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.

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_wp044

Request ID: cder_iqp_wp044_tnx_v01

Request Description: In this report, we aimed to list the most frequent diagnoses, procedures, medications and labs associated with use of Inclisiran, a new molecular entity (NME) approved by the FDA in 2021 using the TriNetX Live™ platform.

Data Source: We ran this query on July 25, 2024, using data from 61 health care organizations (HCOs), provided through the TriNetX Live™ platform in their USA Network with Minimal Shift from December 18, 2020 to February 29, 2024.

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. The USA Network with Minimal Shift contains HCOs that date shift their data by 14 or fewer days (including 0). 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 users of Inclisiran, an injectable medication indicated for lowering low-density lipoprotein cholesterol (LDL-C) levels, over the query period of December 18, 2020 to February 29, 2024. We used the Query Builder module in the TriNetX Live™ platform to create the aforementioned patient cohort.
We used the Analytics module, specifically the Analyze Outcomes Analytics module with the Characteristics analysis type available on the TriNetX Live™ platform to list the common diagnoses, procedures, medications and labs in assessment period between -183 days and -1 day from the index Inclisiran date (i.e., date of first Inclisiran prescription/dispensing/administration in the query period).

Exposures of Interest: We defined the exposure of interest, Inclisiran, using RxNorm medication terms and Healthcare Common Procedure Coding System (HCPCS) codes in the Query Builder module. In order to be included in the cohort, we required evidence of at least one Inclisiran prescription, dispensing or administration between December 18, 2020 and February 29, 2024. Please see Appendix A for the specific terms used to define Inclisiran in this request.

Cohort Eligibility Criteria: We created one cohort for Inclisiran users as detailed in the "Exposures of Interest" section. Patients of all ages were included in the cohort.
Please see Appendix B for the specifications of the cohort parameters as included in the Query Builder.

Baseline Characteristics:
We utilized the Analyze Outcomes Analytics module with the Characteristics analysis type in the TriNetX Live™ platform to assess the most frequent diagnoses, procedures, medication classes prescribed/dispensed/administered and lab terms (with values) in our Inclisiran cohort. The time period for the analysis was from 183 days before to the day before (i.e., -183 to -1 day) the index Inclisiran date.

1. Most frequent diagnoses: We identified the most frequent baseline diagnoses/comorbid conditions defined as 3-digit International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) diagnoses codes using the relevant coding hierarchies in the TriNetX platform. For each 3-digit ICD-10-CM code, we included the most common 4-digit code within the hierarchy (i.e.,4-digit code ABC.X within 3-digit ABC code). Overall, we included up to 40 diagnoses codes using the outlined approach. The codes with the descriptions along with their prevalence in the cohort (over [-183, -1] days from index) are given in Table 1.

2. Most frequent procedures: We identified the most frequent procedures, using International Classification of Diseases, 10th Revision - Procedure Coding System (ICD-10-PCS), Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT) and Systematized Nomenclature of Medicine (SNOMED) codes in the TriNetX platform. We used coding hierarchies, where applicable - the code chapter of the relevant system, followed by codes within, and included up to 40 procedure codes using the outlined approach. In certain situations, we focused on a level of the coding hierarchy that describe a procedure or set of similar procedures, rather than the detailed specific procedure code itself. See the note below for details. The codes with the descriptions along with their prevalence in the cohort are given in Table 2.

Note : TriNetX uses a hierarchical tree system within CPT codes using CPT subsets, which are developed for EHR systems and specific physician specialties for ease of data capture or data retrieval. These CPT subsets are 7-digit codes or parent terms, which encompasses child terms beneath, which could be other 7-digit subset or 5-digit CPT codes. *Additional details can be found at https://cpt-international.ama-assn.org/implementation-framework* . This is distinct from insurance claims databases (most of the Data Partners in the Sentinel Distributed Database), where only 5-digit CPT codes are used for billing purposes.

In the list of most frequent procedure codes, we included 7-digit CPT subset codes (parent terms) in addition to the 5-digit specific CPT codes, where relevant. Specifically, in situations where the procedure or parent term was relevant to the index exposure and was frequent enough to be included in the list but the child terms were not.

