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Cost-effectiveness Analysis of Oral Semaglutide as a Third-line Treatment for Patients with Type 2 Diabetes Mellitus in Taiwan

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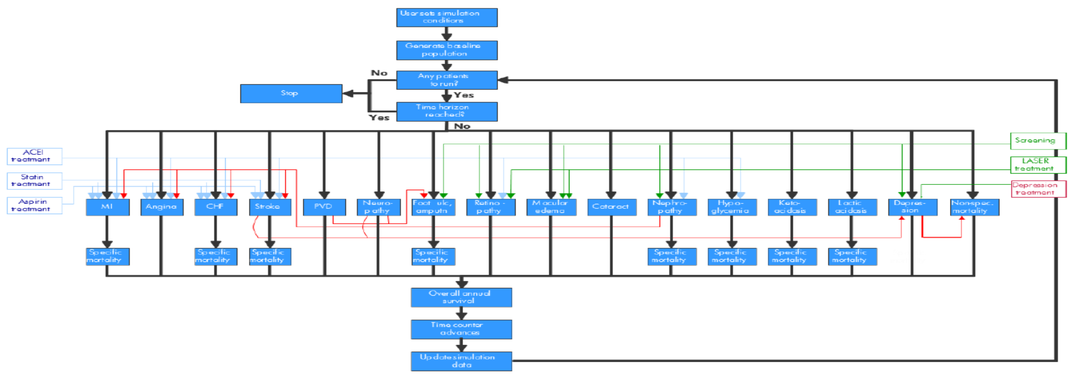
Background Type 2 diabetes (T2D) is the predominant form of diabetes and persists throughout a patient's life, contributing to significant health and economic burdens. Poor glycemic control increases the risk of both macrovascular and microvascular complications, which are major causes of death among T2D patients—CVD (52%), malignant neoplasms (14%), renal disease (11%), and diabetes itself (3%) [1]. These complications also severely impact patients' health-related quality of life (HRQoL).The primary treatment goal for T2D is to maintain glycemic control while minimizing hypoglycemia and other adverse effects to prevent complications. This study evaluates the long-term cost-effectiveness of oral semaglutide in patients with T2D who have inadequate glycemic control on metformin.

Model Overview & Structure

PICOs	
Target Population	T2D patient received metformin or sulfonylurea and combined with DPP4-i or SGLT2-i or SGLT2-i+DPP4-i or insulin for six months, but still inadequate glycemia control (HbA1c >8.0%)
Intervention	Oral semaglutide, 14 mg oral once daily (with metformin 500 mg as background therapy)
Comparators	**GLP-RA+Metformin 500mg QD** • Liraglutide 18mg (1.35mg per day) + Metformin 500mg QD • Dulaglutide 0.75mg once weekly + Metformin 500mg QD **SGLT2-i/DPP4-i combo+Metformin 500mg QD** • Empagliflozin 25mg + Linagliptin 5 mg, oral once daily + Metformin 500mg QD • Dapagliflozin 10mg + Saxagliptin 5mg, oral once daily + Metformin 500mg QD • Ertugliflozin L-PGA 5mg + Sitagliptin 100mg, oral once daily + Metformin 500mg QD
Outcomes	Direct cost, LYs, Quality-adjusted Life-year (QLAYs), Incremental cost-effectiveness ratio (ICER)

Methods	Cost-utility Analysis
Perspective	National Health Insurance Administration (payer perspective)
Time horizon	Lifetime with 1-year cycle length
Price year	2022, reported in Euro (€)
Discount rate	3%
Model	A microsimulation model (IQVIA CORE Diabetes Model, version 9.0)



▲ **Figure 1. Schematic of the IQVIA CORE Diabetes Model version 9.0**

Model Inputs

Baseline characteristics

- Summary statistics for T2D patients in different alternatives were derived from the Taiwan Diabetes Registry data from 2016 to 2018. The cohorts of T2D patients received 3L treatment were identified.

▼ **Table 1. Baseline characteristics of different alternative cohorts (patient cohort n=2,041)**

