PIONEERing Reckoner

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1. Kalra S, Das S, Zargar AH: A Review of Oral Semaglutide Available Evidence: A New Era of Management of Diabetes with Peptide in a Pill Form. Indian J Endocrinol Metab. 2022 Mar-Apr;26(2):98-105. doi:10.4103/ijem.ijem_522_21. Epub 2022 Jun 6. PMID: 35873937; PMCID: PMC9302409.

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Table of Content

PIONEER 1

Key Points

- Oral semaglutide (3 mg, 7 mg, 14 mg) as monotherapy provided clinically significant and superior HbA1c reduction and weight loss in T2DM patients controlled on diet and exercise.[1]
- At 26 week, Oral semaglutide 14 mg dose provided mean reduction of 1.5% from baseline HbA1c (8%) and body weight reduction of 4.1 kg with 80% of patients achieving HbA1c target <7%.

Body weight reduction

Patients achieving HbA1c target <7%

1. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12.
* Oral Semaglutide efficacy and safety vs Placebo

PIONEER 1

Problem

- Peptide-based drugs, including GLP-1 receptor agonists, typically have very low bioavailability when administered orally due to extensive degradation by proteolytic enzymes and poor absorption across the gastrointestinal mucosa. Glucagon-like peptide 1 (GLP-1) receptor agonists are effective treatment options for achieving glycemic control in patients with type 2 diabetes but so far have only been available as subcutaneous injections.

Objective

- To assess the efficacy and safety of oral semaglutide monotherapy in patients with type 2 diabetes managed only with diet and exercise.

Study Design

- 26-week phase 3a, randomized double-blind, placebo-controlled, parallel-group trial conducted in 93 sites in nine countries. Adults with type 2 diabetes insufficiently controlled with diet and exercise were randomized (1:1:1:1) to oncedaily oral semaglutide 3 mg, 7 mg, 14 mg, or placebo.

- The primary end point was change from baseline to week 26 in HbA1c. The confirmatory secondary end point was change from baseline to week 26 in body weight.

Results

- In the 703 patients randomized (mean age 55 years, 50.8% male, mean baseline HbA1c 8.0%, oral semaglutide reduced HbA1c (placebo adjusted treatment differences at week 26:trial product estimand, -0.6% [3 mg], -0.9% [7 mg], and -1.1% [14 mg] for all) and body weight weight (trial product, -0.2 kg [3 mg], -1.0 kg [7 mg, P = 0.01], and -2.6 kg [14 mg, P < 0.001]) With 14 mg 8 out of 10 patients reached the target of HbA1c<7%.

- Mild -to -moderate transient gastrointestinal events were the most common adverse events with oral semaglutide. Trial product discontinuations occurred in 2.3-7.4% with oral semaglutide and 2.2% with placebo.

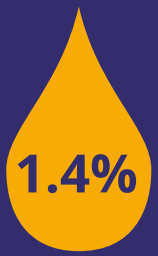
Conclusion

- Oral semaglutide monotherapy achieved superior and clinically relevant improvements in HbA1c (all doses) and body weight loss (14 mg dose) versus placebo, in patients with type 2 diabetes with a safety profile consistent with other GLP-1 receptor agonists.

PIONEER 2

Key Points

- Oral semaglutide 14 mg provided a significant reduction in HbA1c compared with empagliflozin 25 mg at week 26 (1.4% vs. –0.9%) and 52 (1.3% vs. –0.8%).
- Oral semaglutide 14 mg provided significantly greater reduction in body weight versus empagliflozin at week 52 (4.7 vs. 3.8 kg).



HbA1c reduction

Body weight reduction

*Oral Semaglutide 14 mg vs Empagliflozin 25mg

PIONEER 2

Problem

- Many patients with type 2 diabetes fail to achieve or maintain adequate blood glucose control when treated with metformin monotherapy.

Objective

- To assess the efficacy and safety of oral semaglutide with empagliflozin in patients with Type 2 Diabetes uncontrolled on metformin.

