Thames Valley
Family Health Team

THE DOSE

May 2020: It's not all about COVID!

In this issue:

New medication that may impact primary care

Rybelsus® (oral semaglutide)

- First oral GLP-1 agonist approved for the treatment of Type 2 DM. Click here for the indepth details for oral semgalutide

Bottom line: If considering a GLP-1 agonist, preference should be given to the following injectable GLP-1 agonists (**dulaglutide, liraglutide and semaglutide**) as they have demonstrated a reduction in major adverse cardiovascular events (MACE) whereas oral semaglutide was no different than placebo. **Rybelsus®** has **difficult administration requirements** (30-60mins before first meal/other medications with ≤ 120mls of water) that will limited its usefulness in clinical practice.

Vascepa® (icosapent ethyl)

- Purified form of EPA approved for use in combination therapy with statins for patients with triglycerides >1.69mmol/L despite maximal statin dose who are at risk for cardiovascular disease**.** Click here for the indepth details for icosapent ethyl

Bottom line: Vascepa®, unlike other omega 3 products, has demonstrated a reduction of 4.8% in CV composite outcome over 5 years with adjunctive statin therapy. This means, for every 21 patients treated with iscosapent ethyl 2g bid compared to mineral oil there was 1 less composite event of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina over a median of 5 years.

Question of the month: Do vaccine series need to be restarted if interrupted?

- Typically, vaccines series **do not need to be restarted** if they are delayed or interrupted regardless of the duration between the injections. It is important to note that full protection and long-term effectiveness may not occur until the series is complete.
    - **Exceptions** are Dukoral® (cholera/traveller's diarrhea) and rabies vaccination post exposure
- Vaccines should not be given before the minimum interval or they will need to be repeated. The minimal interval for each vaccine can be found at:

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-10-timing-vaccine-administration.html

SGLT-2 inhibitors and peri-operative considerations

FDA now recommends temporary discontinuation of SGLT-2 inhibitors before planned surgery due to a greater risk of diabetic ketoacidosis.

- Canagliflozin, dapagliflozin and empagliflozin should be discontinued 3 days prior to procedure
- Ertugliflozin should be discontinued 4 days prior to procedure

SGLT-2 inhibitors can be restarted once the patient is eating and drinking well and other risk factors for ketoacidosis have returned to baseline.

D Angevine RPh, K Koroluk PharmD, T Kontio RPh, P Patel Pharm D

COVID-19 and office injections

- Medsask has put together a resource on injections (vaccinations, B12, Depo- Provera, Anti-psychotics) during COVID-19 (https://medsask.usask.ca/pharmacist-injections_covid.pdf)

In case your patient asks:

- "*My salbutamol inhaler packing is in Spanish*". Health Canada has given an exemption for this product due to the current salbutamol shortage. The priming of this device is different than the Canadian devices as it **requires only 1 puff before first use** and if the device has not been used for a few days compared to **the Canadian versions that require 4 puffs** before first use and if the device has not been used for more than 5 days.
    - https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/73143a-eng.php
- ODB benefits is currently **waving all co-pays for medications until July 1st, 2020**
- Trillium Drug Benefits: Patients that have had a change of income can request to have their income reassessed. The form can be found at:
    - http://www.forms.ssb.gov.on.ca/mbs/ssb/forms/ssbforms.nsf/FormDetail?OpenForm&ACT=RDR&TAB=PROFILE&ENV=WWE&NO=014-4931-87E

Medications recently added to the ODB formulary:

Sublocade® (extended release injectable buprenorphine) under LU 577

- For patients with Opioid Use Disorder that have been stabilized on transmucosal buprenorphine 8mg-24mg daily for a minimum of 7 days
- Initial dose is 300mg q monthly x 2 months then 100mg q monthly. Patients may be increased to 300mg q monthly if needed
    - Minimum interval is ≥ 26 days
- Requires certification by healthcare providers to prescribe and inject
    - Injection certification can be found at: https://www.sublocaderems.com/
- Medication is sent directly from pharmacy to clinician as it does not contain naloxone
- Cost per month ~ $550

