of death from CV causes, nonfatal stroke, or nonfatal MI.

Table 5 PIONEER 6: Inclusion and Exclusion Criteria

Established CV disease: Age ≥ 50 years and at least one of the following:
• Prior myocardial infarction, stroke, transient ischemic attack
• Coronary, carotid or peripheral arterial revascularization
• ≥ 50% stenosis on angiography or imaging of coronary, carotid or lower extremities arteries
• History of documented symptomatic coronary heart disease (e.g., positive exercise stress test or any cardiac imaging or unstable angina with ECG changes)

• Documented asymptomatic cardiac ischemia (e.g., positive nuclear imaging test or exercise test or stress echo or any cardiac imaging) • Chronic heart failure NYHA class II or III • Moderate renal impairment (eGFR 30-59mL/min/1.73m2)
Age ≥60 years at screening and at least one of the following risk factors:
• Microalbuminuria or proteinuria • Hypertension and left ventricular hypertrophy by electrocardiogram or imaging • Left ventricular systolic or diastolic dysfunction by imaging • Ankle-brachial index less than 0.9
Key Exclusion Criteria (see publication for complete list)
• Prior use of GLP-1 agonists, DPP-4 inhibitors, or pramlintide within 90 days of screening • MI, stroke, hospitalization for UA, or TIA within past 60 days • History of acute or chronic pancreatitis • Chronic or intermittent hemodialysis or peritoneal dialysis or severe renal impairment (eGFR<30) • Planned revascularization of a coronary, carotid, or peripheral artery • Proliferative retinopathy or maculopathy requiring acute treatment • History of diabetic ketoacidosis

Among those who were ≥50 years old with established CV disease or chronic kidney disease (84.7%), 56.5% had established CV disease without CKD, 11.1% had CKD only, and 17.1% had both CV disease and CKD. There were 15.3% who were ≥60 years old with CV risk factors only.

Baseline patient characteristics include mean age 66.7 years, 68.4% male, white 72.3%, weight 90.9kg, BMI 32.3, duration of diabetes 14.9 years, A1C 8.2%, SBP/DBP 136/76mmHg, LDL 78mg/dL, current smoker 11%, and eGFR 74mL/min/1.73m2 (72.5% with eGFR ≥60; 26.9% with eGFR <60), diabetic retinopathy 28%.

Cardiovascular disease and risk factors at screening include: prior MI 36.1%, prior stroke or TIA 15.9%, prior revascularization 47.2%, greater than 50% stenosis of coronary, carotid or lower extremity arteries 27.6%, symptomatic coronary heart disease 23%, NYHA Class 2-4 heart failure 12.2%, moderate renal impairment 28.2%, albuminuria 33%, hypertension and LVH 24.5%, left ventricular systolic or diastolic dysfunction 21%.

Baseline medications: metformin 77.3%, insulin 60.6%, sulfonylurea 32.2%, thiazolidinediones 3.7%, other antiglycemics 4.2%, antihypertensives 94%, lipid-lowering drugs 85%, antithrombotics/antiplatelets 79%, diuretics 40%.

The median time in the trial was 15.9 months. Oral semaglutide was found to be noninferior to placebo for the primary outcome **(Table 6)**. Testing for superiority did not find semaglutide to be superior to placebo for the primary outcome. In a subgroup analysis for the primary outcome, the results did not differ for those with established CV disease versus those with CV risk factors.

Results of primary and secondary outcomes are shown in **Table 6**. All-cause mortality and CV-related death were reduced. For other secondary outcomes, the 95% confidence intervals for the point estimates included one. Microvascular outcomes (retinopathy and nephropathy) were not assessed as an efficacy outcome. However, eGFR was measured as a laboratory safety assessment. There was no change in the eGFR ratio from baseline to end of treatment in either group. Albuminuria was not assessed.

During the trial, fewer patients receiving semaglutide required addition of insulin or other anti-glycemic medications. The addition of antihypertensives, diuretics, anti-lipid agents, and antithrombotic agents during the trial were similar in both groups.

The outcome of the FDA review of the PIONEER 6 trial was that oral semaglutide demonstrated CV safety by meeting the primary endpoint of non-inferiority for the composite MACE endpoint.

Patient recruitment (estimated n=9642) is ongoing for the SOUL trial, A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (NCT03914326). The primary endpoint is MACE; secondary endpoints include renal outcomes. Estimated study completion date is July 2024.