Study Design

- Patients were randomized to once-daily open-label treatment with oral semaglutide 14 mg (n 5 412) or empagliflozin 25 mg (n 5 410) in a 52-week trial.
- Key end points were change from baseline to week 26 in HbA1c (primary) and body weight (confirmatory secondary).

Results

- Change in parameters at week 26

	Oral semaglutide 14 mg	Empagliflozin 25 mg	P value
HbA1C %	1.4	0.9	<0.0001*
Weight, kg	4.2	3.8	0.1358

- Change in parameters at week 52

	Oral semaglutide 14 mg	Empagliflozin 25 mg	P value
HbA1C %	1.3	0.8	<0.0001*
Weight, kg	4.7	3.8	0.0114*

- 70% of the patients achieved HbA1c < 7% with oral semaglutide as compared to 41 % by empagliflozin 25 mg at week 26
- Proportions of patients achieving 5% or 10% weight loss were higher with oral semaglutide 14 mg compared to empagliflozin 25 mg
- Most common adverse event was mild to moderate nausea, which diminished over time. 20% of subjects treated with oral semaglutide experienced nausea at any time during the trial

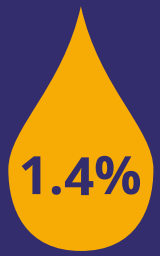
Conclusion

- Oral semaglutide provided superior glycemic reduction at week 26 & 52. Unsurpassed weight reduction as compared to empagliflozin at week 26 and superior at week 52, in patients with type 2 diabetes uncontrolled on metformin.

PIONEER 3

Key Points

- Significantly greater reduction in HbA1c of 1.4% noted in oral Semaglutide 14 mg group vs sitagliptin.
- Significant weight reduction of 3.5 kg from baseline noted in Semaglutide 14 mg group vs sitagliptin at week 78.



HbA1c reduction*

Body weight reduction

* 14mg Oral Semaglutide group vs Sitalgliptin 100mg

PIONEER 3

Problem

- Metformin and Sulfonylurea are common first line drugs prescribed. Due to the progressive nature of diabetes, initial antihyperglycemic therapy is usually unsuccessful to meet the glycaemic targets. Patient would usually need an additional class of drugs to achieve the target

Objective

- To compare efficacy and assess long-term adverse event profiles of all the three doses of once-daily oral Semaglutide (3mg, 7mg, and 14mg) vs sitagliptin (100mg) added on to Metformin with or without sulfonylurea, in patients with type 2 diabetes

Study Design

- 26-week phase 3a, randomized double-blind, placebo-controlled, parallel-group trial conducted in 93 sites in nine countries. Adults with type 2 diabetes insufficiently controlled with diet and exercise were randomized (1:1:1:1) to once-daily oral semaglutide 3 mg, 7 mg, 14 mg, or placebo.
- Randomized, Multicentre, double-blind, double-dummy, parallel-group, phase 3a trial conducted over 78 weeks.1864 adults with T2DM uncontrolled with Metformin with or without sulfonylurea were randomized.
- The primary end point was change from baseline to week 26 in HbA1c. The confirmatory secondary end point was change from baseline to week 26 in body weight.

Results

- Significantly better HbA1c reduction at doses 7 mg and 14 mg compared to sitagliptin at week 26 & sustained at week 78
- Oral semaglutide was significantly better (7 mg &14 mg) in achieving recommended target HbA1c < 7% compared to sitagliptin at week 26 & 78
- Significantly superior in wt. reduction across all doses of 3,7 & 14 mg compared to Sitagliptin 100 mg
- Significantly more effective in all doses to offer body weight loss of more >5% at week 78, & in 7 & 14 mg at week 26 compared to Sitagliptin 100 mg

Conclusion

- In adults with uncontrolled T2DM with metformin with or without sulfonylurea, oral Semaglutide, 7 and 14 mg/d, compared with sitagliptin, resulted in significantly greater reductions in HbA1c over 26 weeks

PIONEER 4

Key Points

- 72.3 % of the patients achieved HbA1c < 7% with oral semaglutide as compared to 65.3 % by liraglutide 1.8 mg at week 26.
- Oral semaglutide provided superior glycemic reduction and weight reduction
- Proportions of patients achieving >5% weight loss were higher with oral semaglutide 14 mg vs liraglutide 1.8 mg.

