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Summary of MID-NET® study No.2022-001

March 5, 2025

Study title

Evaluation of the occurrence of liver function test abnormal in type 2 diabetes mellitus patients prescribed GLP-1 receptor agonists using MID-NET®

Products investigated

- Glucagon-like peptide 1 (hereinafter referred to as "GLP-1") receptor agonists shown below:
  - Dulaglutide (genetical recombination)
  - Liraglutide (genetical recombination)
  - Exenatide
  - Lixisenatide
  - Semaglutide (genetical recombination)
- Combination drugs of GLP-1 receptor agonists and insulin preparations shown below
  - Insulin degludec (genetical recombination)/liraglutide (genetical recombination)
  - Insulin glargine (genetical recombination)/lixisenatide

Background:

- In Japan, GLP-1 receptor agonists and combination drugs of GLP-1 receptor agonists and insulin preparations are indicated for type 2 diabetes mellitus.
- In consideration of the accumulation of individual case reports related to liver disorder-related events for Trulicity Subcutaneous Injection 0.75 mg Ateos (hereinafter referred to as "Trulicity") among other GLP-1 receptor agonists and the differences in the descriptions on liver disorder-related events in the package insert of GLP-1 receptor agonists[*1], PMDA decided to conduct a pharmacoepidemiological study using a medical

information database to quantitatively evaluate the occurrences of liver function test abnormal after prescription of GLP-1 receptor agonists.

*1 None of the GLP-1 receptor agonists list liver disorder-related events in the "Clinically Significant Adverse Reactions" section in the PRECAUTIONS. The following drugs list liver disorder-related events in the "Other Adverse Reactions" section in the PRECAUTIONS. This information was as of March 16, 2022, and there has been no change as of March 4, 2025.

- Victoza Subcutaneous Injection 18 mg (liraglutide (genetical recombination)) (hereinafter referred to as "Victoza") lists hepatic function abnormal (0.2-1%) in hepatobiliary disorders and hepatic function abnormal (increased AST and increased ALT) (0.2-1%) in laboratory tests.
- Byetta Subcutaneous Injection 5 μg Pen 300 and Byetta Subcutaneous Injection 10 μg Pen 300 (exenatide) list hepatic function abnormal (< 1%) in hepatobiliary disorders.
- Bydureon Subcutaneous Injection 2 mg Pen and Bydureon Subcutaneous Injection 2 mg (exenatide) list hepatic function abnormal (< 1%) in hepatobiliary disorders.
- Xultophy combination injection FlexTouch (insulin degludec (genetical recombination)/liraglutide (genetical recombination)) lists hepatic function abnormal (increased AST and ALT, etc.) (frequency unknown) in hepatobiliary disorders.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase

Purpose of the study

To compare the occurrence of liver function test abnormal in patients prescribed Trulicity with that in those prescribed other GLP-1 receptor agonists among type 2 diabetes mellitus patients prescribed GLP-1 receptor agonists using MID-NET®

Reason to select MID-NET® for the study and data period

Reason to select: To perform evaluation with laboratory test results as an index

Data period: January 1, 2009 to March 31, 2022

Data from all healthcare organizations cooperating with MID-NET® (22 hospitals at 10 healthcare organizations) whose data were available throughout the data period

Outline of method

- **Study design:** New-user cohort design
- **Study population:** Patients who were newly prescribed GLP-1 receptor agonists

  This study included patients with type 2 diabetes mellitus, which is the indication of GLP-1 receptor agonists, who satisfied all of the inclusion criteria and none of the exclusion

criteria in Table 1.

