NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Real-World Study Evaluating the Safety of Pantoprazole Sodium intravenous (IV) in Infants Aged 1 Month to <1 Year and Patients Aged 1 to <2 Years Using an Electronic Health Records Database from the United States
Protocol number	B1791096
Protocol version identifier	2.0
Date	10 February 2022
EU Post Authorization Study (PAS) register number	EUPAS45389
Active substance	Pantoprazole sodium (A02BC02)
Medicinal product	Protonix
Research question and objectives	**Research Question:** What are the incidence rates of potential safety events of interest in infants aged 1 month to <1 year and in patients aged 1 to <2 years who were treated with intravenous (IV) pantoprazole in the real-world setting? **Primary Objective**: To estimate the incidence of prespecified outcomes of interest in two separate cohorts, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years with a diagnosis of gastroesophageal reflux disease (GERD)

	with or without erosive esophagitis (EE) and treated with IV pantoprazole. **<u>Secondary Objective 1</u>:** To estimate the incidence of prespecified outcomes of interest in infants aged 1 month to <1 year and patients aged 1 to <2 years treated with IV pantoprazole without a diagnosis of GERD or EE **Secondary Objective 2:** To provide the frequency of the 25 most common diagnostic codes occurring within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) through 90 days of the last treatment with IV pantoprazole among infants aged 1 month to <1 year and patients aged 1 to <2 years with a diagnosis of GERD (regardless of EE diagnosis).
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEP	Aetion Evidence Platform
AE	Adverse event
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
EE	Erosive esophagitis
EHR	Electronic health record
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
GPP	Good Pharmacovigilance Practices
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Nineth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification

ID	Identification
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
NASH	Nonalcoholic steatohepatitis
NDA	New drug application
NDC	National drug code
NEC	Not elsewhere classified
PASS	Post authorization safety study
PK	Pharmacokinetics
PMR	Post-Marketing Requirement
PREA	Pediatric Research Equity Act
SAP	Statistical analysis plan
US	United States
USPI	United States Prescribing Information

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: A Real-World Study Evaluating the Safety of Pantoprazole Sodium IV in Infants Aged 1 Month to <1 Year and Patients Aged 1 to <2 Years Using an Electronic Health Records Database from the United States

Version: 2.0

Date: 10 February 2022

Author: Sampada Gandhi, Pfizer, Inc., Peapack, New Jersey

Rationale and background:

Protonix® (pantoprazole sodium) IV for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with GERD and a history of EE [PROTONIX® IV (pantoprazole sodium) for injection, for intravenous use United States Prescribing Information (USPI)]. It is also indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults. Protonix IV is currently not indicated for use in pediatric patients. The Food and Drug Administration (FDA) issued a requirement for a deferred study under the Pediatric Research Equity Act (PREA) for the treatment of GERD in patients 0 to 16 years of age as a Post-Marketing Requirement (PMR) number 145-1 in December 2004 [06 December 2004 letter to New Drug application (NDA) 20-988/S-027]. Currently, there is an ongoing clinical trial B1791089 conducted in patients 1 to 16 years of age. However, infants aged 1 month to <1 year cannot be enrolled into the ongoing clinical trial. Also, there may be insufficient number of patients aged 1 to <2 years enrolled in the ongoing trial. For these reasons, patients in both these two age-groups are being pursued to be included in this non-interventional study. This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is proposed voluntarily by Pfizer to collect safety data in two separate cohorts of infants aged 1 month to <1 year and patients aged 1 to <2 years who were treated with IV pantoprazole, with a primary focus on patients with a diagnosis of GERD with or without EE using an electronic health records database from the United States. In addition to this study, pharmacokinetic (PK) modeling and simulation is being pursued in lieu of an interventional clinical trial as another strategy to address this PMR.

Research question and objectives

Research Question:

What are the incidence rates of potential safety events of interest in infants aged 1 month to <1 year and in patients aged 1 to <2 years who were treated with IV pantoprazole in the real-world setting?

Within each study cohort (ie, infants aged 1 month to <1 year and in patients aged 1 to <2 years), the primary study objective is:

(1) to estimate the incidence of prespecified outcomes of interest as described below under variables in patients with a diagnosis of GERD with or without EE and treated with IV pantoprazole.