Patients reaching target HbA1c <7%

More patients achieving weight loss

*Oral Semaglutide 14mg vs Liraglutide 1.8 mg

PIONEER 4

Problem

- Glucagon-like peptide-1 (GLP-1) receptor agonists are effective treatments for type 2 diabetes, lowering glycated haemoglobin (HbA1c) and weight, but are currently only available for use as subcutaneous injections.

Objective

- To assess the efficacy and safety of oral semaglutide with subcutaneous liraglutide and placebo in patients with Type 2 Diabetes uncontrolled on metformin ± SGLT2 inhibitors.

Study Design

- Patients were randomized (2:2:1) to once-daily double-blind, treatment with once-daily oral semaglutide (dose escalated to 14 mg; n=285), once-daily subcutaneous liraglutide (dose escalated to 1·8 mg; n=284), or placebo (n=142) for 52 weeks trial.
- Key end points were change from baseline to week 26 in HbA1c (primary) and body weight (confirmatory secondary).

Results

- Change in parameters at week 26

	Oral semaglutide 14 mg	Liraglutide 1.8 mg
HbA1C %	-1.3	-1.1
Weight, kg	-4.7	-3.2

- Change in parameters at week 52

	Oral semaglutide 14 mg	Liraglutide 1.8 mg
HbA1C %	-1.2	-0.9
Weight, kg	-5.0	-3.1

- Significantly better in HbA1c reduction compared to gold standard of GLP-1 RA " Liraglutide" at both week 26 & 52
- Significantly better in Weight reduction compared to gold standard of GLP-1 RA " Liraglutide" at both week 26 & 52 and with up tp 5 kg wt. reduction
- 72.3 % of the patients achieved HbA1c < 7% with oral semaglutide as compared to 65.3 % by subcutaneous liraglutide 1.8 mg and 16.1 % with placebo at week 26.
- Proportions of patients achieving 5% weight loss were higher with oral semaglutide 14 mg compared to subcutaneous liraglutide 1.8 mg.
- Most common adverse event was mild to moderate nausea, which diminished over time.

Conclusion

- Oral semaglutide provided superior glycemic reduction and weight reduction as compared to subcutaneous liraglutide in patients with type 2 diabetes uncontrolled on metformin.

PIONEER 5

Key Points

- Oral semaglutide was superior to placebo indecreasing HbA1c with an estimated mean change of –1.1% in moderate renal impaired patients with diabetes
- Oral semaglutide was superior to placebo in decreasing body weight by an estimated mean change of -3.7 kg

HbA1c reduction

body weight reduction

*Oral Semaglutide 14mg vs Liraglutide 1.8mg

PIONEER 5

Problem

- Type 2 diabetes is often associated with renal impairment. Commonly used oral glucose-lowering drugs either have restrictions for usage, require increased monitoring, dose adjustment and are associated with an increased risk of hypoglycaemia and weight gain in patients with decreased kidney function. Also, Chronic kidney disease is one of the risk factors for hypoglycaemia, and usage of glucose lowering agent among them further perpetuates the risk if hypoglycaemia and weight gain. Therefore, a need exists for improved glucose-lowering treatment options for these patients.

Objective

- To investigate the efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment.

Study Design

- This randomised, double-blind trial among 324 patients aged 18 years and older, with type 2 diabetes, an estimated glomerular filtration rate of 30–59 mL/min per 1.73 m^2, and who had been receiving a stable dose of metformin or sulfonylurea, or both, or basal insulin with or without metformin for the past 90 days were eligible. Participants were randomly assigned (1:1) with stratification by glucose-lowering medication and renal function, to receive oral semaglutide (dose escalated to 14 mg once daily) or matching placebo for 26 weeks, in addition to background medication. The Primary outcome was change in baseline HbA1c Levels at 26 weeks.