Table 1. Inclusion criteria and exclusion criteria for this study

Inclusion criteria	Exclusion criteria
1. There is a prescription date of GLP-1 receptor agonists during the data period. The first prescription date of GLP-1 receptor agonists during the data period is defined as t_0. 2. Patients have a diagnosis of type 2 diabetes mellitus (including suspected disease names) during the period between the start date of the observation period* and t_0 inclusively. 3. The start date of the observation period is 181 days or more before t_0. The period between 180 days before t_0 and t_0 (including 180 days before t_0 and t_0) is defined as the look back period.	1. Multiple GLP-1 receptor agonists are prescribed at t_0. 2. Any of AST, ALT, T-BIL, ALP, and γ-GTP is grade 2 or higher in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 on the test day closest to t_0 (including t_0) for each of AST, ALT, T-BIL, ALP, and γ-GTP tested during the look back period. 3. Anticancer drugs were prescribed, or radiotherapy was performed during the look back period. 4. Antiviral drugs were prescribed for hepatitis B or C during the look back period. 5. t_0 is before the market launch of Trulicity (September 16, 2015), and the GLP-1 receptor agonist at t_0 is a drug other than Victoza. 6. Another GLP-1 receptor agonist was prescribed the day after t_0. 7. t_0 is the end date of the observation period.**

T-BIL: Total bilirubin; ALP: Alkaline phosphatase; γ-GTP: γ-glutamyl transpeptidase

* The start date of the observation period was defined as the latest of the following dates: (1) The first date on which medical information arose among all medical information for each patient, (2) the first date on which all medical information on drugs, diseases, laboratory tests, and medical practice (hereinafter referred to as "medical information to be investigated") became available at the medical institution to which the patient belongs, and (3) the start date of the data period.

** The end date of the observation period was defined as the earliest of the following dates: (1) The last date when the medical information to be investigated arose, and (2) the end date of the data period.

Table 2. Setting of exposure categories (exposure group, comparator groups, and reference groups)

Exposure category*	Brand name	Generic name	Dosing regimen	Market launch
Exposure group	Trulicity	Dulaglutide (genetical recombination)	Once/week as subcutaneous injection	September 16, 2015
Comparator group 1	Victoza	Liraglutide (genetical recombination)	Once/day as subcutaneous injection	June 11, 2010
Comparator group 2**	Victoza	Liraglutide (genetical recombination)	Once/day as subcutaneous injection	June 11, 2010
Reference group 1	Byetta	Exenatide	Twice/day as subcutaneous injection	December 17, 2010
Reference group 2	Bydureon	Exenatide	Once/week as subcutaneous injection	May 29, 2015
Reference group 3	Lyxumia	Lixisenatide	Once/day as subcutaneous injection	September 17, 2013

Reference group 4	Xultophy	Insulin degludec (genetical recombination) /liraglutide (genetical recombination)	Once/day as subcutaneous injection	September 26, 2019
Reference group 5	Soliqua	Insulin glargine (genetical recombination) /lixisenatide	Once/day as subcutaneous injection	June 8, 2020
Reference group 6	Ozempic	Semaglutide (genetical recombination)	Once/week as subcutaneous injection	June 29, 2020
Reference group 7	Rybelsus	Semaglutide (genetical recombination)	Once daily as oral administration	February 5, 2021

* For Comparator group 1 and Reference groups 1 to 7, the enrollment period was between September 16, 2015 and March 31, 2022 to position them as parallel controls for the exposure group from the viewpoint of securing comparability with the exposure group.

** Comparator group 2 was set as a historical control due to a concern that the patients included in the parallel controls are not comparable with the exposure group, and its enrollment period was between June 11, 2010 and September 15, 2015. Comparator group 2 was not used because there was no concern about patient backgrounds for the parallel control in the feasibility assessment process.

■ **Definition of outcome:**

The outcome was set as liver function test abnormal and defined as meeting either 1. or 2. below using five items of liver function test values (AST, ALT, T-BIL, ALP, and γ-GTP). The occurrence date of the outcome was defined as the time of the first occurrence of the outcome after the date after t_0.