3. Most frequent medication classes prescribed/dispensed: We identified the most frequent medication classes prescribed or dispensed using the Veterans Affairs (VA) Drug Classification System, which uses 5-character alphanumeric code to classify all medication products available in the United States. We listed the major classification system, followed by subcategories, and included up to 30 classes along with their prevalence in the cohort (Table 3).
Note : A specific generic ingredient can be listed in multiple classes, based on their route of administration or therapeutic category in the VA classification system.

4. Most common labs: We identified the most frequent lab terms (including vitals) using TriNetX aggregate lab terms (TNX:LAB) that group clinically relevant Logical Observation Identifiers Names and Codes (LOINC) together for each test. We listed the lab terms within the relevant lab categories curated by TriNetX (e.g., metabolic tests, lipid panel, etc.) with their description in Table 4. We also included the proportion of the cohort that had the test performed in the period of [-183, -1] days from index, and certain summary measures of the lab values closest to the index date (the mean and standard deviation, minimum and maximum value).

Limitations: Algorithms used to define exposures, characteristics, and mapping of source data to the data model are imperfect and susceptible to misclassification. Additionally, EHR data in the United States lacks longitudinality. The information before or after patients' healthcare encounters could be missing, especially if patient care was administered across different HCOs that may or 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.

The VA Classification System classifies medication products, rather than the generic ingredient. Hence, the same generic ingredient (e.g., sodium chloride, aspirin, etc.) can be classified in different drug classes, based on what route of administration or therapeutic category it belongs to. TriNetX uses two classification systems on their platform: the VA Classification System (classified available U.S. products) and the Anatomical Chemical and Therapuetic (ATC) Classification Systems (used gloabally), neither of which classifies drugs into mutually exclusive classes.

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The units for lab tests in TriNetX are harmonized across labs when bringing new data onto the network. However, TriNetX does not remove outlier values so as not to bias the data. Hence, certain unexpected or implausible lab values may be observed in the database.

Additionally, lab values of 0 units could be observed in the database, but the interpretation of such a value could be different based on organization-specific practices for rounding, errors, or indicating inconclusive results.

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%.

A subset of HCOs that contribute to the TriNetX USA Minimal Shift network may implement date shifting upto 14 days 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; readers should exercise caution when extrapolating information related to time.

Notes: We ran this query on July 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).

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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.

Glossary of Terms for Analyses Using TriNetX Live™ Platform*

TriNetX Codes - For commonly used laboratory terms, TriNetX aggregates Logical Observation Identifiers Names and Codes (LOINC) laboratory codes at a clinically significant level 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. Values for visit terms include: ambulatory, emergency, field, home health, inpatient encounter, inpatient acute, inpatient non-acute, laboratory, observation, pharmacy, pre-admission, short stay, virtual, and unknown.