Results

- At 26 weeks, oral semaglutide was superior to placebo in decreasing HbA1c (estimated mean change of –1·1 percentage point vs -0.1 with placebo); Change in body weight was (estimated mean change -3.7 kg with oral semaglutide vs -1.1 kg with placebo.
- Gastrointestinal events, mainly mild-to-moderate nausea, were more common with oral semaglutide than with placebo.

Conclusion

- Oral semaglutide is effective in patients with type 2 diabetes with moderate renal impairment, Considering the population, oral semaglutide did not adversely affect renal function and is safe to be used among them.

PIONEER 6

Key Points

- There is a Relative risk reduction of 21% in Major adverse cardiovascular events vs placebo
- The cardiovascular risk profile of oral semaglutide was noninferior to placebo

21%
relative risk reduction in MACE

49%
reduction in all cause death

51%
reduction in CV death

*Oral Semaglutide vs Placebo

PIONEER 6

Problem

- PIONEER Establishing cardiovascular safety of new therapies for type 2 diabetes is important. Safety data was available for the subcutaneous form of the glucagon-like peptide-1 receptor agonist semaglutide but was needed for oral semaglutide.

Objective

- To assess the cardiovascular (CV) safety of oral semaglutide among patients with type 2 diabetes.

Study Design

- An event-driven, randomized, double-blind, placebo-controlled trial involving patients at high cardiovascular risk (age of ≥50 years with established cardiovascular or moderate [stage 3] chronic kidney disease [CKD], or being aged=60 years with ≥1 other CV risk factor) . The trial was conducted at 214 sites in 21 countries .
- Eligible patients were randomized in a 1:1 ratio to once - daily treatment with either oral semaglutide or placebo added to standard of care; with randomization stratified based on evidence of established CVD/moderate CKD at screening or CV risk factors only.
- The primary composite endpoint was time to first occurrence of CV death or non-fatal myocardial infarction or non-fatal stroke (MACE events).
- The primary hypothesis was to exclude an excess in CV risk with oral semaglutide by assessing non-inferiority versus placebo for the primary endpoint.
- PIONEER 6 was event- driven, with follow - up continued until accrual of at least 122 primary outcome events. There was no pre-defined minimal duration.

Results

- Total 3183 patients were randomized to treatment. A maximum of 650 patients (approximately 20%) was permitted within the CV risk factors only stratum to ensure sufficient CV risk within the trial population to accrue enough events.
- 85% of patients in the oral semaglutide arm and 90% in the placebo arm were on-treatment at end of trial; 76 events were seen in the placebo group compared to 61 in the oral semaglutide group
- The hazard ratio for oral semaglutide vs the placebo group was 0.79 with 21% relative risk reduction of MACE for noninferiority
- PIONEER 6 was powered to test for non-inferiority, and this primary endpoint was highly significant for non-inferiority of oral semaglutide compared to placebo with a P-value of less than 0.0001

Conclusion

- Oral semaglutide is non-inferior to placebo in terms of cardiovascular safety in patients with T2D and high cardiovascular risk.

PIONEER 6 & SUSTAIN 6 Pooled Analysis

Key Points

- 24% reduction in 3 point MACE seen with semaglutide as a molecule vs Placebo.
- This was driven mainly by non-fatal stroke that was reduced by 35% vs Placebo.
- The effect appeared to be consistent across the s.c. and oral formulations of semaglutide, and across several clinically relevant subgroups.

