Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request: cder_iqp_wp035

Request ID: cder_iqp_wp035

Request Description: In this report we aimed to characterize patients with an incident medication fact record for select non-insulin antidiabetics between October 1, 2017 to September 30, 2023 in the TriNetX Live™ platform.

Data Source: We ran this query on January 25, 2024. This query was distributed to 81 health care organizations (HCOs) provided through the TriNetX Live™ platform in their USA Network. This query contains data from the 81 HCOs that responded.

TriNetX aggregates electronic health record (EHR) systems data from its partner HCOs to create queryable datasets. TriNetX datasets primarily comprise clinical patient data such as demographics, diagnoses, procedures, labs, and medications. For more information on the TriNetX Live™ platform and the TriNetX data visit their website here: https://trinetx.com/

Study Design: In this retrospective cohort study, we identified counts of individuals with an incident medication fact record for select non-insulin antidiabetics. We built 100 distinct cohorts using the Query Builder module in the TriNetX Live™ platform.

Exposures of Interest: We examined 20 non-insulin antidiabetics of interest. These included: albiglutide, alogliptin, bexagliflozin, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, ertugliflozin, exenatide, glimepiride, glipizide, glyburide, linagliptin, liraglutide, lixisenatide, metformin, saxagliptin, semaglutide, sitagliptin, and tirzepatide.

We used RxNorm medication terms in the Query Builder module. In order to be included in a cohort, we required evidence of a prescription, administration, or dispensing with the relevant non-insulin antidiabetic of interest between October 1, 2017 and September 30, 2023.

Please see Appendix A for the list of RxNorm medication terms used to define the exposures of interest in this request.

Cohort Eligibility Criteria: Individuals of all ages were included. They were eligible to be an incident user in a given cohort if they had:

1) Evidence of a visit between 10/1/17 - 9/30/23, and
2) No evidence of the exposure of interest prior to the window of interest*, and
3) Evidence of the exposure of interest in the window of interest.

Windows of interest included 10/1/17-9/30/23, 10/1/17-9/30/19, 10/1/19-9/30/21, and 10/1/21-9/30/23.

Please see Appendix B for the specifications of the cohort parameters for each of the 100 cohorts as included in the Query Builder.

Limitations: Algorithms used to define exposures, characteristics, pregnancy, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the United Stats (US) lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that may not participate in the TriNetX USA network. We are unable to determine if absence of evidence of a condition implies a true absence of a condition or if the condition was not observed in the data. Furthermore, not all HCOs provide brand name or route information for RxNorm terms or laboratory data. Therefore, data should be interpreted with these limitations in mind.

Overview for Request: cder_iqp_wp035
All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. This rounding affects error, especially as sample sizes decrease. Error due to rounding can range from <0.09% when sample sizes are >10,000 to nearly 20% as sample sizes drop. Thus, all estimates should be interpreted as ranges, and small sample sizes should be interpreted with caution. Additionally, percentages are calculated based on these rounded numerators and denominators. Thus, due to rounding, the sum of each value in a category may not total to 100%. The TriNetX Live™ platform uses RxNorm terms to identify medications, specifically the primary ingredient RxNorm terms. In the case of fixed dose combinations/co-packaged medications, the drugs are identified in the platform as the presence of primary ingredient RxNorm terms for all the individual medications on the same day (even if a multiple ingredient RxNorm term is made available by the National Library of Medicine), under the assumption that this refers only to the combined drugs and not two individual drugs prescribed concomitantly. A subset of HCOs that contribute to the TriNetX USA Network may implement date shifting in either direction. Each HCO chooses the number of days shifted, at the level of the patient record, prior to data ingestion at TriNetX as a method to preserve patient privacy. It is difficult to characterize the full impact of date shifting on a specific set of results. When interpreting the results of an analysis, the impact of date shifting should be considered and readers should exercise caution when extrapolating information related to time. **Notes:** We ran this query on January 25, 2024. A re-run of this query for the same query period in the future may not yield the same results owing to the dynamic nature of the TriNetX Live™ network. Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's querying in the TriNetX platform, please refer to the Sentinel Website (https://www.sentinelinitiative.org/methods-data-tools/methods/trinetx-rapid-querying).

*Due to the visit term being looked for anytime in the window of interest, there may be some patients that indexed into the cohort with their visit term following their drug exposure.