1. AST and ALT are grade 2 or higher on the same date.
2. T-BIL, ALP, and γ-GTP are grade 2 or higher on the same date.

The cut-off values for liver function test values used for the definition of the outcome were set as shown in a) and b) in Table 3 (Appendix) according to the CTCAE grade classification. As a secondary analysis, the cut-off values were alternated to grade 3 liver function test values and this alternated outcome was also analyzed.

■ **Definition of follow-up period:**

Start date of the follow-up period: The date after t_0

End date of the follow-up period: The earliest date among the following:

(1) Occurrence date of the outcome, (2) date before the prescription date of a GLP-1 receptor agonist which is different from that at t_0, (3) end date of a prescription period[*2], and (4) end date of the observation period

*2 Definition of a prescription period: Starting from t_0, prescriptions were considered to be continued if the prescription interval was less than or equal to a gap period (90 days). The end date of a prescription period was defined as the last prescription plus a grace period (90 days). If only t_0 was observed, the end date of a prescription period was defined as t_0 plus a grace period.

■ **Analyses and methods:**

To understand the characteristics of the study population, variables, such as sex, age, and liver function test values during the look back period, were predefined, and summary statistics were calculated. For the exposure group and the comparator group 1, the numbers of each outcome were tabulated, and the incidence rate of each outcome was calculated. The crude hazard ratios and adjusted hazard ratios with their 95% confidence intervals for the exposure group compared with the comparator group1 were estimated using the Cox proportional hazard model. As adjusted hazard ratios, (1) hazard ratios with sex and age as covariates and (2) hazard ratios in the populations weighted by the standardized mortality ratio weighting (SMRW) method using high-dimensional propensity scores calculated with sex, age, and other variables as covariates were estimated. Hazard ratios for the reference groups 1 to 7 compared with the exposure group were estimated as well.

Outline of results

■ **Study population**

The study population consisted of 3,517 patients in the exposure group and 1,995 patients in the comparator group 1. The patient characteristics in the primary analysis population before and after weighting using the SMRW method are as shown in Table 4 (Appendix). For the patient characteristics, the populations weighted by the high-dimensional propensity scores showed a decrease in the standardized mean difference (hereinafter referred to as "SMD") compared with those before weighting.

■ **Occurrence of outcomes**

- Primary analysis: In the SMRW-weighted population with the high-dimensional propensity scores, the hazard ratio for the exposure group compared with the comparator group 1 was 1.41 (95% CI: 0.70-2.82) (Table 5 (Appendix)). A similar trend was observed even when the number of covariates to be included in the model

for calculating the high-dimensional propensity scores was selected at 100, 250, or 500.

- Secondary analysis: In the SMRW-weighted population with the high-dimensional propensity scores, the hazard ratio for the exposure group compared with the comparator group 1 was 1.36 (95% CI: 0.66-2.82) (Table 5 (Appendix)). A similar trend was observed even when the number of covariates to be included in the model for calculating the high-dimensional propensity scores was selected at 100, 250, or 500.
- The sex and age-adjusted hazard ratios for the comparator group 1 and reference groups 1-7 compared with the exposure group are shown in Table 6 (Appendix). The number of outcomes was less than 10 in each reference group.

■ **Discussion based on the results**

- Based on the results of the primary analysis and the secondary analysis, there seemed to be no major difference in the risk of the outcome for Trulicity (exposure group) compared with that for Victoza (comparator group 1), for which hepatic function disorder-related events are already described in the "Other adverse reactions" section in the PRECAUTIONS.
- In this study, confounders were adjusted by using the high-dimensional propensity scores. However, it should be noted that this study has some limitations, such as the possibility that other potential confounders (e.g., general condition of patients, detailed treatment history, etc.) may have affected the results.