The two secondary objectives are as follows: (1) to estimate the incidence of prespecified outcomes of interest in patients treated with IV pantoprazole without a diagnosis of GERD or EE, and (2) to provide the frequency of the 25 most common diagnostic codes occurring within 30 days prior to or on the date of initiation of IV pantoprazole through 90 days of the last treatment with IV pantoprazole in patients with a diagnosis of GERD (regardless of EE diagnosis).

Study design

Retrospective cohort study using Optum's longitudinal electronic health records (EHR) repository from the United States (US).

Study population

Two separate cohorts, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years who received at least one administration of IV pantoprazole during a study period of 01 January 2007 to 31 December 2020 and those enrolled in the database for at least 30 days prior to the date of first administration of IV pantoprazole will be identified from the Optum's longitudinal EHR repository. In both cohorts, patients with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or International Classification of Diseases Tenth Revision, Clinical Modification (ICD-10-CM) codes indicating a preterm birth will be excluded. Within each cohort, 3 subgroups will be identified: (1) patients with ICD-9-CM or ICD-10-CM codes for GERD with EE, (2) patients with ICD-9-CM or ICD-10-CM codes for GERD but without EE, and (3) patients without diagnosis codes for GERD or EE.

Variables Exposure to IV pantoprazole will be identified from inpatient procedure and drug codes including National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes. The date of first administration of IV pantoprazole will be defined as the index date. For each outcome, patients will be followed from the index date to whichever of the following occurs first: occurrence of the outcome of interest, 90 days following the last date of IV pantoprazole administration, initiation of a separate IV pantoprazole infusion within 90 days following the discontinuation of IV pantoprazole administration, death, end of enrollment in the database, or end of study period (ie, 31 December 2020). The following outcomes of interest will be defined based on the presence of at least one ICD-9-CM or ICD-10-CM diagnosis code identified in the inpatient or outpatient setting during the follow-up period:

- Agranulocytosis
- Thrombocytopenia
- Leukopenia

- Pancytopenia
- Hypersensitivity (including anaphylactic reactions and anaphylactic shock)
- Hyperlipidaemia
- Hypertriglyceridemia
- Hyponatraemia
- Hypomagnesaemia
- Hypocalcaemia
- Hypokalaemia
- Diarrhea
- Vomiting
- Abdominal distension
- Hepatobiliary injury
- Urticaria
- Angioedema
- Stevens-Johnson syndrome
- Lyell syndrome
- Erythema multiforme
- Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
- Tubulointerstitial nephritis
- Photosensitivity
- Peripheral edema and
- Injection site thrombophlebitis

The other key variables of interest to be collected include demographic characteristics, comorbidities, and duration and dose of IV pantoprazole.

Data sources

Optum's longitudinal EHR repository from the US will be used for this study. The Optum EHR with Integrated Claims dataset contains electronic health records data with prescriptions, diagnoses, and provider information as well as practice management data and claims information for deterministically-matched patients. This dataset contains a combination of structured data (e.g. diagnoses, procedures, prescriptions) and information from unstructured data (e.g. drug rationale, provider notes) from the electronic health record and corresponding claims information for those instances. The claims are verified, adjudicated, adjusted, and de-identified. The database currently encompasses the claims and EHR data of more than 95 million patients with approximately 1.9 million patients aged less than 2 years from 01 January 2007 through 31 December 2020.

Study size

All eligible patients meeting inclusion/exclusion criteria will be included in the study. Based on preliminary feasibility, it is anticipated that 7,489 infants aged 1 month to <1 year and

6,657 patients aged 1 to <2 years who have been treated with IV pantoprazole will be eligible for inclusion in the study.