Probuphine® (buprenorphine subdermal implant) under LU 578

- For patients with opioid use disorder that have been stabilized on no more than 8mg of transmucosal buprenorphine for the previous 90 days
- Dosing 4 x80mg implants inserted subdermally in the inner side of the upper arm for 6 months
    - Implants need to be removed after 6 months
- Requires clinician training for inserting and removing
- Cost per 6 months of treatment ~$1500

For more information on Opioid Use disorder: https://cep.health/clinical-products/opioid-use-disorder

Referrals to the RAAM clinic: Patient self-referral by drop in or by HCP referral. Referral form and clinic hours can be found at: http://adstv.on.ca/programs-services/rapid-access-addiction-medicine-raam/

Drugs that have been discontinued:

Coumadin (brand name warfarin) has been discontinued by the manufacturer. **The generic versions of warfarin are available**. If a patient is being transitioned from one brand to another consider repeating an INR with this change.

https://www.bms.com/assets/bms/ca/documents/productmonograph/CANADA-Coumadin-deletion_D-HCP-Communication_FINAL_EN_04.23.2020.pdf

Rybelsus® (oral semaglutide)	
Class	GLP-1 receptor agonist
Indication	adjunctive to diet and exercise to improve glycemic control in adults with type 2 diabetes -combination therapy with other hypoglycemics -monotherapy if 1st line metformin is not tolerated or contraindicated
Dosing	Starting dose: 3mg once daily for 30 days, then increase to 7mg once daily If additional glycemic control is needed, can increase to 14mg once daily Key administration points - **Take on an empty stomach 30-60mins before first meal of the day** - ≤120mls (1/2 cup) of water ○ If taken with larger volume of water may reduce drug absorption - Do not administer with other medications
Dose adjustments	**Renal impairment**: no dose adjustment necessary (Not studied in patients with GFR<30mL/min) **Hepatic impairment:** no dose adjustment necessary (limited experience)
Contraindications	Personal/family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN 2) Pregnancy or breast feeding
Precautions	Cardiovascular: can increase heart rate and prolong PR interval Hypoglycemia risk when used with sulfonylureas or insulin History of pancreatitis Diabetic retinopathy can occur with rapid glycemic improvement Renal insufficiency in the setting of dehydration from nausea, vomiting or diarrhea
Special Populations	**Pregnancy:** risk observed in animal studies. Women with childbearing potential are recommended to use contraception when treated with semaglutide Semaglutide should be stopped 2 months prior to attempting to become pregnant **Breast feeding:** No human data- Not recommended **Pediatrics:** Not indicated in patients 18 and under **Geriatrics:** ~30% of the combined trial population was over the age of 65 with no differences in safety detected.
Adverse Events	**Common Side effects** GI: nausea, diarrhea, constipation, vomiting (improves with time; slow dose titration) Increased amylase/lipase Decreased appetite **Less common** Cholelithiasis <2% Pancreatitis <1%
Drug interactions	Semaglutide is not a substrate, inhibitor or inducer of CYP 450 enzymes Levothyroxine (increased absorption of levothyroxine) NOTE: often both dosed before breakfast Medications that affect glucose homeostasis Semaglutide absorption is impaired if taken with other medications (↓AUC/Cmax by 30%)
Outcome data	**Reduction of A1C** ranged from **0.9-1.1%** compared to placebo over 26 weeks Absolute **reduction in weight** compare to placebo of **0.9-2.3kg** over 26 weeks In patients with established or high risk for cardiovascular disease, oral semaglutide was non-inferior to placebo for reduction in MACE outcome over 16 months. ▪ Note this trial had less patients and had a shorter duration compared to LEADER (liraglutide), REWIND (dulaglutide), SUSTAIN-6 (semaglutide), HARMONY (albiglutide) **Comparison to other diabetic agents:** Oral semaglutide 14mg once daily was **more effective** than empagliflozin (Jardiance) and sitagliptin (Januvia®) for **reduction in weight and HbA1C**. It was non-inferior to liraglutide (Victoza®) for reduction in A1C. Click here to see summaries of the Pioneer trials.