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Appendix

Table 3. Grading of liver function test values using CTCAE

	a) Grading of liver function test values for values **within reference ranges during the look back period** using CTCAE		b) Grading of liver function test values for **abnormal values during the look back period** using CTCAE	
Test item	Grade 2	Grade 3	Grade 2	Grade 3
AST*	Within reference range during the look back period (≤ 30 U/L)		Abnormal during the look back period (> 30 U/L)	
	90 U/L < AST ≤ 150 U/L	150 U/L < AST ≤ 600 U/L	×3.0 value during the look back period < AST ≤ ×5.0 value during the look back period	×5.0 value during the look back period < AST ≤ ×20.0 value during the look back period
ALT*	Male: Within reference range during the look back period (≤ 42 U/L)		Male: Abnormal during the look back period (> 42 U/L)	
	126 U/L < ALT ≤ 210 U/L	210 U/L < ALT ≤ 840 U/L	×3.0 value during the look back period < ALT ≤ ×5.0 value during the look back period	×5.0 value during the look back period < ALT ≤ ×20.0 value during the look back period
	Female: Within reference range during the look back period (≤ 23 U/L)		Female: Abnormal during the look back period (> 23 U/L)	
	69 U/L < ALT ≤ 115 U/L	115 U/L < ALT ≤ 460 U/L	×3.0 value during the look back period < ALT ≤ ×5.0 value during the look back period	×5.0 value during the look back period < ALT ≤ ×20.0 value during the look back period
T-BIL*	Within reference range during the look back period (≤ 1.5mg/dL)		Abnormal during the look back period (> 1.5mg/dL)	
	2.25 mg/dL < T-BIL ≤ 4.5 mg/dL	4.5 mg/dL < T-BIL ≤ 15 mg/dL	×1.5 value during the look back period <T-BIL ≤ ×3.0 value during the look back period	×3.0 value during the look back period <T-BIL ≤ ×10.0 value during the look back period
ALP* (JSCC criteria)	Within reference range during the look back period (≤ 322 U/L (JSCC))		Abnormal during the look back period (> 322 U/L (JSCC))	
	805 U/L < ALP ≤ 1,610 U/L	1,610 U/L < ALP ≤ 6,440 U/L	×2.5 value during the look back period < ALP ≤ ×5.0 value during the look back period	×5.0 value during the look back period < ALP ≤ ×20.0 value during the look back period
ALP* (IFCC criteria)	Within reference range during the look back period (≤ 113 U/L (IFCC))		Abnormal during the look back period (> 113 U/L (IFCC))	
	282.5 U/L < ALP ≤ 565 U/L	565 U/L < ALP ≤ 2,260 U/L	×2.5 value during the look back period < ALP ≤ ×5.0 value during the look back period	×5.0 value during the look back period < ALP ≤ ×20.0 value during the look back period
ALP** (Others)	805 U/L < ALP ≤ 1,610 U/L	1,610 U/L < ALP ≤ 6,440 U/L	805 U/L < ALP ≤ 1,610 U/L	1,610 U/L < ALP ≤ 6,440 U/L
γ-GTP*	Male: Within reference range during the look back period (≤ 64 U/L)		Male: Abnormal during the look back period (> 64 U/L)	
	160 U/L < γ-GTP ≤ 320 U/L	320 U/L < γ-GTP ≤ 1,280 U/L	×2.5 value during the look back period < γ-GTP ≤ ×5.0 value during the look back period	×5.0 value during the look back period < γ-GTP ≤ ×20.0 value during the look back period
	Female: Within reference range during the look back period (≤ 32 U/L)		Female: Abnormal during the look back period (> 32 U/L)	
	80 U/L < γ-GTP ≤ 160 U/L	160 U/L < γ-GTP ≤ 640 U/L	×2.5 value during the look back period < γ-GTP ≤ ×5.0 value during the look back period	×5.0 value during the look back period < γ-GTP ≤ ×20.0 value during the look back period

* CTCAE v5.0 - JCOG, the September 1, 2021 edition[1] and CTCAE v5.0 grade definition table[2] corresponding to the JCOG common reference range were referred to.