Data analysis

All statistical analysis will be performed in the two cohorts of interest, ie, infants aged 1 month to <1 year and in patients aged 1 to <2 years, separately using the Aetion Evidence Platform version 4.2. Descriptive statistics will be presented for the key variables to characterize the overall cohort treated with IV pantoprazole and the 3 subgroups defined based on the presence or absence of GERD and EE during the baseline period or on the index date. Incidence rates of outcomes of interest will be estimated as the number of patients with a specific outcome of interest during the follow-up period divided by the total person-time at risk and reported as incidence rate per 1,000 person-years with associated 95% confidence intervals (CIs). The CIs will be estimated using the exact method for event counts less than 10, assuming a Poisson distribution. Incidence rates for all outcomes of interest will be calculated in the overall cohort and in each of the 3 subgroups. Within the overall cohort and in the 3 subgroups, incidence rates will be estimated by duration of IV pantoprazole treatment (<4 days, ≥ 4 days). Two sensitivity analyses will be performed as follows: (1) analysis will be repeated in both cohorts without exclusion criteria of at least 30-day enrollment prior to the index date to test the sensitivity to enforced 30-day enrollment period, and (2) analysis will be repeated in both cohorts, stratified by those patients identified via ICD-9-CM codes versus ICD-10-CM codes, respectively to test the sensitivity to ICD-9-CM versus ICD-10-CM coding for subgroup classification.

Milestones

Study protocol is planned to be submitted to the FDA by 20 August 2021 and study report is planned to be submitted to the FDA by 30 June 2022.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	10 February 2022	4, 8, 9.4.2	-Three outcomes of interest, i.e., hepatocellular injury/failure, jaundice, and hepatitis were consolidated into one category - hepatobiliary injury. -The ICD-9-CM and ICD-10-CM code lists used in the operationalization of some outcomes of interest were updated.	-There is a substantial overlap of hepatic conditions in the three outcomes of interest i.e., hepatocellular injury/failure, jaundice, and hepatitis; hence the outcome is simplified by combining the 3 separate categories into a single category of hepatobiliary injury. -Some inconsistencies in the use of ICD codes were noted; therefore, the code lists were updated.
1	10 February 2022	4, 9.4.2	- The outcomes of interest will be defined based on the presence of at least one ICD-9-CM or ICD-10-CM diagnosis code identified in the inpatient or outpatient setting during the follow-up period instead of only inpatient setting.	The outcomes of interest may occur in both inpatient and outpatient setting; hence it was added.
1	10 February 2022	4, 9.3.1, Table 2, 9.8, 9.10	The term ‘dispensing’ is replaced by ‘administration’	Protonix IV administration is a correct term.
1	10 February 2022	9.8	An inconsistency in subgroups with respect to the primary objective and secondary objective 1 was corrected.	Primary objective includes analysis in 2 subgroups, i.e., patients with GERD and EE and patients with GERD, but without EE. The Secondary objective 1 includes analysis in the 3rd subgroup of patients without a diagnosis of GERD or EE.

6. MILESTONES

Milestone	Planned date
Registration in the European Union (EU) PAS register	03 February 2022
Start of data collection	4 February 2022
End of data collection	31 March 2022
Final study report	30 June 2022

7. RATIONALE AND BACKGROUND

Protonix® (pantoprazole sodium) IV for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with GERD and a history of EE [PROTONIX® IV (pantoprazole sodium) for injection, for intravenous use USPI]. It is also indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults. Protonix IV is currently not indicated for use in pediatric patients.

The FDA issued a requirement for a deferred study under the PREA for the treatment of GERD in patients 0 to 16 years of age as a PMR number 145-1 in December 2004 (06 December 2004 letter to NDA 20-988/S-027). Currently, there is an ongoing clinical trial B1791089 conducted in patients 1 to 16 years of age. However, infants aged 1 month to <1 year cannot be enrolled into the ongoing clinical trial. Also, there may be insufficient number of patients aged 1 to <2 years enrolled in the ongoing trial. For these reasons, patients in both these two age-groups are being pursued to be included in this non-interventional study.
This non-interventional study is designated as a PASS and is proposed voluntarily by Pfizer to collect safety data in two separate cohorts of infants aged 1 month to <1 year and patients aged 1 to <2 years who were treated with IV pantoprazole, with a primary focus on patients with a diagnosis of GERD with or without EE using an electronic health records database from the United States. In addition to this study, PK modeling and simulation is being pursued in lieu of an interventional clinical study as another strategy to address this postmarketing requirement.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question: What are the incidence rates of potential safety events of interest in infants aged 1 month to <1 year and in patients aged 1 to <2 years who were treated with IV pantoprazole in the real-world setting?