*all terms may not be used in this report

Table 1. Most Frequent Diagnoses* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran Users	
	N	%
Total Number of Patients	2,590	100.0
Endocrine, nutritional and metabolic diseases (E00-E89)	2,060	79.5
Disorders of lipoprotein metabolism and other lipidemias (E78)	1,930	74.5
Hyperlipidemia, unspecified (E78.5)	1,140	44.0
Mixed hyperlipidemia (E78.2)	730	28.2
Pure hypercholesterolemia (E78.0)	670	25.9
Type 2 diabetes mellitus (E11)	580	22.4
Type 2 diabetes mellitus without complications (E11.9)	430	16.6
Overweight and obesity (E66)	390	15.1
Obesity, unspecified (E66.9)	220	8.5
Other hypothyroidism (E03)	330	12.7
Hypothyroidism, unspecified (E03.9)	300	11.6
Diseases of the circulatory system (I00-I99)	1,950	75.3
Essential (primary) hypertension (I10)	1,350	52.1
Chronic ischemic heart disease (I25)	1,330	51.4
Atherosclerotic heart disease of native coronary artery (I25.1)	1,290	49.8
Heart failure (I50)	310	12.0
Systolic (congestive) heart failure (I50.2)	130	5.0
Diastolic (congestive) heart failure (I50.3)	130	5.0
Factors influencing health status and contact with health services (Z00-Z99)	1,660	64.1
Presence of cardiac and vascular implants and grafts (Z95)	570	22.0
Presence of coronary angioplasty implant and graft (Z95.5)	280	10.8
Long term (current) drug therapy (Z79)	560	21.6
Other long term (current) drug therapy (Z79.8)	440	17.0
Encounter for screening for malignant neoplasms (Z12)	490	18.9
Encounter for screening for malignant neoplasms of breast (Z12.3)	260	10.0
Encounter for general examination without complaint, suspected or reported diagnosis (Z00)	450	17.4
Encounter for general adult medical examination (Z00.0)	430	16.6
Body mass index [BMI] (Z68)	450	17.4
Body mass index [BMI] 30-39, adult (Z68.3)	230	8.9
Other specified health status (Z78)	370	14.3
Other specified health status (Z78.9)	300	11.6
Personal history of certain other diseases (Z86)	330	12.7
Personal history of diseases of the circulatory system (Z86.7)	200	7.7
Personal history of other diseases and conditions (Z87)	320	12.4
Personal history of other specified conditions (Z87.8)	250	9.7
Other postprocedural states (Z98)	310	12.0
Other specified postprocedural states (Z98.8)	200	7.7
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99)	1,590	61.4
Abnormalities of breathing (R06)	400	15.4
Dyspnea (R06.0)	380	14.7
Pain in throat and chest (R07)	390	15.1
Chest pain, unspecified (R07.9)	290	11.2
Elevated blood glucose level (R73)	330	12.7
Abnormal glucose (R73.0)	270	10.4
Diseases of the musculoskeletal system and connective tissue (M00-M99)	1,120	43.2
Other joint disorder, not elsewhere classified (M25)	400	15.4
Pain in joint (M25.5)	370	14.3
Dorsalgia (M54)	400	15.4
Radiculopathy (M54.1)	170	6.6
Other and unspecified soft tissue disorders, not elsewhere classified (M79)	370	14.3
Pain in limb, hand, foot, fingers and toes (M79.6)	200	7.7

Table 1. Most Frequent Diagnoses* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran Users	
	N	%
Diseases of the nervous system (G00-G99)	830	32.0
Sleep disorders (G47)	440	17.0
Sleep apnea (G47.3)	360	13.9
Diseases of the digestive system (K00-K95)	810	31.3
Gastro-esophageal reflux disease (K21)	460	17.8
Gastro-esophageal reflux disease without esophagitis (K21.9)	450	17.4
Diseases of the genitourinary system (N00-N99)	720	27.8
Chronic kidney disease (CKD) (N18)	300	11.6
Chronic kidney disease, stage 3 (moderate) (N18.3)	210	8.1

*Diagnoses were assessed using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnoses codes over the period of -183 to -1 days before index Inclisiran date.