** CTCAE v4.0 - JCOG, the September 12, 2017 edition[3] and CTCAE v4.0 grade definition table[4] corresponding to the JCOG common reference range were referred to. The grading of laboratory test values is used when it cannot be distinguished between JSCC criteria and IFCC criteria.

[1] Common Terminology Criteria for Adverse Events v5.0 Japanese translation JCOG version (abbreviated as CTCAE v5.0 - JCOG) [Corresponding to CTCAE v5.0/MedDRA v20.1 (Japanese description: MedDRA/J v24.1) - September 1, 2021]. http://www.jcog.jp/doctor/tool/CTCAEv5J_20210901_v24_1.pdf (accessed on February 16, 2022)

[2] CTCAE v5.0 grade definition table corresponding to the JCOG common reference range. http://www.jcog.jp/doctor/tool/JCOG_kyouyoukijunchi-CTCAE_50_20210901.pdf (accessed on February 16, 2022)

[3] Common Terminology Criteria for Adverse Events v4.0 Japanese translation JCOG version (abbreviated as CTCAE v4.0 - JCOG) [Corresponding to CTCAE v4.03/MedDRA v12.0 (Japanese description: MedDRA/J v20.1) - September 12, 2017]. http://www.jcog.jp/doctor/tool/CTCAEv4J_20170912_v20_1.pdf (accessed February 16, 2022)

[4] CTCAE v4.0 grade definition table corresponding to the JCOG common reference range. http://www.jcog.jp/doctor/tool/JCOG_kyouyoukijunnchi-CTCAE.pdf (accessed on February 16, 2022)

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Table 4. Characteristics of patients in the primary analysis before and after SMRW