Primary Objective: To estimate the incidence of the following outcomes of interest in infants aged 1 month to <1 year and patients aged 1 to <2 years with a diagnosis of GERD with or without EE and treated with IV pantoprazole:

- Agranulocytosis
- Thrombocytopenia
- Leukopenia
- Pancytopenia
- Hypersensitivity (including anaphylactic reactions and anaphylactic shock)
- Hyperlipidaemia
- Hypertriglyceridemia
- Hyponatraemia
- Hypomagnesaemia
- Hypocalcaemia
- Hypokalaemia
- Diarrhea
- Vomiting
- Abdominal distension
- Hepatobiliary injury
- Urticaria
- Angioedema
- Stevens-Johnson syndrome
- Lyell syndrome
- Erythema multiforme
- DRESS
- Tubulointerstitial nephritis
- Photosensitivity
- Peripheral edema
- Injection site thrombophlebitis

Secondary Objective 1: To estimate the incidence of the above-mentioned outcomes of interest in infants aged 1 month to <1 year and patients aged 1 to <2 years treated with IV pantoprazole without a diagnosis of GERD or EE.

Secondary Objective 2: To provide the frequency of the 25 most common diagnostic codes occurring within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) through 90 days of the last treatment with IV pantoprazole among infants aged 1 month

to <1 year and patients aged 1 to <2 years with a diagnosis of GERD (regardless of EE diagnosis).

9. RESEARCH METHODS

9.1. Study design

This will be a retrospective cohort study with no comparator group. No a priori hypotheses are specified. Descriptive analyses including an estimation of incidence rates will be performed.

9.2. Setting

The study will be conducted using Optum's longitudinal integrated EHR from the US[1], which is described in Section 9.5 This data source includes data from adjudicated administrative insurance claims, inpatient electronic health records, as well as outpatient EHR enabling capture of exposure to IV pantoprazole in the study population of interest. The study period will be defined from 01 January 2007 to 31 December 2020.

9.3. Study population

Two separate cohorts, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years will be identified during the study period using the following inclusion and exclusion criteria.

9.3.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. At least one administration of IV pantoprazole during the study period from January 1, 2007 to December 31, 2020, and

2. For the cohort of infants aged 1 month to <1 year (Cohort 1): Age 1 month to < 1 year on the index date (ie, the date of first administration of IV pantoprazole); For the cohort of patients aged 1 to <2 years (Cohort 2): Age 1 to <2 years on the index date.

3. Patients must be enrolled in the database for at least 30 days prior to the index date

In addition to this 30-day lookback window, patients will be further excluded based on the occurrence of a history of outcomes of interest identified in Table 3 occurring prior to the index date.

9.3.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients with any of the following ICD-9-CM or ICD-10-CM codes occurring prior to or on the index date indicating a preterm birth or birth weight less than 2.36 kilograms will be excluded:

   ICD-9-CM codes: 765.01-765.08; 765.10-765.19; 765.21-765.28

   ICD-10-CM codes: P07.21-P07.26; P030-P039; P07.01-P07.03; P07.14-P07.18

The cut-off of birth weight less than 2.36 kilograms is defined based on a birth weight that is less than third percentile weight for males at birth obtained from Centers for Disease Control and Prevention (CDC) infant weight-for-age charts (available at URL: https://www.cdc.gov/growthcharts/html_charts/wtageinf.htm). It is reasonable to assume that infants with birth weight less than 2.36 kilograms are most likely born preterm.

9.3.3. Subgroups

Within each cohort (ie, Cohort 1 and 2), 3 subgroups will be identified as follows:

(1) Patients who have a diagnosis of GERD with EE: defined based on the presence of at least one of the ICD-9-CM or ICD-10-CM codes as shown in Table 1 and the presence of an additional ICD-9-CM or ICD-10-CM code for ulcer of the esophagus during the baseline period or on the index date, as shown in Table 1.

(2) Patients who have a diagnosis of GERD without EE: defined based on the presence of at least one of the ICD-9-CM or ICD-10-CM codes and no ICD-9-CM or ICD-10-CM code for ulcer of esophagus during the baseline period or on the index date, as shown in Table 1.

(3) Patients without a diagnosis of GERD or EE: defined as patients who do not have any of the ICD-9-CM or ICD-10-CM codes as shown in Table 1 during the baseline period or on the index date.