Table 6 PIONEER 6: Cardiovascular and Microvascular Outcomes

Outcome	Semaglutide (n=1591)		Placebo (n=1592)		HR [95%CI]
	N (%)	N/100 ppy	N (%)	N/100 ppy	
Primary Composite Outcome CV death, nonfatal MI, nonfatal stroke	61 (3.8)	2.9	76 (4.8)	3.7	0.79 [0.57, 1.11] **
Expanded Composite Outcome CV death, nonfatal MI, nonfatal stroke, hosp. for UA or HF	83 (5.2)	4.0	100 (6.3)	4.9	0.82 [0.61, 1.10]
Composite of all-cause death, nonfatal MI, nonfatal stroke	69 (4.3)	3.3	89 (5.6)	4.4	0.77 [0.56, 1.05]
All-cause death	23 (1.4)	1.1	45 (2.8)	2.2	0.51 [0.31, 0.84]
CV-related death	15 (0.9)	0.7	30 (1.9)	1.4	0.49 [0.27, 0.92]
Nonfatal MI	37 (2.3)	1.8	31 (1.9)	1.5	1.18 [0.73, 1.90]
Nonfatal stroke	12 (0.8)	0.6	16 (1.0)	0.8	0.74 [0.35, 1.57]
Hospitalization for UA	11 (0.7)	0.5	7 (0.4)	0.3	1.56 [0.60, 4.01]
Hospitalization for HF	21 (1.3)	1.0	24 (1.5)	1.2	0.86 [0.48, 1.55]

Abbreviations: CV=cardiovascular; HF=heart failure; HR=hazard ratio; MI=myocardial infarction; NS=not significant; PPY=per patient-year; UA=unstable angina

** p-value <0.001 for noninferiority and p=0.17 for superiority

Safety

For more detailed information, refer to the prescribing information.

Boxed Warning

In rodents, semaglutide causes thyroid C-cell tumors. It is unknown whether semaglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of semaglutide-induced rodent thyroid C cell tumors has not been determined.

Semaglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors.

Contraindications

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2
- Known hypersensitivity to semaglutide or any of the product components

Warnings / Precautions

- Pancreatitis: Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed.
- Diabetic Retinopathy Complications: Has been reported in a clinical trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions

Adverse Reactions

Common Adverse Reactions

The most common adverse reactions, reported in ≥5% of patients treated with oral semaglutide are: nausea, abdominal pain, diarrhea, decreased appetite, vomiting, and constipation

Deaths / Serious Adverse Events / Discontinuations Due to Adverse Reactions

Serious adverse events and deaths were balanced across groups **(Appendix 1).** There were more discontinuations due to adverse reactions with oral semaglutide than with placebo and active-comparators. The most common reason for discontinuation was due to GI adverse events.

Safety Considerations

Retinopathy

In the SUSTAIN-6 trial of once weekly injectable semaglutide, there was an increased risk of retinopathy complications defined as need for retinal photocoagulation or treatment with intravitreal administered agents, vitreous hemorrhage, or onset of DM-related blindness with injectable semaglutide than placebo (3% versus 1.8% HR=1.76; 95% CI 1.11, 2.78). The absolute risk increase for diabetic retinopathy (DR) complications was larger among patients with a history of DR at baseline.

In a pooled analysis of glycemic control trials with oral semaglutide, diabetic retinopathy related adverse reactions during the trial were reported in 4.2% and 3.8% of patients receiving oral semaglutide and comparator respectively.

Hypoglycemia

Hypoglycemia was defined as severe or blood glucose-confirmed symptomatic hypoglycemia <56mg/dL. In PIONEER 6, only severe hypoglycemia was assessed.

Hypoglycemia was more frequent when oral semaglutide was used in combination with sulfonylureas or insulin. Hypoglycemia events were comparable between oral semaglutide and the active-comparators **(Appendix 1).**

Gastrointestinal

Gastrointestinal (GI) adverse events, such as nausea, vomiting and diarrhea are commonly associated with GLP-1 agonist therapy.

In the pooled-placebo controlled trials GI adverse events occurred in 32%, 41%, and 21% of patients receiving semaglutide 7mg, 14mg, and placebo. Most events occurred during dosage escalation. More patients

discontinued semaglutide due to adverse GI events (4%, 8%, 1% respectively). Adverse GI events occurred more frequently with oral semaglutide versus active-comparators. **Appendix 1**

Pancreatitis

In clinical trials, pancreatitis was reported as a serious adverse event in six oral semaglutide-treated patients (0.1 events per 100 patient years) versus 1 in comparator-treated patients (<0.1 events per 100 patient years).

Increases in Amylase and Lipase

In placebo-controlled trials, patients receiving oral semaglutide 7 mg and 14 mg had a mean increase from baseline in amylase of 10% and 13%, respectively, and lipase of 30% and 34%, respectively. These changes were not observed in placebo-treated patients.