Variable number			Before weighting			After weighting		
			Exposure group: Trulicity	Comparator group 1: Victoza (reference)	SMD	Exposure group: Trulicity	Comparator group 1: Victoza (reference)	SMD
	Number of patients	(N, (%))	3,517 (100.00 %)	1,995 (100.00 %)		3,517 (100.00 %)	3,387 (100.00 %)	
1	Male	(N, (%))	2,138 (60.79 %)	1,214 (60.85 %)	-0.001	2,138 (60.79 %)	2,205 (65.10 %)	-0.088
	Age	(Mean, SD)	66.60 ± 13.89	61.04 ± 14.14		66.60 ± 13.89	65.23 ± 17.12	
2	< 65 years	(N, (%))	1,347 (38.30 %)	1,096 (54.94 %)	-0.338	1,347 (38.30 %)	1,297 (38.30 %)	0.000
	Laboratory test values during the look back period							
3	AST* abnormal (grade 1)	(N, (%))	583 (16.58 %)	356 (17.84 %)	-0.034	583 (16.58 %)	559 (16.52 %)	0.002
4	ALT* abnormal (grade 1)	(N, (%))	733 (20.84 %)	469 (23.51 %)	-0.064	733 (20.84 %)	658 (19.44 %)	0.034
5	T-BIL* abnormal (grade 1)	(N, (%))	53 (1.51 %)	39 (1.95 %)	-0.034	53 (1.51 %)	84 (2.48 %)	-0.074
6	ALP* abnormal (grade 1)	(N, (%))	454 (12.91 %)	243 (12.18 %)	0.022	454 (12.91 %)	427 (12.61 %)	0.009
7	γ-GTP* abnormal (grade 1)	(N, (%))	668 (18.99 %)	430 (21.55 %)	-0.064	668 (18.99 %)	598 (17.66 %)	0.033
8	HbA1c* (based on NGSP) < 6.0%	(N, (%))	93 (2.64 %)	72 (3.61 %)	-0.055	93 (2.64 %)	81 (2.38 %)	0.015
9	HbA1c* (based on NGSP) ≥ 6.0% - < 7.0%	(N, (%))	398 (11.32 %)	246 (12.33 %)	-0.031	398 (11.32 %)	454 (13.41 %)	-0.065
10	HbA1c* (based on NGSP) ≥ 7.0% - < 8.0%	(N, (%))	918 (26.10 %)	485 (24.31 %)	0.041	918 (26.10 %)	937 (27.68 %)	-0.036
11	HbA1c* (based on NGSP) unknown	(N, (%))	141 (4.01 %)	67 (3.36 %)	0.035	141 (4.01 %)	134 (3.94 %)	0.003
12	ALBI* grade 2 or higher	(N, (%))	1,253 (35.63 %)	681 (34.14 %)	0.031	1,253 (35.63 %)	1,309 (38.64 %)	-0.063
13	ALBI* calculated value unknown	(N, (%))	719 (20.44 %)	380 (19.05 %)	0.035	719 (20.44 %)	597 (17.63 %)	0.071
	Prescription history of antidiabetic drugs (look back period)							
14	Insulin preparations	(N, (%))	2,077 (59.06 %)	1,552 (77.79 %)	-0.412	2,077 (59.06 %)	2,313 (68.31 %)	-0.203
15	Sulfonylureas	(N, (%))	823 (23.40 %)	269 (13.48 %)	0.258	823 (23.40 %)	622 (18.35 %)	0.131
16	Biguanides	(N, (%))	1,682 (47.82 %)	946 (47.42 %)	0.008	1,682 (47.82 %)	1,434 (42.33 %)	0.110
17	Thiazolidines	(N, (%))	291 (8.27 %)	134 (6.72 %)	0.059	291 (8.27 %)	278 (8.21 %)	0.002
18	Alpha-glucosidase inhibitors	(N, (%))	679 (19.31 %)	333 (16.69 %)	0.068	679 (19.31 %)	624 (18.43 %)	0.023
19	Glinides	(N, (%))	548 (15.58 %)	236 (11.83 %)	0.109	548 (15.58 %)	473 (13.96 %)	0.047
20	DPP-4 inhibitors	(N, (%))	2,270 (64.54 %)	1,057 (52.98 %)	0.236	2,270 (64.54 %)	1,944 (57.41 %)	0.146
21	SGLT2 inhibitors	(N, (%))	1,267 (36.03 %)	577 (28.92 %)	0.152	1,267 (36.03 %)	1,277 (37.70 %)	-0.036
	Diseases (look back period)							
22	Diabetic complication	(N, (%))	2,205 (62.70 %)	1,379 (69.12 %)	-0.136	2,205 (62.70 %)	2,226 (65.74 %)	-0.064
23	Hepatic steatosis	(N, (%))	392 (11.15 %)	219 (10.98 %)	0.005	392 (11.15 %)	339 (10.02 %)	0.036
24	Hepatitis (viral, autoimmune, etc.)	(N, (%))	691 (19.65 %)	395 (19.80 %)	-0.004	691 (19.65 %)	658 (19.43 %)	0.005
25	Cholecystitis, cholangitis, gallbladder stone, or bile duct stone	(N, (%))	236 (6.71 %)	110 (5.51 %)	0.050	236 (6.71 %)	239 (7.06 %)	-0.015

SMD: Standardized Mean Difference, SD: Standard Deviation, ALBI: Albumin-Bilirubin

Look back period: The period between 180 days before t_0 and t_0 (including 180 days before t_0 and t_0), with t_0 being as the first prescription date of a GLP-1 receptor agonist during the data period.

* Results on the test date closest to t_0 (including t_0) are obtained for each of AST, ALT, T-BIL, ALP, γ-GTP, and HbA1c tested during the look back period. If there are multiple test results on the same date, a clinically worse liver function value is selected.