<table>
<tr><td></td><td>Unfortunately, there have been no direct comparison trials with once weekly injectable semaglutide. Once weekly injectable semaglutide demonstrated a reduction of MACE outcomes compared to placebo where as oral semaglutide was non-inferior.</td></tr>
<tr><td>Place in therapy</td><td>Patients without cardiovascular disease
- 2nd or 3rd line after metformin depending on patient factors and cost
- Consider oral semaglutide must be taken 30-60mins before first meal with less than 120mls of water as this may be difficult for some patients

Patients with cardiovascular disease or high risk for cardiovascular disease currently on metformin:
-Oral semaglutide not a preferred agent. Agents with cardiovascular benefit are preferred such as:
• SGLT-2 inhibitors (canagliflozin, empagliflozin)
○ Dapagliflozin was neutral for reduction in MACE outcomes but in heart failure patients was shown to reduce worsening of HF and CV mortality.
• GLP-1 agonist (dulaglutide, liraglutide, injectable semaglutide)

Summary chart on outcomes can be found at:
https://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf

Updated 2020 American Diabetes guidelines pharmacotherapy algorithm
https://care.diabetesjournals.org/content/43/Supplement_1/S98#F1</td></tr>
<tr><td>Switching between semaglutide oral and Injectable</td><td>
<table>
<tr><th>From Injectable to Oral</th><th>From Oral to injectable</th></tr>
<tr><td>▪ If using Ozempic 0.5 mg/week, can start oral semaglutide within 7 days after the last Ozempic injection.
▪ Can transition to 7 mg or 14 mg/day of oral semaglutide.</td><td>If taking 14 mg/day, can transition to Ozempic 0.5 mg/week. (no recommendations for switch from 3 mg or 7 mg of oral semaglutide)

- Begin weekly injectable semaglutide the day after the last dose of oral.</td></tr>
</table>
</td></tr>
<tr><td>Cost</td><td>$220 + pharmacy fee for 30 days
Not covered by ODB</td></tr>
</table>

Vascepa® (Icosapent Ethyl)

Class	Purified form of an Omega -3 fatty acid EPA (Eicosapentaenoic acid)
Indication	adjunctive therapy to statin treated patients with elevated triglycerides who are at risk of cardiovascular disease due to 1. Established cardiovascular disease 2. DM plus one other cardiovascular risk factor
Dosing	2g (2x1g capsules) orally twice daily with meals
Dose adjustments	**Renal impairment**: no dose adjustment provided- EPA and DHA are not renally eliminated **Hepatic impairment:** has not been studied at present
Contraindications/ Precautions	Shellfish or fish allergy: possible increased risk of allergic reaction Increase risk of bleeding if taking concurrent antithrombotic therapy
Special Populations	**Pregnancy:** no human data, risk observed when administered to pregnant rats **Breast feeding:** No human data- Not recommended **Pediatrics:** Not indicated in patients 18 and under **Geriatrics:** consistent benefit and tolerability was seen in this age group. 45% of patients in RCTs were 65 years of age and over
Adverse Reactions (drug vs placebo)	Peripheral edema (6.5% vs 5%) Constipation (5.4% vs 3.6%) Atrial Fibrillation (3.1% vs 2.1%) Bleeding (11.8% vs 9.9%) - No difference vs. placebo for hemorrhagic stroke or serious GI bleed Diarrhea? (9% vs 11.1% - Mineral oil placebo used in trial is a laxative…)
Drug interactions	No effect was seen on CYP P450 enzymes Anti-thrombotics: increased risk of bleeding
Outcome data Trial: REDUCE-IT	See table below

Patient	45 years and older if had established cardiovascular disease 50 years and older if they had DM and one additional CVD risk factor Required a fasting triglyceride level between 1.69 to 5.63mmol/L +/-10% for variation (at least 1.52mmol/L) LDL level between 1.06-2.59mmol/L Stable statin dose for at least 4 weeks Note: 29% primary prevention and 71% secondary prevention. Most of the population was white males with an average age of ~65.
Intervention	2g (2x1g capsules) orally twice daily with meals
Comparator	Mineral Oil Placebo
Outcome	Hard outcomes: 4.8% absolute reduction of CV events (17.2% vs 22.0%) over 5 years. For every 21 patients treated with iscosapent ethyl 2g bid compared to mineral oil there was 1 less composite event of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization or unstable angina over a median of 5 years. Benefits appear attenuated in primary prevention (vs 2^{o} prev.)