ICD-9-CM codes will be used to identify the subgroups prior to October 2015, after which ICD-10-CM codes will be used. No validated algorithm for GERD with or without EE were found to be available via literature review, therefore, a combination of clinical input, and the available codes identified in the literature will be used.[2] Additionally, there is no explicit ICD-9-CM code for GERD with/without esophagitis. Therefore, based on a cross-sectional study that examined the validity of diagnosis codes of benign upper gastrointestinal disorders using electronic patient records[2], and an online conversion tool maintained by the Center for Medicare Services and the Centers for Disease Control and Prevention (available at URL: https://icd.codes/convert/icd10-to-icd9-cm), the subgroups of GERD with or without EE will be determined using the operational definitions shown in Table 1:

Table 1. Operationalization of subgroups

Subgroup	ICD-10-CM Code	Description of ICD-10-CM code	ICD-9-CM Code	Description of ICD-9-CM code
GERD without EE*	K21.0	GERD with esophagitis	530.10, 530.11, 530.12, 530.19	Esophagitis unspecified Reflux esophagitis, Acute esophagitis, Other esophagitis
	K21.9	GERD without esophagitis	530.81	Esophageal reflux
GERD with EE	K21.0, K21.9	GERD with or without esophagitis	530.10, 530.11, 530.12, 530.19, 530.81	Esophagitis unspecified Reflux esophagitis, Acute esophagitis, Other esophagitis Esophageal reflux
	AND			
	K22.1	Ulcer of esophagus	530.2	Ulcer of esophagus

* Patients with any of the listed ICD-9-CM or ICD-10-CM codes and no ICD-9-CM code of 530.2 or ICD-10-CM code of K22.1 during the baseline period or on the index date will be included in the GERD without EE subgroup.

9.4. Variables

9.4.1. Exposure ascertainment

Exposure to IV pantoprazole will be identified from inpatient procedure and drug codes including any of the following NDC and HCPCS codes shown in Table 2. Only the first treatment episode during the study period will be of interest.

Table 2. NDC and HCPCS Codes indicating IV administration of pantoprazole

Code	Description
NDC	
0008-0941-01	40 mg/vial pantoprazole
0008-0941-02	40 mg/vial pantoprazole (10 vials)
0008-0941-03	40 mg/vial pantoprazole (25 vials)
0008-2001-01	40 mg/vial pantoprazole Single vial
0008-2001-10	40 mg/vial pantoprazole 10 vials
0008-2001-25	40 mg/vial pantoprazole 25 vials
0008-4001-01	40 mg/vial pantoprazole Single vial
0008-4001-10	40 mg/vial pantoprazole 10 vials
0008-4001-25	40 mg/vial pantoprazole 25 vials
0008-0923-51	40 mg/vial pantoprazole Single vial
0008-0923-55	40 mg/vial pantoprazole 10 vials
0008-0923-60	40 mg/vial pantoprazole 25 vials)
HCPCS	
S0164	Injection pantoprazole sodium, 40 mg
C9113	Injection, pantoprazole sodium, per vial

9.4.2. Outcomes of interest

The outcomes of interest are listed in Table 3 below. These outcomes were based on the Investigator's Brochure (version 4.0 June 2021) and expert clinical judgment. The first occurrence of each outcome is defined based on the presence of at least one ICD-9-CM or ICD-10-CM diagnosis code identified in the inpatient or outpatient setting during the follow-up period.

Table 3. Operationalization of outcomes of interest

Outcome of interest	Operationalization: ICD-10-CM code	Operationalization: ICD-9-CM code
Agranulocytosis	D70.2 Other drug-induced agranulocytosis D70.1 Agranulocytosis secondary to cancer chemotherapy	288.03 Drug induced neutropenia
Thrombocytopenia	D69.3 Immune thrombocytopenic purpura D69.59 Other secondary thrombocytopenia D69.6 Thrombocytopenia, unspecified D69.41 Evans syndrome D69.49 Other primary thrombocytopenia	287.31 Immune thrombocytopenic purpura 287.49 Other secondary thrombocytopenia 287.5 Thrombocytopenia, unspecified 287.30 Primary thrombocytopenia, unspecified 287.32 Evans syndrome 287.39 Other primary thrombocytopenia
Leukopenia	D72.810 Lymphocytopenia D72.818 Other decreased white blood cell count D72.819 Decreased white blood cell count, unspecified D70.8 Other neutropenia D70.9 Neutropenia, unspecified D70.0 Congenital agranulocytosis	288.51 Lymphocytopenia 288.59 Other decreased white blood cell count 288.50 Leukocytopenia, unspecified 288.09 Other neutropenia 288.00 Neutropenia, unspecified
Pancytopenia	D61.811 Other drug-induced pancytopenia D61.818 Other pancytopenia	284.12 Other drug-induced pancytopenia 284.19 Other pancytopenia