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Glossary of Terms for Analyses Using TriNetX Live™ Platform*

Characteristic - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or before the cohort-defining index event.

Explore Cohort - A description module on the TriNetX platform that presents a clinical profile of patients in a given cohort. Patient counts are rounded up to the nearest 10 before percentages are calculated, so the sum each of the values in one category may not total to 100%.

Date Shifting - A data obfuscation technique that some HCOs use to preserve patient privacy. Date shifting entails assigning each patient a random number of days (e.g., -365 to +365 days) and consistently adjusting each of their dates by that number of days, thus maintaining temporal relationships between records within a single patient.

Fact - (Medical Fact) A unit of utilization that represents a medical observation on a patient (e.g., diagnosis, procedure, clinical observation).

Filter - A method of limiting terms included in queries to a specific subset of data. Filters include age at time of event, data source (electronic health record or natural language processing); brand name, route, and strength for medication terms; occurrence (first or most recent) for lab terms; and priority for diagnosis and procedure terms.

Group - A series of codes and terms defined with Boolean logic that are used to create a query cohort. For each group, users have the ability to specified time periods of interest, and the number of instances that the group must occur for cohort entry.

> **Subgroup -** Within a group, additional subgroups can be specified to define temporal relationships between the terms in the subgroup (e.g., terms in subgroup B must occur within 5 days after terms in subgroup A). Users can require that these temporal constraints be applied to the 1) first, 2) last, or 3) any instance of each subgroup.

Health Care Organization (HCO) - Organizations that contribute electronic healthcare record data to the TriNetX data networks. HCOs include academic institutions and community health provider systems and a single HCO may contain one or more individual sites or facilities.

Index - The first date when a patient meets all of the cohort-defining criteria. In Analytics modules, the index can be defined as the date when a patient meets all of the cohort criteria, or only one specific group's criteria.

Module - A subsection of the TriNetX platform that performs a distinct functionality. Cohorts are created using the Query Builder module. Descriptive modules include Healthcare Organizations, Explore Cohorts, Rate of Arrival, Summary Statistics, and Analyze Criteria. Advanced analytic modules include Analyze Outcomes, Compare Outcomes, Compare Cohorts, Treatment Pathways, and Incidence and Prevalence.

Network - An aggregation of HCOs contributing data to the platform. Multiple networks are available for querying on the platform; the different networks represent subsets of HCOs organized by date-shifting practices or availability of downloadable datasets.

Outcome - A medical fact (e.g., diagnosis, procedure, lab result) that occurred on or after the cohort-defining index event.

Query - In the TriNetX platform, a query is a distinct cohort with a unique set of terms and logic. Query cohorts are created using the Query Builder platform module.

Risk - In Advanced Analytics modules, risk refers to the percentage of patients in each cohort with the specified outcome of interest.

Priority - An indication whether the code was the condition that the provider spent the most time evaluating or treating during a visit. Possible values include primary, secondary, or unknown.

Term - The codes used to specify patient cohort criteria in a query. Code options include diagnoses, procedures, medications, labs, demographics, genomics, and visits. Terms can be linked together using and/or Boolean logic. TriNetX also creates terms that group together multiple medical codes into single clinical concepts.

Cannot Have Term - A category of terms within a query group that patients must not have evidence of to be included in the cohort.

Must Have Term - A category of terms within a query group that patients must have evidence of to be included in the cohort.

Time Constraint - used to define time periods of interest for each group within a query. Time constraints can be defined relative to the date the query was run (e.g., any time before today), or defined based on specific dates (e.g., January 1, 2015 to September 30, 2020).

Treatment Pathway - In Advanced Analytics modules, the Treatment Pathways module returns the order in which patients received treatment and the prevalence of treatments, including combination of medications, following an index event.

TriNetX Codes - For certain laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes to new queryable TNX:LAB terms.

Visit - A type of term used to specify the type of medical encounter or facility where the encounter was recorded. Visit terms are derived by TriNetX from the source data. Visits are recorded separately from the codes or labs that occurred during the encounter; care settings are not attached to individual codes.