Demographics and risk factors	Mean	SD	Baseline renal complications, %	%
Age (years)	58.01	13.40	Microalbuminuria	12.85
Duration of diabetes (years)	6.23	8.66	Gross proteinuria	7.88
Proportion of Male(%)	50.48		End-stage renal disease	9.47
HbA1c (%)	10.63	6.81	**Baseline retinopathy complications, %**	
Systolic blood pressure (mmHg)	132.21	17.71	Background diabetic retinopathy	21.59
Diastolic blood pressure (mmHg)	78.36	11.85	Proliferative diabetic retinopathy	13.58
Total cholesterol (mg/dL)	172.22	40.30	Severe vision loss	0.13
HDL cholesterol (mg/dL)	46.06	16.54	Macular edema	0.26
LDL cholesterol (mg/dL)	94.05	29.34	Cataract*	0.66
Triglycerides (mg/dL)	210.58	138.12	**Baseline neuropathy, ulcer and amputation, %**	
BMI (kg/m^2)	26.93	6.32	Neuropathy	27.09
eGFR (ml/min/1.73m^2)	78.15	28.81	Uninfected ulcer	4.57
Heart rate (bpm)	83.07	11.46	Infected ulcer	18.41
Waist: hip ratio	0.72	0.12	Healed ulcer	17.88
Serum creatinine (mg/dl)	0.48	5.48	Amputation	0.53
uACR (mg/mmol)	0.95	0.77	Baseline depression, %	10.60
Hemoglobin (gr/dl)	39.01	6.26		
WBC (10^6/ml)	15.07	38.13		
Serum Albumin (mg/dl)	4.33	3.35		
Percentage smokers (%)	34.5			
Cigarettes per day	17.66	12.24		
Baseline cardiovascular complications, %	**%**			
Myocardial infarction	3.91			
Angina	7.42			
Peripheral vascular disease	5.76			
Stroke	11.59			
Congestive heart failure	13.97			
Atrial fibrillation	4.50			
Left ventricular hypertrophy	0.00			

Healthcare resource use and cost inputs

Adult patients with T2D were identified from the National Health Insurance Research Database (NHIRD) from 2021 to 2023 and cost of each complication/adverse event were defined using the diagnoses.

▼ **Table 2. The annual cost (€) of complication and adverse events**

	Annual cost of event year (1st year)		Annual cost of follow-up (2nd year)	
	Mean	SE	Mean	SE
CVD complication				
MI	22,266.66	1,402.02	8,309.11	789.44
Angina	11,892.79	2,873.40	7,015.70	1,297.51
CHF	39,911.41	4,035.91	24,668.09	4,893.24
Stroke	5,085.36	107.17	1,161.91	52.72
Stroke death within 30 days (per event)	3,002.87	135.55		
PVD	21,815.52	3,163.94	14,446.60	3,274.47
Renal complication				
Hemodialysis	14,470.45	482.60	9,069.75	426.46
Peritoneal Dialysis	13,412.89	840.52	10,232.23	1,118.69
Renal Transplant	12,032.40	1,163.48	5,652.45	1,192.18
Acute adverse event (per event)				
Non-severe hypoglycemia	152.62	4.68		
Severe hypoglycemia	2,586.50	720.99		
Keto event	1,805.38	1,182.90		
Lactic acid event	2,353.86	389.61		
Macular Edema	587.67	86.19	407.51	79.43
Eye disease				
Laser treatment (per event)	156.64	4.85		
Cataract operation (per event)	601.94	1.84		
Post cataract surgery care	719.59	245.92	541.47	245.84
Blindness	2,609.88	802.64	240.81	82.39
Neuropathy complication				
Neuropathy	1,188.59	27.79	1,032.69	26.84
Gangrene treatment	2,810.92	167.58	1,222.46	133.73
Infected ulcer	658.93	40.63	330.54	31.69
Amputation (per event)	7,059.69	430.64		

Treatment effects and adverse event

- **The treatment effects at 52 weeks and adverse events data were obtained from the Asian population extracted via PIONEER trials (PIONEER 4 and 10) and meta-analyses.**
  - The comparative efficacy with Liraglutide and Dulaglutide is based on the Asian population data from PIONEER 4 and PIONEER 10.
  - The comparative efficacy of empagliflozin + linagliptin [2, 3], dapagliflozin + saxagliptin [4, 5], and ertugliflozin + sitagliptin [5, 6] are derived from clinical trials and network meta-analyses.

Health Utility Inputs

- The baseline utility of type 2 diabetes patients in Taiwan were sourced from Taiwan Diabetes Registry data from 2016 to 2018 (0.943±0.079). Utilities associated with diabetes-related complications were taken from previously published studies listed in Table 3, including a retrospective study in Taiwan conducted by Kuo et al. in 2021 [7], a review by Beaudet et al. in 2014 [8]. If Taiwan-specific utility data are unavailable, literature will be referenced [9, 10].