Surrogate markers:

	Alone	In combination with a statin
LDL	-	Additional ↓ 6.2%
HDL	-	-
Triglycerides	↓27%	Additional ↓ 21.5%

Place in therapy	Consider for patients at high risk of CVD or established CVD with TG > 1.69 mmol/L despite maximum tolerated statin therapy. Not currently listed in guidelines (trial published January 2019). Comparison to other Omega-3 therapies:

	- Natural health product or OTC omega 3 have not shown comparable benefits, likely due to lower EPA content and higher saturated fatty acid content - Negative results in ASCEND and STRENGTH trials show composition and dose matters for potential benefit
Cost	$294/month + pharmacy fees Not currently covered by ODB

References

- Semaglutide. Lexi-Drugs. [updated 2020 May 14 ; cited 2020 May 14] In Lexicomp Online [Internet]. Wolters Kluwer Clinical Drug Information, Inc. Hudson, Ohio. Available at: http://online.lexi.com/lco/action/home
- Aroda VR, Rosenstock J, Terauchi Y, et al, Effect and safety of oral semaglutide monotherapy in type 2 diabetes—PIONEER 1 trial. *Diabetes.* 2018;67(Suppl. 1). https://doi.org/10.2337/db18-2-LB.
- Montanya E, Rosenstock J, Canani LH, et al. Oral Semaglutide vs Empagliflozin Added-on to Metformin Monotherapy in Uncontrolled Type 2 Diabetes: PIONEER 2. Presented at: American Diabetes Association 79th Scientific Sessions, San Francisco, CA; 7–11 June 2019. Abstr 54-OR.
- Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. Jama. 2019;321(15):1466-1480
- Pratley RE, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial. *Lancet.* 2019; DOI:https://doi.org/10.1016/S0140-6736(19)31271–1.
- Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial. *Lancet Diabetes and Endocrinology.* 2019; DOI:https://doi.org/10.1016/S2213-8587(19)30192-5.
- Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;381:841-51
- Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial. *Lancet Diabetes and Endocrinology.* 2019; DOI:https://doi.org/10.1016/S2213-8587(19)30194-9.
- Zinman B, Aroda V, Buse JB, et al. 985-P: Oral semaglutide as add-on to insulin in T2D: PIONEER 8. *Diabetes.* 2019;68 (Suppl. 1): DOI:https://doi.org/10.2337/db19-985-P.
- **Centre for drug evaluation and research. A division of Drug information.** FDA Approves Label Changes to SGLT2 Inhibitors Regarding Temporary Discontinuation of Medication Before Scheduled Surgery. Accessed May 6, 2020. http://s2027422842.t.en25.com/e/es?s=2027422842&e=312220&elqTrackId=376c7bc788024cd5a73d955f2e3dcbdc&elq=88805802632f4dc88dd18426307959d3&elqaid=11643&elqat=1
- Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2020.* American Diabetes Association. Diabetes Care Jan 2020, 43 (Supplement 1) S98-S110; **DOI:** 10.2337/dc20-S00
- *Vascepa Product Monograph*. Etobicoke, Ontario: HLS Therapeutics. December 30, 2019.
- Bhatt DL, Miller M, Brinton EA, et al., on behalf of the REDUCE-IT Investigators. REDUCE-IT USA: Results From the 3,146 Patients Randomized in the United States. *Circulation* 2019;Nov 11
- Bhatt DL, Steg G, Miller M, et al., on behalf of the REDUCE-IT Investigators. Cardiovascular Risk Reduction With Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019;380:11-22.