In the active-comparator trials, the increase in lipase was significantly greater with oral semaglutide than empagliflozin (estimated ratio to baseline was 1.23 and 1.09 respectively). There was no difference between treatments for amylase. Changes in lipase and amylase were comparable between oral semaglutide versus sitagliptin and liraglutide.

Cholelithiasis

Some injectable GLP-1 agonists have been associated with an increased risk of bile duct and gallbladder disease. In placebo-controlled trials, cholelithiasis was reported in 1% of patients treated with oral semaglutide 7 mg and in none of the semaglutide 14 mg or placebo-treated patients.

Blood Pressure

Across the clinical trials, mean reduction in systolic blood pressure (SBP) for oral semaglutide 7mg was -2 to -3mmHg. For the 14mg dose, the mean change in SBP ranged from -3mmHg to -5mmHg. In the moderate renal impairment trial, the mean change was -7mmHg.

For diastolic blood pressure, the mean reduction across studies for both doses ranged from -1 to -2mmHg. The decrease in SBP and DBP was similar between semaglutide 14mg and empagliflozin. The decrease in SBP was greater with semaglutide than liraglutide or sitagliptin; the differences in DBP were comparable.

Pulse Rate

In placebo-controlled trials, semaglutide 7 mg and 14 mg resulted in a mean increase in heart rate of 2 to 3 beats per minute. There was no change in heart rate in placebo-treated patients.

There was no significant difference in HR between oral semaglutide and empagliflozin (0 vs. -1 bpm), semaglutide and liraglutide (2 vs. 3 bpm), or semaglutide and sitagliptin (1-2 vs. 1 bpm).

Immunogenicity

Across the placebo-and active-controlled glycemic control trials with antibody measurements, 14 (0.5%) oral semaglutide-treated patients developed anti-drug antibodies (ADAs) to semaglutide. Of the 14 semaglutide-treated patients that developed semaglutide ADAs, 7 patients (0.2% of the overall population) developed antibodies cross-reacting with native GLP-1. The neutralizing activity of the antibodies is uncertain at this time.

Drug Interactions

Drug-Drug Interactions

- Semaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Levothyroxine exposure was increased 33% (90% CI: 125-142) when administered with semaglutide tablets in a drug interaction study. Consider increased clinical or laboratory monitoring for medications that have a narrow therapeutic index or that require clinical monitoring.
- When semaglutide is added to a sulfonylurea or basal insulin, there is an increased risk of hypoglycemia. The risk may be lessened by reducing the dose of sulfonylurea or basal insulin.

Special Populations (Adults)

Elderly

In the pool of placebo- and active-controlled glycemic control trials, 1229 (29.9%) and 199 (4.8%) of semaglutide-treated patients were ≥65 years old and ≥75 years old respectively.

In PIONEER 6, the cardiovascular outcome trial, 691 (43.4%) and 195 (12.3%) of semaglutide -treated patients were ≥ 65 years old and ≥75 years old respectively.

No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pregnancy

There are insufficient data with oral semaglutide use in pregnant women to inform a drug-associated risk for major birth defects, miscarriage or other adverse maternal or fetal outcomes. In pregnant rats administered semaglutide during organogenesis, embryo fetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC.

In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and ≥10-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species.

Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. Oral semaglutide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Salcaprozate sodium (SNAC), an absorption enhancer oral semaglutide, crosses the placenta and reaches fetal tissues in rats. In a pre-and postnatal development study in pregnant Sprague Dawley rats, SNAC was administered orally at 1,000 mg/kg/day (exposure levels were not measured) on Gestation Day 7 through lactation day 20. An increase in gestation length, an increase in the number of stillbirths and a decrease in pup viability were observed.

Lactation

There is no information regarding the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. However, semaglutide is present in the milk of lactating rats at levels 3 to 12-fold lower than maternal plasma.

SNAC and/or its metabolites were detected in milk of lactating rats following a single maternal administration on lactation day 10. Mean levels of SNAC and/or its metabolites in milk were approximately 2 to 12-fold higher than in maternal plasma. There are no data on the presence of SNAC in human milk. Since the activity of UGT2B7, an enzyme involved in SNAC clearance, is lower in infants compared to adults, higher SNAC plasma levels may occur in neonates and infants

Because of the unknown potential for serious adverse reactions in the breastfed infant due to the possible accumulation of SNAC from breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise patients that breastfeeding is not recommended during treatment with oral semaglutide.

Females and Males of Reproductive Potential
Discontinue oral semaglutide in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Renal/Hepatic Impairment
No dose adjustment of oral semaglutide is recommended for patients with renal or hepatic impairment.