▼ **Table 3. Health state utilities**

Diabetes-related complications complication	Taiwan Utility	Utility
Myocardial infarction event		-0.055
Post-myocardial infarction	0.678	
Angina	0.576	
Congestive heart failure	0.478	
Stroke event		-0.164
Post-stroke	0.638	
Peripheral vascular disease	0.783	
Microalbuminuria	0.831	
Gross proteinuria	0.813	
Hemodialysis	0.578	
Peritoneal dialysis	0.578	
Renal transplant	0.523	
Background diabetic retinopathy	0.786	
Background diabetic retinopathy wrongly treated	0.770	
Proliferative diabetic retinopathy laser treated	0.759	
Proliferative diabetic retinopathy no Laser	0.786	
Macular edema	0.802	
Severe vision loss	0.759	
Cataract		0.769
Neuropathy	0.725	
Healed ulcer	0.724	
Active ulcer	0.691	
Amputation event		-0.280
Post-amputation	0.585	

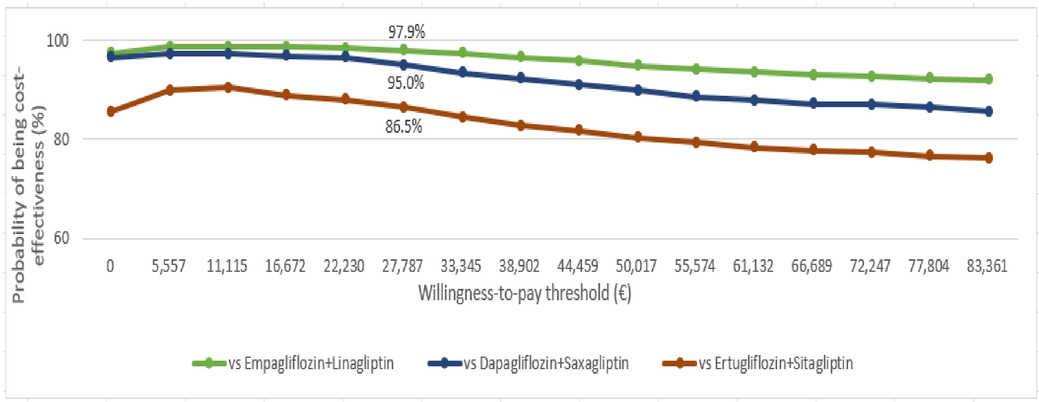
Results

- Oral semaglutide increased QALYs by 0.134 and 0.035 and costs by €510.92 and €618.98, the ICERs were €3,801.49 and €17,534.91 compared to liraglutide and dulaglutide. Additionally, oral semaglutide was dominant compared to other treatments, ex. empagliflozin plus linagliptin, dapagliflozin plus saxagliptin, ertugliflozin plus sitagliptin (Table 3).
- The results of PSA showed that, when using Taiwan's 2022 GDP per capita(€27,787.14)as the willingness-to-pay threshold, the probabilities of oral semaglutide being cost-effective were 97.9% (compared to empagliflozin plus linagliptin), 95.0% (compared to dapagliflozin plus saxagliptin), and 86.5% (compared to ertugliflozin plus sitagliptin).

▼ **Table 3. Base-case results: Oral semaglutide vs. other injection GLP-1 RA, Oral semaglutide vs. SGLT2-i/DPP4-i combo**

Oral semaglutide vs. other injection GLP-1 RA	Difference (Δ) mean (95% CI)
Oral semaglutide vs Liraglutide	
QALY	0.134 (0.123,0.146)
Direct costs (€)	510.92(211.56,810.28)
ICER per QALY gained(€)	3,801.49(1,449.06,6,587.60)
Oral semaglutide vs Dulaglutide	
QALY	0.035 (0.023,0.047)
Direct costs (€)	618.98(323.29,914.68)
ICER per QALY gained(€)	17,534.91(6,878.40,39,768.69)

Oral semaglutide vs. SGLT2-i/DPP4-i combo	Difference (Δ) mean (95% CI)
Oral semaglutide vs Empagliflozin+Linagliptin	
QALY	0.181 (0.169,0.193)
Direct costs (€)	-8,680.17(-8,958.37,-8,401.97)
ICER per QALY gained(€)	Dominant
Oral semaglutide vs Dapagliflozin+Saxagliptin	
QALY	0.107 (0.095-0.119)
Direct costs (€)	-8,171.42(-8,441.83,-7,901.01)
ICER per QALY gained(€)	Dominant
Oral semaglutide vs Ertugliflozin + Sitagliptin	
QALY	0.089 (0.077,0.101)
Direct costs (€)	-4,833.91(-5,109.79, -4,558.04)
ICER per QALY gained(€)	Dominant



▲ **Figure 2. Cost-effectiveness acceptability curve (CEAC)**

Conclusion

Oral semaglutide is a cost-effective option for T2DM patients who have received metformin or sulfonylurea combined with DPP4 inhibitors, SGLT2 inhibitors, SGLT2-i/DPP4-i combo, or insulin for six months but continue to experience inadequate glycemic control (HbA1c>8.0).

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