Hypersensitivity (including anaphylactic reactions and anaphylactic shock)	K52.2x Allergic and dietetic gastroenteritis and colitis M31.0 Hypersensitivity angiitis T78.2x Anaphylactic shock, unspecified T78.4x Other and unspecified allergy M36.4x Arthropathy in hypersensitivity reactions classified elsewhere	558.3 Allergic gastroenteritis and colitis 446.20 Hypersensitivity angiitis, unspecified 446.21 Goodpasture's syndrome 446.29 Other specified hypersensitivity angiitis 995.0 Other anaphylactic reaction, Not elsewhere classified (NEC) 995.3 Allergy, unspecified, NEC 713.6 Arthropathy associated with hypersensitivity reaction
Hyperlipidemia	E78.49 Other hyperlipidemia E78.5 Hyperlipidemia, unspecified	272.4 Other and unspecified hyperlipidemia
Hypertriglyceridemia	E78.1 Pure hyperglyceridemia	272.1 Pure hyperglyceridemia
Hyponatremia	E87.1 Hypo-osmolality and hyponatremia	276.1 Hypo-osmolality and/or hyponatremia
hypomagnesemia	E83.42 Hypomagnesemia	275.2 Disorders of magnesium metabolism
Hypocalcaemia	E83.51 Hypocalcemia	275.41 Hypocalcemia
Hypokalemia	E87.6 Hypokalemia	276.8 Hypopotassemia
Diarrhea	R19.7 Diarrhea, unspecified	787.91 Diarrhea
Vomiting	R11.10 …… unspecified R11.11 …… without nausea	536.2 Persistent vomiting 078.82 Epidemic vomiting syndrome

	R11.12 Projectile vomiting R11.13 Vomiting of fecal matter R11.2 Nausea with vomiting, unspecified	787.03 Vomiting alone 569.87 Vomiting of fecal matter 787.01 Nausea with vomiting
Abdominal distension	R14.0 Abdominal distension (gaseous)	787.3 Flatulence, eructation, and gas pain
Hepatobiliary injury	K71x Toxic liver disease K72x Hepatic failure, not elsewhere classified K72.00 Acute and subacute hepatic failure without coma K72.01 Acute and subacute hepatic failure with coma K72.10 Chronic hepatic failure without coma K72.11Chronic hepatic failure with coma K72.90 Hepatic failure, unspecified without coma K72.91 Hepatic failure, unspecified with coma K73x Chronic hepatitis K73.0 Chronic persistent hepatitis, not elsewhere classified K73.1 Chronic lobular hepatitis, not elsewhere classified K73.2 Chronic active hepatitis, not elsewhere classified K73.8 Other chronic hepatitis, not elsewhere classified K73.9 Chronic hepatitis, unspecified K74 Fibrosis and cirrhosis of the liver	573.3 Hepatitis, unspecified 570 Acute and subacute necrosis of liver 572.2 Hepatic encephalopathy. 572.8 Other sequelae of chronic liver disease 571.41 Chronic persistent hepatitis 571.49 Other chronic hepatitis 571.4 Chronic hepatitis 571.5 Cirrhosis of liver without mention of alcohol 571.9 Unspecified chronic liver disease without mention of alcohol 571.6 Biliary cirrhosis 571.42 Autoimmune hepatitis 571.8 Other chronic nonalcoholic liver disease 573 Other disorders of the liver 573.0 Chronic passive congestion of liver 573.8 Other specified disorders of liver 573.4 Hepatic infarction 572.3 Portal hypertension 572.4 Hepatorenal syndrome 573.5 Hepatopulmonary syndrome 573.9 Unspecified disorder of liver 782.4 Jaundice, unspecified, not of newborn