Trial Name	Intervention	Patient Population	Changes in A1c	Changes in Weight	Adverse Effects (AE)
PIONEER-1: Oral Semaglutide Compared to Placebo for Medication-naive T2DM Patients					
PIONEER-1	Oral semaglutide (3,7, or 14 mg) vs Placebo for **26 weeks**	N=703 Patients ≥ 18 years old T2DM pts inadequately controlled with **diet and exercise.**	By week 26, average A1c reductions relative to placebo were between **0.6-1.1%** - 3 mg: -0.6% - 7 mg: -0.9% - 14 mg: -1.1%	Semaglutide: - 7 mg: -2.3 kg - 14 mg: -3.7 kg Placebo: -1.4 kg	Nausea was most common AE : **5-16%** of pts treated with oral semaglutide vs **6%** with placebo. Treatment discontinuation due to AEs with oral semaglutide was 2-7% vs 2% with placebo
Key Findings					
- Oral semaglutide demonstrated clinically relevant improvements in A1c at all doses. - Higher dose oral semaglutide (14 mg) produced statistically significant weight reduction compared to placebo (weight reduction of 44% compared to 16% with placebo).					
PIONEER-2: Oral Semaglutide Compared to an SGLT2 Inhibitor for T2DM Patients On Metformin					
PIONEER-2	Oral semaglutide 14 mg/day vs Empagliflozin 25 mg/day for **52 weeks**	N = 822 Patients ≥ 18 years old T2DM pts on stable daily **metformin**	Semaglutide: at 26 weeks: -1.3% At 52 weeks: - 1.4% Empagliflozin: At 26 weeks: -0.9% At 52 weeks: -0.8%	Semaglutide: At 26 weeks: -3.8 kg At 52 weeks: - 4.7 kg Empagliflozin: At 26 and 52 weeks: - - 3.8 kg	With semaglutide, the most common AE was mild-mod nausea (diminished over time and occurred in **20%** of patients) **11%** of pts discontinued semaglutide due to AEs compared to **4%** with empagliflozin
Key Findings					
- Oral semaglutide at 14 mg/day was significantly more efficacious than the SGLT2 inhibitor, empagliflozin, at 26 weeks (1.3% vs 0.9% A1c reductions) - Weight loss with oral semaglutide was significantly greater than with empagliflozin at the 52-week time point. (4.7 kg vs 3.8 kg respectively)					
PIONEER-3: Oral Semaglutide Compared to a DPP4 Inhibitor for T2DM Patients on Metformin +/- A Sulfonylurea					
PIONEER-3	Oral semaglutide (3 mg, 7 mg, or 14 mg/day) vs Sitagliptin 100 mg/day for **26 weeks**	N=1864 Patients ≥ 18 years old T2DM pts on daily dose of **metformin +/- a sulfonylurea**	Semaglutide: 3 mg: -0.6% 7 mg: -1.0% 14 mg:-1.3% Sitagliptin: -0.8%	Semaglutide: 3 mg: -1.2 kg 7 mg: -2.2 kg 14 mg: -3.1 kg Sitagliptin: -0.6 kg	Most common AE was mild-mod nausea (**7-15%** in semaglutide group vs **7%** in sitagliptin group.) **6-12%** of pts on oral semaglutide discontinued due to AEs vs **5%** with sitagliptin
Key Findings					
- Semaglutide 7 and 14 mg significantly reduced HbA_{1c} compared to sitagliptin. - There were statistically significant and superior reductions in weight with oral semaglutide 7 and 14 mg compared to sitagliptin. - The two higher doses of oral semaglutide (7 and 14 mg/day) were able to reduce A1c by an additional 0.3-0.5% and body weight by an additional 1.6-2.5 kg compared to sitagliptin.					
Trial Name	**Intervention**	**Patient Population**	**Changes in A1c**	**Changes in Weight**	**Adverse Effects (AE)**
PIONEER-4: Oral Semaglutide Compared to an Injectable GLP-1 Agonist in T2DM Patients on Metformin +/- an SGLT2 Inhibitor					
PIONEER-4	Oral semaglutide vs Injectable Liraglutide(up to 1.8 mg) vs Placebo for **26 weeks**	N=711 Patients ≥ 18 years old T2DM pts on daily dose of **metformin +/- an SGLT2 inhibitor**	Oral Semaglutide: -1.2% Injectable Liraglutide: -1.1% Placebo: -0.2% -	Oral Semaglutide: -4.4 kg Injectable Liraglutide: -3.1 kg Placebo: -0.5 kg	Most common AE was mild-moderate nausea Occurred in **20%** of pts with semaglutide vs **18%** with liraglutide vs **4%** with placebo **11%** of pts on semaglutide **discontinued due to AE**s vs **9%** with liraglutide vs **4%** with placebo
Key Findings					
- Oral semaglutide was noninferior to injectable liraglutide (at 1.8 mg) for A1c reduction (both groups had similar A1c reductions that were significantly better than placebo). - Oral semaglutide demonstrated significantly greater weight loss than injectable liraglutide after 26 weeks of treatment (4.4 vs 3.1 kg). - **Disclaimer: Liraglutide dose used in trial is not maximum clinical dose used in Canada (ie. 1.8 mg/day)**					