*all terms may not be used in this report

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Table 1. Frequency of Non-Insulin Antidiabetic Incident Use[7] in the TriNetX Live™ USA Network[1] from October 1, 2017 to September 30, 2023

	Incident Use[7] 10/1/17 - 9/30/23		Incident Use[7] 10/1/17 - 9/30/19		Incident Use[7] 10/1/19 - 9/30/21		Incident Use[7] 10/1/21 - 9/30/23	
	Number	Percent[2]	Number	Percent[2]	Number	Percent[2]	Number	Percent[2]
Non-Insulin Antidiabetic[3] Incident Users[7]	**2,629,200**	**100.0%**	**732,260**	**27.9%**	**841,470**	**32.0%**	**1,055,480**	**40.1%**
2nd Generation Sulfonylurea	**848,170**	**100.0%**	**313,320**	**36.9%**	**308,670**	**36.4%**	**226,190**	**26.7%**
glimepiride	335,780	100.0%	129,910	38.7%	123,570	36.8%	82,300	24.5%
glipizide	552,740	100.0%	198,020	35.8%	199,950	36.2%	154,780	28.0%
glyburide	69,600	100.0%	31,490	45.2%	23,830	34.2%	14,300	20.5%
Dipeptidyl Peptidase-4 (DPP-4) Inhibitor	**523,800**	**100.0%**	**197,630**	**37.7%**	**186,960**	**35.7%**	**139,210**	**26.6%**
alogliptin	25,510	100.0%	7,720	30.3%	10,170	39.9%	7,630	29.9%
linagliptin	141,050	100.0%	52,680	37.3%	49,660	35.2%	38,720	27.5%
saxagliptin	17,760	100.0%	9,530	53.7%	5,750	32.4%	2,490	14.0%
sitagliptin	456,830	100.0%	174,910	38.3%	164,320	36.0%	117,600	25.7%
Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA)	**975,500**	**100.0%**	**148,000**	**15.2%**	**259,680**	**26.6%**	**567,830**	**58.2%**
albiglutide[4]	1,170	100.0%	1,090	93.2%	70	6.0%	10	0.9%
dulaglutide	468,510	100.0%	104,210	22.2%	158,950	33.9%	205,360	43.8%
exenatide	48,570	100.0%	24,880	51.2%	16,410	33.8%	7,290	15.0%
liraglutide	257,100	100.0%	87,770	34.1%	81,170	31.6%	88,170	34.3%
lixisenatide[5]	12,830	100.0%	4,290	33.4%	4,720	36.8%	3,840	29.9%
semaglutide	684,680	100.0%	44,670	6.5%	153,440	22.4%	486,580	71.1%
tirzepatide	98,290	100.0%	1,200	1.2%	1,460	1.5%	95,640	97.3%
Metformin	**2,688,640**	**100.0%**	**901,160**	**33.5%**	**960,090**	**35.7%**	**827,400**	**30.8%**
Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitor	**796,800**	**100.0%**	**119,550**	**15.0%**	**240,770**	**30.2%**	**436,490**	**54.8%**
bexagliflozin[6]	30	100.0%	0	0.0%	0	0.0%	30	100.0%
canagliflozin	78,220	100.0%	34,390	44.0%	29,740	38.0%	14,110	18.0%
dapagliflozin	298,840	100.0%	38,420	12.9%	82,790	27.7%	177,630	59.4%
empagliflozin	631,240	100.0%	103,270	16.4%	197,860	31.3%	330,120	52.3%
ertugliflozin	16,780	100.0%	4,030	24.0%	6,600	39.3%	6,160	36.7%

NOTE: All counts provided through the TriNetX Live™ platform are rounded up to the nearest 10 to protect patient privacy. For this reason, number of incident users in each time period may not sum to the number in the overall query period. Percentages were calculated based on the rounded estimates, and are presented here rounded to the tenths position to avoid mischaracterizing the precision of the measurement. Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range and the lower value of the range ≤ 0.05% less than the presented value (unless otherwise noted).

[1]A subset of HCOs that contribute to the TriNetX USA network may implement date shifting - between 0 and 365 days shifted in either direction - at the level of the patient record prior to data ingestion at TriNetX as a method to preserve patient privacy. When interpreting the results of an analysis, the impact of date shifting should be considered and readers should exercise caution when extrapolating information related to time.