	K74.00 Hepatic fibrosis, unspecified K74.01 Hepatic fibrosis, early fibrosis K74.02 Hepatic fibrosis, advanced fibrosis K74.1 Hepatic sclerosis K74.3 Primary biliary cirrhosis K74.4 Secondary biliary cirrhosis K74.5 Biliary cirrhosis, unspecified K74.60 Unspecified cirrhosis of liver K74.69 Other cirrhosis of liver K75x Other inflammatory liver diseases K75.2 Nonspecific reactive hepatitis K75.3 Granulomatous hepatitis, not elsewhere classified K75.4 Autoimmune hepatitis K75.81 Nonalcoholic steatohepatitis (NASH) K75.89 Other specified inflammatory liver diseases K75.9 Inflammatory liver disease, unspecified K76x Other diseases of the liver K76.0 Fatty (change of) liver, not elsewhere classified K76.1 Chronic passive congestion of liver K76.2 Central hemorrhagic necrosis of liver K76.3 Infarction of liver K76.4 Peliosis hepatis K76.5 Hepatic veno-occlusive disease	

	K76.6 Portal hypertension K76.7 Hepatorenal syndrome K76.81 Hepatopulmonary syndrome K76.89 Other specified diseases of liver K76.9 Liver disease, unspecified K77 Liver disorders in diseases classified elsewhere K71.6 Toxic liver disease with hepatitis, not elsewhere classified K71.2 Toxic liver disease with acute hepatitis K71.3 Toxic liver disease with chronic persistent hepatitis K71.4 Toxic liver disease with chronic lobular hepatitis K71.50 Toxic liver disease with chronic active hepatitis without ascites K71.51 Toxic liver disease with chronic active hepatitis with ascites R17 Unspecified jaundice	
Urticaria	L50.0 Allergic urticaria L50.1 Idiopathic urticaria L50.8 Other urticaria L50.9 Urticaria, unspecified	708.0 Allergic urticaria 708.1 Idiopathic urticaria 708.8 Other specified urticaria 708.9 Urticaria, unspecified
Angioedema	T78.3XXA Angioneurotic edema initial encounter T78.3XXD Angioneurotic edema subsequent encounter T78.3XXS Angioneurotic edema sequela	995.1 Angioneurotic edema, not elsewhere classified

Stevens- Johnson syndrome	L51.1 Stevens-Johnson syndrome L51.3 Stevens-Johnson syndrome -toxic epidermal necrolysis overlap syndrome	695.13 Stevens-Johnson syndrome 695.14 Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
Lyell syndrome	L51.2 Toxic epidermal necrolysis [Lyell]	695.15 Toxic epidermal necrolysis
Erythema multiforme	L51.0 Nonbullous erythema multiforme L51.8 Other erythema multiforme L51.9 Erythema multiforme, unspecified	695.10 Erythema multiforme, unspecified 695.11 Erythema multiforme minor 695.12 Erythema multiforme major 695.19 Other erythema multiforme
DRESS	D72.12 Drug rash with eosinophilia and systemic symptoms syndrome	Not available
Interstitial nephritis Interstitial nephritis, also known as tubulointerstitial nephritis, is inflammation of the area of the kidney	N14.1 Nephropathy induced by other drugs, medicaments and biological substances N14.2 Nephropathy induced by unspecified drug, medicament or biological substance N14.4 Toxic nephropathy, not elsewhere classified N15.8 Other specified renal tubulo-interstitial diseases N15.9 Renal tubulo-interstitial disease, unspecified	583x Nephritis and nephropathy not specified as acute or chronic
Photosensitivity	L56.0 Drug phototoxic response	692.72 Acute dermatitis due to solar radiation