24%
reduction in MACE

35%
reduction in non-fatal stroke incidence

*Oral Semaglutide vs Placebo

PIONEER 6 & SUSTAIN 6

Problem

- PIONEER 6 was a preapproval event driven CVOT to prove non inferiority of oral semaglutide vs placebo. SUSTAIN 6 was a preapproval CVOT for subcutaneous semaglutide which was both event and time driven to prove the cardiovascular safety vs placebo. Given the long duration of the trial, it was powered enough to prove the superiority of the molecule vs placebo in terms of reduction in 3-point MACE. Therefore, given that both trials were CVOTs for same molecule with different routes of administration, this pooled analysis was performed to assess the overall effect of semaglutide with respect to reduction in 3-point MACE.

Objective

- To investigate the effects of semaglutide versus comparators on major adverse cardiovascular events (MACE: cardiovascular [CV] death, nonfatal myocardial infarction [MI] and nonfatal stroke) and hospitalization for heart failure (HF) in the SUSTAIN (subcutaneous semaglutide) and PIONEER (oral semaglutide) trials across subgr oups of varying CV risk.

Study Design

- Post hoc analyses of individual patient-level data combined from SUSTAIN 6 and PIONEER 6 were performed to assess MACE and HF. MACE were analysed in subjects with and without established CV disease and/or chronic kidney disease; prior MI or stroke; and prior HF. MACE in the SUSTAIN and PIONEER glycaemic efficacy trials were also assessed.

Results

- In SUSTAIN 6 and PIONEER 6 combined, the hazard ratio (HR) for effect of semaglutide versus placebo on overall MACE was 0.76 (95% CI 0.62, 0.92), which was mainly driven by the effect on nonfatal stroke (HR 0.65 [95% CI 0.43, 0.97]).
- The HR for hospitalization for HF was 1.03 (95% CI 0.75, 1.40). The HRs for MACE were 0.05, except for HF (0.046). In the combined glycaemic efficacy trials, the HR for effect of semaglutide versus comparators on MACE was 0.85 (95% CI 0.55, 1.33).

Conclusion

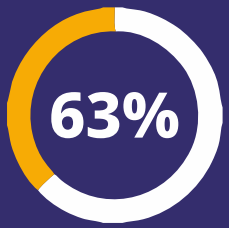
- In SUSTAIN and PIONEER combined, glucagon-like peptide-1 analogue semaglutide showed consistent effects on MACE versus comparators across varying CV risk.
- No effect of semaglutide on MACE was observed in subjects with prior HF.

MACE: Major Adverse Cardiovascular Event, s.c: subcutaneous, CVOT: Cardiovascular Outcome Trial, HR: Hazard Ratio

PIONEER 7

Key Points

- 63% of participants achieved HbA1c reduction <7% from baseline (8.3%).
- Superior body weight reduction from baseline at 52 weeks (-2.2 kg).



patients achieved <7% HbA1c

reduction in body weight

* Oral Semaglutide efficacy and safety with flexible dosing vs Sitagliptin 100 mg

PIONEER 7

Problem

• In clinical practice, lack of treatment individualisation can lead to suboptimum clinical outcomes and tolerability issues in patients

Objective

• To compare the efficacy and safety of flexible dose adjustments of oral semaglutide with sitagliptin 100 mg..

Study Design

• This is a 52-week, multicentre, randomised, open-label, phase 3a trial with 504 patients with T2DM. The patients were randomised (1:1) to either oral semaglutide once daily with flexible dose adjustment or oral sitagliptin 100 mg once daily in addition to existing background glucose lowering medications.

• Primary endpoint was reduction in HbA1c of less than 7% at week 52. Confirmatory secondary endpoint was change in bodyweight from baseline to week 52.

Results

• The HbA1c target of less than 7% at week 52:

1. Oral semaglutide group: 123 (63%) of 196 participants

2. Sitagliptin group: 52 (28%) of 184 participants

• Odds of achieving HbA1c of less than 7% at week 52 were significantly better with oral semaglutide (OR 5.54, 95% CI 3.54 – 8.68; p<0.0001).

• Oral semaglutide was superior to sitagliptin in decreasing bodyweight from baseline to week 52 (estimated treatment difference [ETD] -2.2kg, -2.9 to -1.5; p<0.0001).