[2]Percentages in this row are calculated using the count of total incident users during 10/1/2017-9/30/2023 of the drug/class described in the row header as the denominator.

[3]Non-Insulin Antidiabetics include medication products with the following ingredients: albiglutide, alogliptin, bexagliflozin, canagliflozin, dapagliflozin, dulaglutide, empagliflozin, ertugliflozin, exenatide, glimepiride, glipizide, glyburide, linagliptin, liraglutide, lixisenatide, metformin, saxagliptin, semaglutide, sitagliptin, and tirzepatide.

[4]Albiglutide: Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range. Due to a small denominator in this row, and the lower value of the range is 0.77% less than the presented value.

[5]Lixisenatide: Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range. Due to a small denominator in this row, and the lower value of the range is 0.07% less than the presented value.

[6]Bexagliflozin: Due to rounding, all estimates should be interpreted as ranges, with the presented value equivalent to the high end of the range. Due to a small denominator in this row, and the lower value of the range is 30.0% less than the presented value.

[7]Cohorts for this query had an inclusion criteria that looked for a visit term anytime in the window of interest. Because of this, there may be a small percentage of patients who indexed into a cohort with their visit term following their drug exposure.

Appendix A. List of RxNorm Medication Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
Non-Insulin Antidiabetics of Interest				
1534763	albiglutide	Medication	RxNorm	Not applicable
1368001	alogliptin	Medication	RxNorm	Not applicable
2627044	bexagliflozin	Medication	RxNorm	Not applicable
OMOP5174738	BEXAGLIFLOZIN	Medication	RxNorm	Not applicable
1373458	canagliflozin	Medication	RxNorm	Not applicable
1488564	dapagliflozin	Medication	RxNorm	Not applicable
1551291	dulaglutide	Medication	RxNorm	Not applicable
1545653	empagliflozin	Medication	RxNorm	Not applicable
1992672	ertugliflozin	Medication	RxNorm	Not applicable
60548	exenatide	Medication	RxNorm	Not applicable
25789	glimepiride	Medication	RxNorm	Not applicable
4821	glipizide	Medication	RxNorm	Not applicable
4815	glyburide	Medication	RxNorm	Not applicable
1100699	linagliptin	Medication	RxNorm	Not applicable
475968	liraglutide	Medication	RxNorm	Not applicable
1440051	lixisenatide	Medication	RxNorm	Not applicable
6809	metformin	Medication	RxNorm	Not applicable
857974	saxagliptin	Medication	RxNorm	Not applicable
1991302	semaglutide	Medication	RxNorm	Not applicable
593411	sitagliptin	Medication	RxNorm	Not applicable
2601723	tirzepatide	Medication	RxNorm	Not applicable
2nd Generation Sulfonylurea				
25789	glimepiride	Medication	RxNorm	Not applicable
4821	glipizide	Medication	RxNorm	Not applicable
4815	glyburide	Medication	RxNorm	Not applicable
Dipeptidyl Peptidase-4 (DPP-4) Inhibitor				
1368001	alogliptin	Medication	RxNorm	Not applicable
1100699	linagliptin	Medication	RxNorm	Not applicable
857974	saxagliptin	Medication	RxNorm	Not applicable
593411	sitagliptin	Medication	RxNorm	Not applicable
Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA)				
1534763	albiglutide	Medication	RxNorm	Not applicable
1551291	dulaglutide	Medication	RxNorm	Not applicable
60548	exenatide	Medication	RxNorm	Not applicable
475968	liraglutide	Medication	RxNorm	Not applicable
1440051	lixisenatide	Medication	RxNorm	Not applicable
1991302	semaglutide	Medication	RxNorm	Not applicable
2601723	tirzepatide	Medication	RxNorm	Not applicable
Metformin				
6809	metformin	Medication	RxNorm	Not applicable

Appendix A. List of RxNorm Medication Terms Used to Define Exposures in this Request

Code	Description	Code Category	Code Type	Filter
Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitor				
2627044	bexagliflozin	Medication	RxNorm	Not applicable
OMOP5174738	BEXAGLIFLOZIN	Medication	RxNorm	Not applicable
1373458	canagliflozin	Medication	RxNorm	Not applicable
1488564	dapagliflozin	Medication	RxNorm	Not applicable
1545653	empagliflozin	Medication	RxNorm	Not applicable
1992672	ertugliflozin	Medication	RxNorm	Not applicable