Table 2. Most Frequent Procedures* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran	
	N	%
Total Number of Patients	2,590	100.0
Most Frequent Procedure ICD-10-PCS/CPT/HCPCS/SNOMED* Codes		
Evaluation and Management (CPT: 1013625)	1,580	61.0
Office or Other Outpatient Services (CPT: 1013626)	1,480	57.1
Emergency Department Services (CPT: 1013711)	270	10.4
Medicine Services and Procedures (CPT: 1012569)	1,210	46.7
Electrocardiogram, routine ECG with at least 12 leads (CPT: 1013012)	700	27.0
Electrocardiogram, routine ECG with at least 12 leads; tracing only, without interpretation and report (CPT: 93005)	440	17.0
Echocardiography Procedures (CPT: 1013050)	330	12.7
Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, with spectral Doppler echocardiogram (CPT: 93306)	290	11.2
Non-Invasive Vascular Diagnostic Studies (CPT: 1013175)	240	9.3
Hydration, Therapeutic, Prophylactic, Diagnostic Injections and Infusions, and Chemotherapy and Other Highly Complex Drug or Highly Complex Biologic Administration (CPT: 1019103)	230	8.9
Vaccines, Toxoids (CPT: 1012602)	170	6.6
Physical Medicine and Rehabilitation Evaluations (CPT: 1013483)	140	5.4
Pathology and Laboratory Procedures (CPT: 1011136)	1,200	46.3
Lipid panel This panel must include the following: Cholesterol, serum, total (82465) Lipoprotein, direct measurement, high density cholesterol (HDL cholesterol) (83718) Triglycerides (84478) (CPT: 80061)	740	28.6
Comprehensive metabolic panel This panel must include the following: Albumin (82040) Bilirubin, total (82247) Calcium, total (82310) Carbon dioxide (bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Phosphatase, alkaline (84075) Potassium (84132) Protein, total (84155) Sodium (84295) Transferase, alanine amino (ALT) (SGPT) (84460) Transferase, aspartate amino (AST) (SGOT) (84450) Urea nitrogen (BUN) (84520) (CPT: 80053)	740	28.6
Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC, and platelet count) and automated differential WBC count (CPT: 85025)	650	25.1
Hemoglobin; glycosylated (A1C) (CPT: 83036)	540	20.8
Thyroid stimulating hormone (TSH) (CPT: 84443)	380	14.7
Basic metabolic panel (Calcium, total) This panel must include the following: Calcium, total (82310) Carbon dioxide (bicarbonate) (82374) Chloride (82435) Creatinine (82565) Glucose (82947) Potassium (84132) Sodium (84295) Urea nitrogen (BUN) (84520) (CPT: 80048)	380	14.7
Microbiology Procedures (CPT: 1012124)	300	11.6
Urinalysis, by dip stick or tablet reagent for bilirubin, glucose, hemoglobin, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, any number of these… (CPT: 1011224)	290	11.2
Vitamin D (CPT: 1020198)	220	8.5
Prothrombin time (CPT: 85610)	220	8.5
Creatinine (CPT: 1011373)	210	8.1
Immunology Procedures (CPT: 1011874)	210	8.1
C-reactive protein (CPT: 1014273)	130	5.0
Magnesium (CPT: 83735)	200	7.7
Blood count; complete (CBC), automated (Hgb, Hct, RBC, WBC, and platelet count) (CPT: 85027)	190	7.3
Troponin, quantitative (CPT: 84484)	170	6.6
Thromboplastin time, partial (PTT) (CPT: 1011869)	140	5.4
Surgery (CPT: 1003143)	1,040	40.2
Surgical Procedures on the Cardiovascular System (CPT: 1006056)	860	33.2
Collection of venous blood by venipuncture (CPT: 36415)	820	31.7
Surgical Procedures on the Musculoskeletal System (CPT: 1003679)	170	6.6
General Surgical Procedures on the Musculoskeletal System (CPT: 1003680)	130	5.0
Radiology Procedures (CPT: 1010251)	990	38.2

Table 2. Most Frequent Procedures* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran	
	N	%
Radiologic examination, chest (CPT: 1031050)	320	12.4
Diagnostic Radiology (Diagnostic Imaging) Procedures of the Lower Extremities (CPT: 1010477)	180	6.9
Breast, Mammography (CPT: 1015090)	180	6.9
Screening mammography, bilateral (2-view study of each breast), including computer-aided detection (CAD) when performed (CPT: 77067)	150	5.8
Diagnostic Ultrasound Procedures (CPT: 1010759)	170	6.6
Diagnostic Radiology (Diagnostic Imaging) Procedures of the Abdomen (CPT: 1010520)	180	6.9
Diagnostic Radiology (Diagnostic Imaging) Procedures of the Spine and Pelvis (CPT: 1010367)	160	6.2
Diagnostic Radiology (Diagnostic Imaging) Procedures of the Head and Neck (CPT: 1010253)	160	6.2
HCPCS G: Temporary Procedures & Professional Services (G)	650	25.1
Hospital outpatient clinic visit for assessment and management of a patient (HCPCS: G0463)	320	12.4
Annual wellness visit, includes a personalized prevention plan of service (pps), subsequent visit (HCPCS: G0439)	160	6.2
HCPCS J: Drugs Administered Other Than Oral Method, Chemotherapy Drugs (J)	410	15.8
Injection, fentanyl citrate, 0.1 mg (HCPCS: J3010)	120	4.6
HCPCS Q: Temporary Codes (Q)	260	10.0
Low osmolar contrast material, 300-399 mg/ml iodine concentration, per ml (HCPCS: Q9967)	180	6.9
HCPCS C: Temporary Hospital Outpatient Prospective Payment System (C)	250	9.7
Guide wire (HCPCS: C1769)	110	4.2

* The procedures were assessed over the period of -183 to -1 days before index Inclisiran date using the following coding systems: ICD-10-PCS: International Classification of Diseases, Tenth Revision, Procedure Coding System; CPT - Current Procedural Terminology, HCPCS: Healthcare Common Procedure Coding System; SNOMED: Systemized Nomenclature of Medicine – Clinical Terms

The 7-digit CPT codes in the list of procedure codes refer to the CPT subsets, which are developed for EHR systems and specific physician specialties for ease of data capture or data retrieval (hierarchical tree). The CPT subsets are parent terms, which encompass child terms beneath, which could be other 7-digit subset or 5-digit CPT codes.