Conclusion

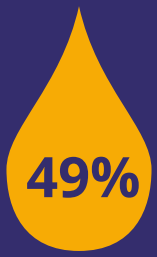
• The flexible dose adjustment of oral semaglutide provided superior glycaemic control and weight loss compared with sitagliptin and a safety profile consistent with GLP-1 receptor agonist class.

PIONEER 8

Key Points

- Observed proportion of patients achieving 5% weight loss was 48.7% at week 52 with 14 mg oral semaglutide
- Observed proportion of patients achieving <7% HbA1c was 49.3% at week 26 with 14 mg oral semaglutide

patients had weight loss > 5%



patients achieved <7% HbA1c

*As an add on to insulin with or without metformin

PIONEER 8

Problem

- Along with other OADs, insulins such as basal, basal-bolus, or premixed insulins are being used with or without metformin remains initial option in managing type 2 diabetes with nearly 10-15 years later Insulins + multiple other OADs come into mainstream management still, significant % of people remain uncontrolled.GLP-1RAs reduce HbA1c and body weight with a low risk of hypoglycemia, and some GLP-1RAs also provide cardiovascular benefits. They are recommended for early initiation after metformin by guidelines for patients with T2D.

Objective

- PIONEER 8 was conducted to investigate the efficacy, safety, and tolerability of oral semaglutide added to insulin with or without metformin.

Study Design

- Patients with type 2 diabetes uncontrolled on insulin with or without metformin were randomized to oral semaglutide 3 mg, 7 mg, or 14 mg or to placebo in a 52-week, double-blind trial.52-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational trial. The total trial duration for the individual patient was approximately 59 weeks. The 52-week randomized treatment period was split into two treatment periods; an initial 26-week fixed insulin treatment period where the insulin treatment was restricted, followed by a 26-week period where the insulin treatment was adjustable without any restrictions.
- End points were change from baseline to week 26 in HbA1c (primary) and body weight (confirmatory secondary).

Results

- Significant HbA1c reduction of 0.5,0.8 & 1.2 % with oral semaglutide 3,7 & 14 mg respectively
- Significant weight reduction of 2.9 and 4.3 kg with oral semaglutide 7 & 14 mg respectively
- Significantly higer precentage of patients achieved <7% HbA1c target (36%: 3m g, 47%: 7 mg, 64%: 14 mg)

Conclusion

- Oral semaglutide added to insulin in the setting of inadequately controlled type 2 diabetes, was superior to placebo at improving glycemic control and reducing body weight over 26 weeks, with significant differences also seen at 52 weeks, and with no increase in the risk of hypoglycemia.
- Improvements in glycemic control were achieved with oral semaglutide 7 and 14 mg despite the use of lower total daily insulin dosages relative to baseline compared with placebo
- The safety and tolerability profile was consistent with other oral semaglutide trials1–3 and other GLP-1RAs,4 and there was no increased risk of hypoglycemia.

PIONEER 9

Key Points

- Significant reduction in HbA1c of 1.7% at 26 weeks was seen with 14 mg oral semaglutide
- Significant reduction in weight of 2.8 kg at 52 weeks was seen with 14 mg oral semaglutide

HbA1c reduction

body weight reduction

*Japanese population - Compared to Placebo & 0.9 mg Liraglutide

PIONEER 9

Problem

• Compared to western population, the east Asian Diabetic patients especially Japanese, have a different clinical phenotype and pathophysiology of Type 2 DM having a propensity for β-cell dysfunction and reduced insulin secretory capacity rather than insulin resistance due to adiposity, and differences in BMI and susceptibility to some diabetic complications.

Objective

• To assess the dose response relationship of oral semaglutide in the Japanese population and compared the efficacy and safety of oral semaglutide with placebo and the subcutaneous GLP-1 receptor agonist liraglutide.