Risk Evaluation

As of 19/17/2019

Sentinel Event Advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike / Sound-alike Error Potential

- Semaglutide: semaglutide injection, liraglutide, dulaglutide (clinical judgement)
- RYBELSUS: Belsomra, Mibelas 24 FE

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)
Note: LASA potentials listed are not all-inclusive as other medications may be mistaken due to LASA similarities

Other Considerations

Trials of interest

- PIONEER 9 and PIONEER 10 were conducted in Japanese patients. PIONEER 9 compared oral semaglutide to liraglutide and PIONEER 10 compared oral semaglutide to dulaglutide. These trials were not published at the time of this writing.

Projected Place in Therapy

Until more information is available regarding cardiovascular outcomes, oral semaglutide is not recommended as a second-line option for those with established CV disease. Oral semaglutide might be considered a third-line option for those without CV disease, similar to the injectable GLP1-agonists provided eventual cost is lower or comparable.

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Appendix 1: Safety Outcomes (%)

Study	Weeks	Patients	Treatment arms	n	SAE	d/c due to AE	Deaths	Hypoglycemia**	N/V/D	DR	Acute pancreatitis	Malignant neoplasm
PIONEER 1	26	Diet and exercise alone	SEMA (esc to 7mg)	175	1.7	4.0	0	1.1	5.1/4.6/5.1	3.4	0	0
			SEMA (es to 14mg)	175	1.1	7.4	0.6	0.6	16/6.9/5.1	1.1	0	0
			PBO	178	4.5	2.2	0	0.6	5.6/2.2/2.2	1.7	0	1.7
PIONEER 2	52	Add-on to MET	SEMA 14mg	412	6.6	10.7	0	1.7	20/7/9	3.4	0.2	1.7
			EMPA 25mg	410	9.0	4.4	0.2	2.0	2/2/3	1.2	0.2	0.5
PIONEER 3	78	Add-on to MET ± SU	SEMA (esc to 7mg)	465	10.1	5.8	0.6	5.2	13.4/6/11.4	5.2	0.2	1.9
			SEMA (esc to 14mg)	465	9.5	11.6	0.2	7.7	15.1/9/12.8	3.4	0.2	0.6
			SITA 100mg	467	12.4	5.2	0.6	8.4	6.9/4.1/7.9	5.8	0.2	1.5
PIONEER 4	52	Add-on to MET±SGLT2	SEMA (esc to 14mg)	285	11	10.9	1.1	1.0	20/9/15	2.8	0	1.1
			LIRA (esc to 1.8mg)	284	8	9.2	1.4	2.0	18/5/11	1.4	0.4	1.1
			PBO	142	11	3.5	0.7	2.0	4/2/8	1.4	0.7	0
PIONEER 5 **Renal impairment**	26	Add-on to MET ± SU or BI ± MET	SEMA (esc to 14mg)	163	10	15	1.0	6.0	19/12/10	3.1	0	1.2
			PBO	161	11	5.0	1.0	2.0	7/1/4	1.2	0	1.9
PIONEER 6 **CV safety**	f/u 15.9 mos.	Add-on to usual care	SEMA (esc to 14mg)	1591	18.9	11.6	1.4	1.4	6.8‡	7.1	0.1	2.6
			PBO	1592	22.5	6.5	2.8	0.8	1.6‡	6.3	0.2	3.0
PIONEER 7	52	Add-on to 1-2 OADs	SEMA flex dose adjustment**	253	9	9	0	5.5	21/6/9	2	0	3.2
			SITA 100mg	252	10	3	0.8	5.6	2/1/3	2	0	0.8
PIONEER 8	52	Add-on to insulin	SEMA 7mg	181	10.5	8.8	0	26.0	17/8/12	7.7	0	1.1
			SEMA 14mg	181	6.6	13.3	1.7	26.5	23/10/15	7.2	0	1.1
			PBO	184	9.2	2.7	0	29.3	7/4/6	6.0	0	0

Abbreviations: AE=adverse events; BI=basal insulin; D=diarrhea; d/c=discontinued; DR=diabetic retinopathy; DULA=dulaglutide; EMPA=empagliflozin; esc=escalate; LIRA=liraglutide; MET=metformin; N=nausea; OAD=oral anti-glycemic drugs; PBO=placebo; SAE=serious adverse event; SEMA=semaglutide; SGLT2= sodium-glucose cotransporter-2; SITA=sitagliptin; V=vomiting

**Hypoglycemia defined as severe or blood glucose confirmed symptomatic hypoglycemia. For PIONEER 6, only severe hypoglycemia is shown.

‡ All GI disorders