Appendix B. Specifications Defining Query Builder Modules in this Request

Network:
TriNetX Live™ USA Network

Cohort 1A (query name: Incident Non-Insulin Antidiabetic 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of			
	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First antidiabetic			
must have any of			
	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:6809	metformin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:593411	sitagliptin
	medication	NLM:RXNORM:2601723	tirzepatide
event relationship	Any instance of Group 2B (No antidiabetic) occurred at least 1 day before the first instance of Group 2A (First antidiabetic)		
Group 2B No antidiabetic			
cannot have any of			

Appendix B. Specifications Defining Query Builder Modules in this Request

	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:6809	metformin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:593411	sitagliptin
	medication	NLM:RXNORM:2601723	tirzepatide
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No antidiabetic before 10/1/17[4]			
cannot have any of			
	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:6809	metformin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:593411	sitagliptin
	medication	NLM:RXNORM:2601723	tirzepatide
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
Antidiabetic 10/1/17 - 9/30/23[2]			
must have any of			
	medication	NLM:RXNORM:1534763	albiglutide

Appendix B. Specifications Defining Query Builder Modules in this Request

medication	NLM:RXNORM:1368001	alogliptin
medication	NLM:RXNORM:2627044	bexagliflozin
medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
medication	NLM:RXNORM:1373458	canagliflozin
medication	NLM:RXNORM:1488564	dapagliflozin
medication	NLM:RXNORM:1551291	dulaglutide
medication	NLM:RXNORM:1545653	empagliflozin
medication	NLM:RXNORM:1992672	ertugliflozin
medication	NLM:RXNORM:60548	exenatide
medication	NLM:RXNORM:25789	glimepiride
medication	NLM:RXNORM:4821	glipizide
medication	NLM:RXNORM:4815	glyburide
medication	NLM:RXNORM:1100699	linagliptin
medication	NLM:RXNORM:475968	liraglutide
medication	NLM:RXNORM:1440051	lixisenatide
medication	NLM:RXNORM:6809	metformin
medication	NLM:RXNORM:857974	saxagliptin
medication	NLM:RXNORM:1991302	semaglutide
medication	NLM:RXNORM:593411	sitagliptin
medication	NLM:RXNORM:2601723	tirzepatide

Cohort 1B (query name: Incident Non-Insulin Antidiabetic 10/1/17 - 9/30/19)

The following parameters change from Cohort 1A:

[1] Oct 1 2017 and Sep 30 2019

[2] 10/1/17 - 9/30/19

Cohort 1C (query name: Incident Non-Insulin Antidiabetic 10/1/19 - 9/30/21)

The following parameters change from Cohort 1A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 1D (query name: Incident Non-Insulin Antidiabetic 10/1/21 - 9/30/23)

The following parameters change from Cohort 1A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

[4] 10/1/21

Cohort 2A (query name: Incident 2nd Generation Sulfonylurea 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1 *date constraint:* *The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*

Any Visit 10/1/17 - 9/30/23

must have any of

visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter

Appendix B. Specifications Defining Query Builder Modules in this Request

	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First 2nd Generation Sulfonylurea			
must have any of			
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
event relationship	Any instance of Group 2B (No 2nd Generation Sulfonylurea) occurred at least 1 day before the first instance of Group 2A (First 2nd Generation Sulfonylurea)		
Group 2B No 2nd Generation Sulfonylurea			
cannot have any of			
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No 2nd Generation Sulfonylurea before 10/1/17[4]			
cannot have any of	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
2nd Generation Sulfonylurea 10/1/17 - 9/30/23[2]			
must have any of			
	medication	NLM:RXNORM:25789	glimepiride
	medication	NLM:RXNORM:4821	glipizide
	medication	NLM:RXNORM:4815	glyburide

Cohort 2B (query name: Incident 2nd Generation Sulfonylurea 10/1/17 - 9/30/19)

The following parameters change from Cohort 2A:

[1] Oct 1 2017 and Sep 30 2019

[2] 10/1/17 - 9/30/19

Cohort 2C (query name: Incident 2nd Generation Sulfonylurea 10/1/19 - 9/30/21)