Study Design

• To This is a phase 3a randomised, double-blind, placebo-controlled and open-label, active controlled trial for 52 weeks. Patients were randomised to one of the five arms with- Placebo, Oral Semaglutide 3mg, 7mg, 14mg and subcutaneous Liraglutide 0.9mg. Primary endpoint was to evaluate the change from baseline at week 26 in HbA1c.

Results

The change in parameters were as follows in the corresponding arms:

Treatment	Change in HbA1c @26 wks (%)	Change in HbA1c @ 52 wks (%)	% achieving HbA1c <7.0% @ 52 wks (%)	Change in Body weight @ 26 wks (%)	Change in Body weight @ 52 wks (%)
Placebo	-0.1	+0.5	12	-1.2	-1.0
Oral Semaglutide 3mg	-1.1	-0.9	50	-0.5	0.0
Oral Semaglutide 7mg	-1.5	-1.3	67	-1.0	-0.6
Oral Semaglutide 14mg	-1.7	-1.5	80	-2.4	-2.8
SC Liraglutide 0.9mg	-1.4	-1.1	49	-0.0	+0.4

• The most frequently reported class of adverse events with Oral Semaglutide was Gastrointestinal events which predominantly were of mild to moderate severity.

Conclusion

• In Japanese patients with type 2 diabetes, oral semaglutide provides significant reductions in HbA1c compared to placebo in a dose-dependent manner its safety profile is consistent with that of other GLP-1 receptor agonists.

PIONEER 10

Key Points

- Significant reduction in HbA1c of 2.0% at 26 weeks was seen with 14 mg oral semaglutide
- Significant reduction in weight of 2.3 kg at 26 weeks was seen with 14 mg oral semaglutide

HbA1c reduction

body weight reduction

*Japanese population - Compared to Placebo & 0.9 mg Liraglutide

PIONEER 10

Problem

- Since the characteristics of type 2 diabetes differ between western and east Asian patients, new glucose-lowering medications need to be investigated in east Asian populations the clinical.

Objective

- The present open-label, randomised, multicentre, phase 3a trial evaluated the safety and efficacy of oral semaglutide compared with dulaglutide in Japanese patients with type 2 diabetes treated with one oral antidiabetic drug.

Study Design

- Open-label, randomised, active-controlled, phase 3a trial conducted at 36 sites (clinics and university hospitals) in Japan. Patients aged 20 years and older with uncontrolled type 2 diabetes were randomly assigned (2:2:2:1) to receive oncedaily oral semaglutide 3 mg, 7 mg, or 14 mg, or once-weekly subcutaneous dulaglutide 0·75 mg for 52 weeks, as an addon to their background medication. The primary endpoint was the number of treatment-emergent adverse events over 57 weeks. Supportive secondary endpoints (not controlled for multiplicity) included mean change from baseline in HbA1c and body weight at 52 weeks..

Results

- Oral semaglutide 14 mg demonstrated significantly greater reductions in both HbA1c and bodyweight compared with the established maintenance dose (in Japan) of dulaglutide 0·75 mg weekly.
- Oral semaglutide 7 mg provided similar glycaemic control and significantly greater reductions in bodyweight compared with dulaglutide.
- Once-daily oral semaglutide was well tolerated when compared with dulaglutide, with similar rates of adverse events in the oral semaglutide and dulaglutide groups.
- Most adverse events were mild or moderate in severity and few patients discontinued because of adverse events.
- Gastrointestinal events were the most common adverse events. Unlike in global clinical trials, constipation (rather than nausea) was the most commonly reported gastrointestinal adverse event, which might reflect differences between populations in diet or in reporting tendencies for adverse events. This observation has been evident in previous Japanese trials of GLP-1 receptor agonists.

Conclusion

- Oral semaglutide seems to be well tolerated and effective (greater HbA1c and bodyweight reductions) than subcutaneous dulaglutide 0·75 mg weekly in Japanese patients with type 2 diabetes. An oral formulation of a GLP-1 receptor agonist might encourage more effective and earlier use of these glucose lowering drugs for glycaemic control and bodyweight reduction.

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