PIONEER-5: Oral Semaglutide Compared to Placebo in T2DM Patients with Mild-Mod Renal Impairment					
PIONEER -5	Oral Semaglutide (escalated to 14 mg/day) vs Placebo for **26 weeks**	N=324 Patients ≥ 18 years old Moderate renal impairment (eGFR: 30-59 mL/min). T2DM pts taking **metformin +/- a sulfonylurea OR basal insulin +/- metformin**	Oral Semaglutide (14 mg/day): -1.0 % Placebo:- 0.2 %	Oral Semaglutide: -3.4 kg Placebo: -0.3 kg	Most common AEs with was mild-mod nausea (occurred **74%** with semaglutide vs **65%** with placebo Treatment discontinuation due to AEs was **15%** with semaglutide vs **5%** with placebo.

Key Findings

- Oral semaglutide (dose escalated to 14 mg/day) was associated with an additional A1c reduction of 0.8% compared to placebo.
- Oral semaglutide was effective in T2DM patients with moderate renal impairment.
- No change in renal function with treatment – renal safety of oral semaglutide was consistent with the GLP-1 agonist class.

Trial Name	Intervention	Patient Population	Primary Endpoints	Adverse Events (AE)
PIONEER-6: Oral Semaglutide and Cardiovascular Outcomes in T2DM Patients				
PIONEER-6 **(Primary Outcome was Incidence of CVD)**	Oral Semaglutide 14 mg/day vs. Placebo for **15.9 months**	N=3183 Patients ≥ 18 years old T2DM pts and **high CVD risk (85% with established disease)**	**Occurrence of MACE (Major Adverse Cardiology Events)** - Oral Semaglutide: 3.8% - Placebo: 4.8% **Death from CVD causes:** - Oral Semaglutide: 0.9% - Placebo: 1.9% **Nonfatal MI:** - Oral Semaglutide: 2.3% - Placebo: 1.9% **Nonfatal stroke:** - Oral semaglutide: 0.08% - Placebo: 1.0% **Death from any cause:** - Oral Semaglutide: 1.3% - Placebo: 2.8%	GI adverse events leading to discontinuation were more common with oral semaglutide.

Key Findings

- Trial demonstrated that oral semaglutide was noninferior to placebo with respect to incidence of CVD events.
- Event-driven trial → did not have statistical power to show superiority of semaglutide in reducing CVD risk.
- However, did show trend in that direction (3.8% of pts in semaglutide group had a MACE compared to 4.8% with placebo)
- Failure of semaglutide to show superiority to placebo in terms of CVD risk, suggests that the injectable form may be better than the oral form in this aspect. (CVOT showed significant reduction in stroke and non-fatal MI with injectable semaglutide compared to placebo.

Trial Name	Intervention	Patient Population	Changes in A1c	Changes in Weight	Adverse Events (AE)
PIONEER-7: Oral Semaglutide with Flexible Dosing Compared to a DPP4 Inhibitor in T2DM Patients on Metformin +/- A Sulfonylurea					
PIONEER-7	Oral Semaglutide (started on 3 mg/day and titrated up to 7 or 14 mg/day) vs Sitagliptin 100 mg/day for **52 weeks**	N=504 Patients ≥ 18 years old T2DM pts taking **metformin +/- a sulfonylurea**	Oral Semaglutide: -1.4% Sitagliptin: -0.7%	Oral Semaglutide: -2.9 kg Sitagliptin: -0.9 kg	AEs occurred in **78%** of pts taking semaglutide and in **69%** of patients taking sitagliptin Nausea was the most common side effect with semaglutide

Key Findings

- Rather than monthly titration from 3 mg to 7 mg to 14 mg, investigators performed a slower titration with the aim of enhancing tolerability.
  - Dose was only increased if patients were considered to need greater A1c reduction
- After 52 weeks the oral semaglutide group experienced a statistically significant reduction in A1c and weight compared to the sitagliptin group.
- Oral semaglutide with flexible dose adjustments was found to provide superior glycemic control and weight loss compared to sitagliptin.