The following parameters change from Cohort 2A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 2D (query name: Incident 2nd Generation Sulfonylurea 10/1/21 - 9/30/23)

The following parameters change from Cohort 2A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

[4] 10/1/21

Replicate Cohorts A-D for each generic name in this drug class

Cohort 3A (query name: Incident DPP-4i 10/1/17 - 9/30/23)

Appendix B. Specifications Defining Query Builder Modules in this Request

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of			
	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First DPP-4i			
must have any of			
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
event relationship	Any instance of Group 2B (No DPP-4i) occurred at least 1 day before the first instance of Group 2A (First DPP-4i)		
Group 2B No DPP-4i			
cannot have any of			
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No DPP-4i before 10/1/17[4]			
cannot have any of			
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
DPP-4i 10/1/17 - 9/30/23[2]			
must have any of			
	medication	NLM:RXNORM:1368001	alogliptin
	medication	NLM:RXNORM:1100699	linagliptin
	medication	NLM:RXNORM:857974	saxagliptin
	medication	NLM:RXNORM:593411	sitagliptin

Cohort 3B (query name: Incident DPP-4i 10/1/17 - 9/30/19)

The following parameters change from Cohort 3A:

[1] Oct 1 2017 and Sep 30 2019

Appendix B. Specifications Defining Query Builder Modules in this Request

[2] 10/1/17 - 9/30/19

Cohort 3C (query name: Incident DPP-4i 10/1/19 - 9/30/21)

The following parameters change from Cohort 3A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 3D (query name: Incident DPP-4i 10/1/21 - 9/30/23)

The following parameters change from Cohort 3A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

[4] 10/1/21

Replicate Cohorts A-D for each generic name in this drug class

Cohort 4A (query name: Incident GLP-1 RA 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of			
	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First GLP-1 RA			
must have any of			
	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:2601723	tirzepatide
event relationship	Any instance of Group 2B (No GLP-1 RA) occurred at least 1 day before the first instance of Group 2A (First GLP-1 RA)		
Group 2B No GLP-1 RA			
cannot have any of			

Appendix B. Specifications Defining Query Builder Modules in this Request

	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:2601723	tirzepatide
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No GLP-1 RA before 10/1/17[4]			
cannot have any of			
	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:2601723	tirzepatide
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
GLP-1 RA 10/1/17 - 9/30/23[2]			
must have any of			
	medication	NLM:RXNORM:1534763	albiglutide
	medication	NLM:RXNORM:1551291	dulaglutide
	medication	NLM:RXNORM:60548	exenatide
	medication	NLM:RXNORM:475968	liraglutide
	medication	NLM:RXNORM:1440051	lixisenatide
	medication	NLM:RXNORM:1991302	semaglutide
	medication	NLM:RXNORM:2601723	tirzepatide

Cohort 4B (query name: Incident GLP-1 RA 10/1/17 - 9/30/19)

The following parameters change from Cohort 4A:

[1] Oct 1 2017 and Sep 30 2019

[2] 10/1/17 - 9/30/19

Cohort 4C (query name: Incident GLP-1 RA 10/1/19 - 9/30/21)

The following parameters change from Cohort 4A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 4D (query name: Incident GLP-1 RA 10/1/21 - 9/30/23)

The following parameters change from Cohort 4A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

[4] 10/1/21

Replicate Cohorts A-D for each generic name in this drug class

Cohort 5A (query name: Incident Metformin 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*

Appendix B. Specifications Defining Query Builder Modules in this Request

Any Visit 10/1/17 - 9/30/23			
must have any of			
	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First Metformin			
must have any of			
	medication	NLM:RXNORM:6809	metformin
event relationship	Any instance of Group 2B (No Metformin) occurred at least 1 day before the first instance of Group 2A (First Metformin)		
Group 2B No Metformin			
cannot have any of			
	medication	NLM:RXNORM:6809	metformin
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No Metformin before 10/1/17[4]			
cannot have any of			
	medication	NLM:RXNORM:6809	metformin
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
Metformin 10/1/17 - 9/30/23[2]			
must have any of			
	medication	NLM:RXNORM:6809	metformin

Cohort 5B (query name: Incident Metformin 10/1/17 - 9/30/19)

The following parameters change from Cohort 5A:

[1] Oct 1 2017 and Sep 30 2019

[2] 10/1/17 - 9/30/19

Cohort 5C (query name: Incident Metformin 10/1/19 - 9/30/21)

The following parameters change from Cohort 5A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 5D (query name: Incident Metformin 10/1/21 - 9/30/23)

The following parameters change from Cohort 5A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

Appendix B. Specifications Defining Query Builder Modules in this Request

[4] 10/1/21

Cohort 6A (query name: Incident SGLT2 inhibitor 10/1/17 - 9/30/23)

This query was run on the USA network with 81 HCO(s) queried and 81 HCO(s) responded.