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Table 5. Incidences and hazard ratios of outcomes for the exposure group (Trulicity) versus the comparator group 1 (Victoza)

			Number of patients (person)	Total follow-up period (person-years)	Number of outcomes (person)	Incidence rate (/1000 person-years)	Crude hazard ratio (95%CI)	Sex and age-adjusted hazard ratio (95%CI)	SMRW-weighted hazard ratio* (95%CI)
Primary analysis	Exposure group	Trulicity	3,517	3,537.24	98	27.71	1.29 (0.90 - 1.85)	1.11 (0.77 - 1.60)	1.41 (0.70 - 2.82)
	Comparator group 1	Victoza	1,995	1,992.93	42	21.07	1.00 (reference)	1.00 (reference)	1.00 (reference)
Secondary analysis	Exposure group	Trulicity	3,517	3,566.00	55	15.42	1.53 (0.92 - 2.55)	1.36 (0.81 - 2.29)	1.36 (0.66 - 2.82)
	Comparator group 1	Victoza	1,995	2,006.78	20	9.97	1.00 (reference)	1.00 (reference)	1.00 (reference)

SMRW: standardized mortality ratio weighting, CI: confidence interval

Primary outcome: Grade 2 or higher hepatic function disorder; Secondary outcome: Grade 3 or higher hepatic function disorder

* The high-dimensional propensity scores were calculated with 1/10 covariates of the number of patients in the group with a small number of patients among the two groups to be compared after M-bias values were calculated from the top 200 codes in terms of frequency in each dimension of disease, drug, and procedure. For the primary and secondary analyses, the high-dimensional propensity scores were calculated with 200 variables, including the 25 variables predefined in Table 4.

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Table 6. Incidences and hazard ratios of outcomes (CTCAE grade 2 or higher hepatic function disorder) in the comparator group (Victoza) or reference groups 1-7 versus the exposure group (Trulicity)

		Number of patients (person)	Total follow-up period (person-years)	Number of outcomes (person)	Incidence rate (/1000 person-years)	Crude hazard ratio (95%CI)	Sex and age-adjusted hazard ratio (95%CI)	SMRW-weighted hazard ratio* (95%CI)
Exposure group	Trulicity	3,517	3,537.24	98	27.71	1.00 (reference)	1.00 (reference)	1.00 (reference)
Comparator group 1	Victoza	1,995	1,992.93	42	21.07	0.78 (0.54 - 1.12)	0.90 (0.63 - 1.30)	0.71 (0.35 - 1.43)
Reference group 1	Byetta	14	12.45	0	-	-	-	-
Reference group 2	Bydureon	31	42.54	< 10	< 235.07	0.96 (0.13 - 7.17)	1.29 (0.17 - 9.95)	0.31 (0.05 - 2.09)
Reference group 3	Lyxumia	94	103.32	< 10	< 96.79	1.09 (0.36 - 3.34)	1.42 (0.46 - 4.37)	0.63 (0.10 - 3.76)
Reference group 4	Xultophy	386	212.15	< 10	< 47.14	0.26 (0.06 - 1.05)	0.26 (0.06 - 1.08)	0.33 (0.06 - 1.75)
Reference group 5	Soliqua	98	52.81	< 10	< 189.36	0.51 (0.07 - 3.67)	0.59 (0.08 - 4.13)	0.62 (0.07 - 5.55)
Reference group 6	Ozempic	313	118.85	0	-	-	-	-
Reference group 7	Rybelsus	499	90.16	< 10	< 110.91	0.62 (0.19 - 2.00)	0.75 (0.23 - 2.40)	1.57 (0.38 - 6.44)

SMRW: Standardized mortality ratio weighting, CI: Confidence interval

Data are masked so that the number of patients (less than 10) cannot be identified according to the MID-NET® publication criteria.

* The high-dimensional propensity scores were calculated with 1/10 covariates of the number of patients in the group with a small number of patients among the two groups to be compared after M-bias values were calculated from the top 200 codes in terms of frequency in each dimension of disease, drug, and procedure. For the comparison of the exposure group with the comparator group 1, the high-dimensional propensity scores were calculated using 200 variables with 25 variables predefined in Table 4. If the number of patients was less than 250, the high-dimensional propensity scores were calculated using only 25 variables predefined.