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Table 3. Most Frequent Prescribed Medication Classes* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran Users	
	N	%
Total Number of Patients	2,590	100.0
Cardiovascular medications (CV000)	1,760	68.0
Antilipemic agents (CV350)	1,210	46.7
Beta blockers/related (CV100)	700	27.0
Antiarrhythmics (CV300)	540	20.8
Diuretics (CV700)	470	18.1
Loop diuretics (CV702)	240	9.3
Angiotensin ii inhibitor (CV805)	430	16.6
Calcium channel blockers (CV200)	420	16.2
Antianginals (CV250)	360	13.9
Central nervous system medications (CN000)	1,220	47.1
Non-opioid analgesics (CN103)	690	26.6
Opioid analgesics (CN101)	570	22.0
Local anesthetics, injection (CN204)	540	20.8
Sedatives/hypnotics (CN300)	510	19.7
Benzodiazepine derivative sedatives/hypnotics (CN302)	440	17.0
Antidepressants (CN600)	380	14.7
Hormones/synthetics/modifiers (HS000)	1,150	44.4
Glucocorticoids (HS051)	670	25.9
Blood glucose regulation agents (HS500)	530	20.5
Oral hypoglycemic agents, oral (HS502)	300	11.6
Dermatological agents (DE000)	1,060	40.9
Dermatologicals, topical other (DE900)	680	26.3
Local anesthetics, topical (DE700)	520	20.1
Anti-inflammatory, topical (DE200)	450	17.4
Ophthalmic agents (OP000)	1,010	39.0
Ophthalmics, other (OP900)	780	30.1
Anesthetics, topical ophthalmic (OP700)	520	20.1
Nasal and throat agents, topical (NT000)	940	36.3
Nasal and throat, topical, other (NT900)	690	26.6
Anesthetics, mucosal (NT300)	530	20.5
Anti-inflammatories, nasal (NT200)	350	13.5
Respiratory tract medications (RE000)	910	35.1
Respiratory agents,other (RE900)	600	23.2
Antiasthma/bronchodilators (RE100)	550	21.2
Bronchodilators,sympathomimetic,inhalation (RE102)	400	15.4
Gastrointestinal medications (GA000)	900	34.7
Sodium bicarbonate containing antacids (GA110)	470	18.1
Gastric medications, other (GA900)	440	17.0
Antiemetics (GA605)	380	14.7
Laxatives (GA200)	330	12.7

*The medication drug classes coded based on Veterans Affairs (VA) drug classification system were assessed over the period of -183 to -1 days before index Inclisiran date. The VA classification system classifies all medication products available in the United States. Please note that a specific generic ingredient can be listed in multiple classes, based on their route of administration.