Group 1	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023*	
Any Visit 10/1/17 - 9/30/23			
must have any of			
	visit	UMLS:HL7V3.0:VisitType:AMB	Visit: Ambulatory
	visit	UMLS:HL7V3.0:VisitType:EMER	Visit: Emergency
	visit	UMLS:HL7V3.0:VisitType:HH	Visit: Home Health
	visit	UMLS:HL7V3.0:VisitType:IMP	Visit: Inpatient Encounter
	visit	UMLS:HL7V3.0:VisitType:NONAC	Visit: Inpatient Non-acute
	visit	UMLS:HL7V3.0:VisitType:LAB	Visit: Laboratory
	visit	UMLS:HL7V3.0:VisitType:OBSENC	Visit: Observation Encounter
	visit	UMLS:HL7V3.0:VisitType:PHARM	Visit: Pharmacy
	visit	UMLS:HL7V3.0:VisitType:PRENC	Visit: Pre-admission
	visit	UMLS:HL7V3.0:VisitType:SS	Visit: Short Stay
	visit	UMLS:HL7V3.0:VisitType:UNKNOWN	Visit: Unknown
	visit	UMLS:HL7V3.0:VisitType:VR	Visit: Virtual
Group 2			
Group 2A First SGLT2 inhibitor			
must have any of			
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
event relationship	Any instance of Group 2B (No SGLT2 inhibitor) occurred at least 1 day before the first instance of Group 2A (First SGLT2 inhibitor)		
Group 2B No SGLT2 inhibitor			
cannot have any of			
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
Group 3	*date constraint:*	*The terms in this group occurred between Jan 1, 1900 and Sep 30, 2017* [3]	
No SGLT2 inhibitor before 10/1/17[4]			
cannot have any of			
	medication	NLM:RXNORM:2627044	bexagliflozin
	medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
	medication	NLM:RXNORM:1373458	canagliflozin
	medication	NLM:RXNORM:1488564	dapagliflozin
	medication	NLM:RXNORM:1545653	empagliflozin
	medication	NLM:RXNORM:1992672	ertugliflozin
Group 4	*date constraint:*	*The terms in this group occurred between Oct 1, 2017 and Sep 30, 2023* [1]	
SGLT2 inhibitor 10/1/17 - 9/30/23[2]			

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must have any of

medication	NLM:RXNORM:2627044	bexagliflozin
medication	NLM:RXNORM:OMOP5174738	BEXAGLIFLOZIN
medication	NLM:RXNORM:1373458	canagliflozin
medication	NLM:RXNORM:1488564	dapagliflozin
medication	NLM:RXNORM:1545653	empagliflozin
medication	NLM:RXNORM:1992672	ertugliflozin

Cohort 6B (query name: Incident SGLT2 inhibitor 10/1/17 - 9/30/19)

The following parameters change from Cohort 6A:

[1] Oct 1 2017 and Sep 30 2019

[2] 10/1/17 - 9/30/19

Cohort 6C (query name: Incident SGLT2 inhibitor 10/1/19 - 9/30/21)

The following parameters change from Cohort 6A:

[1] Oct 1 2019 and Sep 30 2021

[2] 10/1/19 - 9/30/21

[3] Jan 1 1900 and Sep 30 2019

[4] 10/1/19

Cohort 6D (query name: Incident SGLT2 inhibitor 10/1/21 - 9/30/23)

The following parameters change from Cohort 6A:

[1] Oct 1 2021 and Sep 30 2023

[2] 10/1/21 - 9/30/23

[3] Jan 1 1900 and Sep 30 2021

[4] 10/1/21

Replicate Cohorts A-D for each generic name in this drug class

DPP-4i = dipeptidyl peptidase IV inhibitors