Trial Name	Intervention	Population	Changes in A1c	Changes in Weight	Adverse Events (AE)
PIONEER 8 – Oral Semaglutide Compared to Placebo in T2DM Patients taking Basal Insulin +/- Metformin					
PIONEER-8	Oral Semaglutide (3 mg, 7 mg, or 14	N=731	Oral Semaglutide: 3 mg: - 0.6%	Oral Semaglutide 3 mg: -1.4 kg	GI adverse effects (nausea) most

	mg) vs **Placebo** **for 52 weeks**	Patients ≥ 18 years old T2DM pts taking **basal insulin +/- metformin**	7 mg: - 0.9% 14 mg: - 1.3% **Placebo:** - 0.1%	7 mg: -2.4 kg 14 mg: -3.7 kg **Placebo**: -0.4 kg	commonly lead to discontinuation in the **oral semaglutide** group Incidence of **severe hypoglycemia** did not differ between **oral semaglutide** and **placebo** groups (26.0% vs 28.3%).
Key Findings					
- Oral semaglutide all three doses provided superior A1c and bodyweight reductions when added onto basal insulin. - In addition to superior reductions in A1c and bodyweight, using semaglutide also allowed patients to reduce their average insulin dose.					
PIONEER 9 – Oral Semaglutide Compared to Victoza and Placebo in T2DM Patients Taking One Antidiabetic Medication or None					
PIONEER-9 (Completed but results not yet published)	**Oral Semaglutide** (3, 7 or 14 mg) vs **Placebo** vs **Injectable Liraglutide (Victoza** 0.9 mg/day for **52 weeks**	N=243 patients Japanese pts with T2DM **taking one antidiabetic medication OR treated with diet/exercise alone**	**Oral Semaglutide:** 3 mg: - 1.1% 7 mg: - 1.5% 14 mg: - 1.7% **Placebo**: -0.5% **Liraglutide (Victoza)**: -1.4%	**Oral Semaglutide:** 3 mg: 0.0 kg, 7 mg: - 0.6 kg 14 mg: - 2.8 kg **Placebo:** -1.0 kg **Liraglutide:** +0.4 kg	Mild and transient **nausea** most common AE in oral semaglutide group.
Key Findings					
- Not yet published, but company press release reported that at six months, all three doses of the oral semaglutide provided a statistically significantly greater reduction in HbA1c than placebo. - The highest dose of oral semaglutide, 14mg, was superior to Liraglutide (Victoza) **at the 0.9 mg dose** in A1c reduction (-1.7% vs -1.4%.). - Body weight reduction, measured at one year, was 2.8kg with the highest dose of oral semaglutide, making this statistically superior to both placebo (1.0kg) and Victoza (weight increase of 0.4 kg). - **Disclaimer: Study did not compare oral semaglutide to Victoza at a dose used in clinical practice in Canada .**					
PIONEER 10 – Oral Semaglutide Compared to Injectable Dulaglutide in T2DM Patients Taking One Antidiabetic Medication					
PIONEER-10 (Completed but results not yet published)	**Oral Semaglutide** (3 mg, 7 mg and 14 mg) vs **Dulaglutide** 0.75 mg once weekly for **57 weeks**	N= 458 Japanese pts with T2DM **taking one antidiabetic medication**	**Oral Semaglutide:** 3mg: -0.7% 7 mg: -1.4% 14 mg: -1.8% **Dulaglutide**: - 1.3%	**Oral Semaglutide:** 3 mg: +0.1 kg 7 mg: -1.0 kg 14 mg: -1.9 kg **Dulaglutide:** + 1.1 kg	Most frequently reported AEs were **constipation and nausea** - in **31%** with 3 mg, **39%** with 7 mg, and **54 %** with 14 mg of oral semaglutide - occurred in **40%** of **dulaglutide** group.
Key Findings					
- Trial results are not yet published but from company press release, it demonstrated greater reductions in A1c and body weight with oral semaglutide 7 and 14 mg/day compared to **low dose dulaglutide (0.75 mg/week).** - **Disclaimer: Dulaglutide dose used in trial is not maximum clinical dose used in Canada. (ie. 1.5 mg/week)**					

Pioneer trial summaries prepared by: Lamis Khadir, Pharmacy Student