Table 4. Most Frequent Lab Terms* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran Users		Mean ± SD	Min	Max
	N	%			
Total Number of Patients	2,590	100.0	-	-	-
Most Frequent Lab Terms (and Vitals)*					
Lab Category: Metabolic Panel:**					
Chloride (mmol/L) in Serum, Plasma or Blood (TNX: 9023)	1,570	60.6	103 ± 3.25	87	117
Creatinine (mg/dL) in Serum, Plasma or Blood (TNX: 9024)	1,570	60.6	1.09 ± 3.52	0	139
Sodium (mmol/L) in Serum, Plasma or Blood (TNX: 9029)	1,560	60.2	139 ± 2.85	126	147
Potassium (mmol/L) IN Serum, Plasma or Blood (TNX: 9028)	1,560	60.2	4.31 ± 0.443	3	5.7
Urea nitrogen (mg/dL) in Serum, Plasma or Blood (TNX: 9030)	1,560	60.2	18.7 ± 8.1	4	89
Glucose (mg/dL) in Serum, Plasma or Blood (TNX: 9025)	1,560	60.2	116 ± 44.2	1	442
Calcium (mg/dL) in Serum, Plasma or Blood (TNX: 9022)	1,560	60.2	9.48 ± 0.506	7	12.2
Bicarbonate (mmol/L) in Serum, Plasma or Blood (TNX: 9021)	1,550	59.8	26 ± 2.98	2	35
Magnesium (mg/dL) in Serum, Plasma or Blood (TNX: 9026)	360	13.9	1.99 ± 0.274	1	2.8
Phosphate (mg/dL) in Serum, Plasma or Blood (TNX: 9027)	240	9.3	3.44 ± 0.717	1.7	7.6
Lab Category: Complete Blood Count:**					
Hemoglobin (g/dL) in Blood (TNX: 9014)	1,260	48.6	13.5 ± 1.77	7.3	19.4
Hematocrit (%) of Blood (TNX: 9013)	1,260	48.6	41 ± 5.01	22.7	57.2
Platelets (10^3/uL) in Blood (TNX: 9020)	1,250	48.3	248 ± 73.8	9.5	679
Erythrocytes (10^6/uL) in Blood (TNX: 9012)	1,250	48.3	4.44 ± 0.811	0.00308	6.93
Leukocytes (10^3/uL) in Blood (TNX: 9015)	1,140	44.0	7.05 ± 2.35	0.0059	21.8
Lab Category: Liver Function:**					
Alanine aminotransferase (U/L) in Serum, Plasma or Blood (TNX: 9044)	1,400	54.1	24.6 ± 17.5	4	188
Aspartate aminotransferase (U/L) in Serum or Plasma (TNX: 9047)	1,380	53.3	25.1 ± 14.5	8	208
Alkaline phosphatase (U/L) in Serum, Plasma or Blood (TNX: 9046)	1,360	52.5	78.8 ± 29.3	24	442
Bilirubin.total (mg/dL) in Serum, Plasma or Blood (TNX: 9050)	1,350	52.1	0.551 ± 0.321	0	3.5
Bilirubin.direct (mg/dL) in Serum or Plasma (TNX: 9048)	150	5.8	0.219 ± 0.463	0	5.3
Bilirubin.indirect (mg/dL) in Serum or Plasma (TNX: 9049)	70	2.7	0.52 ± 0.283	0	1.3
Albumin (g/dL) in Serum, Plasma or Blood (TNX: 9045)	1,340	51.7	4.14 ± 0.444	2	5.3
Protein (g/dL) in Serum or Plasma (TNX: 9053)	1,270	49.0	7.02 ± 0.578	4.6	9
Lactate dehydrogenase (U/L) in Serum or Plasma (TNX: 9052)	40	1.5	287 ± 226	109	1389
Gamma glutamyl transferase (U/L) in Serum or Plasma (TNX: 9051)	20	0.8	225 ± 478	12	1984
Lab Category: Lipid Panel:**					
Triglyceride (mg/dL) in Serum, Plasma or Blood (TNX: 9004)	1,410	54.4	167 ± 169	30	4,613
Cholesterol in HDL (mg/dL) in Serum or Plasma (TNX: 9001)	1,400	54.1	52.6 ± 16.3	18	168
Cholesterol in LDL (mg/dL) in Serum or Plasma (TNX: 9002)	1,400	54.1	128 ± 57.2	5	421
Cholesterol (mg/dL) in Serum or Plasma (TNX: 9000)	1,390	53.7	211 ± 67.7	49	829
Lab Category: Cardiology:**					
Natriuretic peptide B [pg/mL] in Serum, Plasma or Blood (TNX: 9003)	130	5.0	439 ± 1,765	9	19,180
Natriuretic peptide B prohormone N-Terminal [pg/mL] in Serum, Plasma and Blood (TNX: 9072)	120	4.6	1,768 ± 5,065	31	33,630
Troponin l.cardiac [ng/mL] in Serum, Plasma or Blood (TNX: 9005)	50	1.9	6.08 ± 23.1	0	121
Lab Category: Endocrinology:**					

cder_iqp_wp044_tnx_v01

Table 4. Most Frequent Lab Terms* Among Patients with Inclisiran Exposures in the TriNetX USA Network (Minimal Date Shift) from December 18, 2020 through February 29, 2024

	Inclisiran Users		Mean ± SD	Min	Max
	N	%			
Hemoglobin A1c/Hemoglobin.total in Blood (TNX: 9037)	870	33.6	6.42 ± 1.34	4.1	16.3
Thyrotropin [m(IU)/L] in Serum, Plasma or Blood (TNX: 9040)	740	28.6	2.54 ± 6.48	0	166
Thyroxine (T4) (ug/dL) in Serum, Plasma or Blood (TNX: 9041)	30	1.2	7.5 ± 2.89	1.1	12
Lab Category: Other Chemistry:**					
Cobalamin (Vitamin B12) (pg/mL) in Serum, Plasma or Blood (TNX: 9065)	220	8.5	636 ± 383	161	2,380
C reactive protein (mg/L) in Serum, Plasma or Blood (TNX: 9063)	180	6.9	8.15 ± 18.3	0	171
Erythrocyte sedimentation rate (mm/hr) (TNX: 9066)	120	4.6	22 ± 17.1	0	86
Folate (ng/mL) in Serum, Plasma or Blood (TNX: 9067)	70	2.7	14.3 ± 6.14	4.2	39
Rheumatoid factor (IU/ml) in Serum or Plasma (TNX: 9070)	20	0.8	20.6 ± 19.6	9.4	59
Lab Category: Findings:**					
Corrected QT Interval (QTc, msec) (TNX: 2001)	380	14.7	439 ± 31.6	316	539
Left Ventricular Ejection Fraction (LVEF) (%) (TNX: 2003)	150	5.8	57.2 ± 12.8	14	85
NYHA Classification (TNX: 2004)	10	0.4	2.33 ± 0.577	2	3
Lab Category: Vitals:**					
Body height (inches) (TNX: 9077)	1,860	71.8	66.3 ± 4.12	56	79
Body weight (pounds) (TNX: 9081)	1,530	59.1	185 ± 43.9	86.2	408
BMI (kg/m^2) (TNX: 9083)	1,320	51.0	29.3 ± 6.02	13.2	56.9
Blood pressure, systolic (mm Hg) (TNX: 9085)	1,630	62.9	132 ± 18.1	80	225
Blood pressure, diastolic (mm Hg) (TNX: 9086)	1,640	63.3	75 ± 11.2	1	198
Heart rate (beats/min) (TNX: 9074)	1,550	59.8	73.2 ± 13.1	37	142
Body temperature (°F) (TNX: 9076)	940	36.3	86.6 ± 23.6	35.7	105
Respiratory rate (breaths/min) (TNX: 9073)	920	35.5	17.1 ± 2.66	10	70
Oxygen saturation (%) (TNX: 9075)	290	11.2	93.6 ± 13.3	8	100
Body surface area (m^2) (TNX: 9087)	90	3.5	2.02 ± 0.243	1.51	2.54

* The lab terms presented were assessed over the period of -183 to -1 days before index Inclisiran date using TriNetX aggregate lab terms (TNX:LAB) that group clinically relevant Logical Observation Identifiers Names and Codes (LOINC) together for each test.

** The lab tests within categories were curated by TriNetX internal team to harmonize related codes

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

Code Type	Code	Description
RxNorm	2588243	Inclisiran
RxNorm	OMOP5051438	Inclisiran
HCPCS	J1306	Injection, inclisiran, 1 mg

Appendix B. Specifications Defining Query Builder Modules in this Request

Network:	
USA Minimal Shift Network	
Cohort 1: Atogepant	
Group 1:	**Time Restrictions**
Subgroup 1A	
Must Have:	
Inclisiran	December 18, 2020 - February 29, 2024

Appendix C. Specifications Defining Analytic Modules in this Request

#	Module	Analysis Type	Cohort(s)	Window	Index Event(s)	Characteristics or Outcomes
1	Analyze Outcomes	Characteristics	Inclisiran	[-183, -1]	Inclisiran	Most frequent diagnoses
2	Analyze Outcomes	Characteristics	Inclisiran	[-183, -1]	Inclisiran	Most frequent procedures
3	Analyze Outcomes	Characteristics	Inclisiran	[-183, -1]	Inclisiran	Most frequent medications
4	Analyze Outcomes	Characteristics	Inclisiran	[-183, -1]	Inclisiran	Most frequent labs