	L56.1 Drug photoallergic response L56.2 Photocontact dermatitis [berloque dermatitis] L56.4 Polymorphous light eruption L56.8 Other specified acute skin changes due to ultraviolet radiation	692.79 Other dermatitis due to solar radiation
Peripheral edema	R60.0 Localized edema R60.9 Edema, unspecified R60.9 Edema, unspecified	782.3 Edema
Injection site thrombophlebitis	I80.8 Phlebitis and thrombophlebitis of other sites I80.9 Phlebitis and thrombophlebitis of unspecified site T80.1 Vascular complications following infusion, transfusion and therapeutic injection T80.81 Extravasation of vesicant agent T80.90 Unspecified complication following infusion and therapeutic injection	451.89 Phlebitis and thrombophlebitis of other sites 451.9 Phlebitis and thrombophlebitis of unspecified site 999.2 Other vascular complications of medical care, NEC 909.3 Late effect of complications of surgical and medical care 999.82 Extravasation of another vesicant agent V58.89 Other specified aftercare 999.88 Other infusion reaction

9.4.3. Key variables of interest

The following key variables will be of interest.

9.4.3.1. Demographic characteristics

Age on the index date will be calculated by subtracting the birth week from the index date. Sex will be either male or female. Race/ethnicity will be categorized as follows: White,

Black, Asian, Hispanic, Other. Sex and race will be defined using all available data during the baseline period.

9.4.3.2. Comorbidities

The following comorbidities will be identified based on the presence of at least one ICD-9-CM/ICD-10-CM diagnosis code or NDC/HCPCS codes identified using all available data during the baseline period and are operationalized in Table 4.

Table 4. Operationalization of comorbidities

History or presence of upper gastrointestinal anatomic or motor disorders	Operationalization: ICD-10-CM code	Operationalization: ICD-9-CM code
Esophageal strictures, webs, diverticula, or other gastroduodenal pathology seen on esophagogastroduodenoscopy	K22.2 Esophageal obstruction K57 Diverticular disease of intestine K22.5 Diverticulum of esophagus, acquired K31.5 Obstruction of duodenum Q39.3 Congenital stenosis and stricture of esophagus Q39.4 Esophageal web	530.3 Stricture and stenosis of esophagus 537.3 Other obstruction of duodenum 530.6 Diverticulum of esophagus, acquired 562 Diverticula of intestine 750.3 Congenital tracheoesophageal fistula, esophageal atresia and stenosis
Gastrointestinal strictures of any kind	K56.69x Other intestinal obstruction K50 Crohn's Disease	555 Regional enteritis 560.9 Unspecified intestinal obstruction, Enterostenosis; of intestine or colon: obstruction, occlusion, stenosis, stricture.
Esophageal or gastric motor disorders (eg, scleroderma)	C15 Malignant neoplasm of esophagus Z85.01 Personal history of malignant neoplasm of esophagus K31.84 Gastroparesis K91.1 Postgastric surgery	150 Malignant neoplasm of esophagus 530 Diseases of esophagus 787.1 Heartburn V10.03 Personal history of malignant neoplasm of esophagus

	syndromes K20 Esophagitis K21 Gastro-esophageal reflux disease K22 Other diseases of esophagus R12 Heartburn K30 Functional dyspepsia K23 Disorders of esophagus in diseases classified elsewhere Q39 Congenital malformations of esophagus	536.3 Gastroparesis 564.2 Postgastric surgery syndromes 750.3 Congenital tracheoesophageal fistula, esophageal atresia and stenosis 750.4 Other specified congenital anomalies of esophagus 536.8 Dyspepsia and other specified disorders of function of stomach
Barrett's esophagus	K22.7x Barrett's esophagus	530.85 Barrett's esophagus
Peptic ulcer disease, erosive gastritis and/or erosive duodenitis	K25 Gastric ulcer K26 Duodenal ulcer K27.x Peptic ulcer, site unspecified K28 Gastrojejunal ulcer	531 Gastric ulcer 532 Duodenal ulcer 533 Peptic ulcer site unspecified 534 Gastrojejunal ulcer
Eosinophilic esophagitis by histology (eosinophils per high powered field)	K20.0 Eosinophilic esophagitis	530.13 Eosinophilic esophagitis
Gastrointestinal malabsorption	K90 Intestinal malabsorption	579 Intestinal malabsorption
H. pylori infection within the past 6 months	B96.81 Helicobacter pylori [H. pylori] as the cause of diseases classified elsewhere	041.86 Helicobacter pylori [H. pylori]

Cystic Fibrosis	E84 Cystic fibrosis E84.8 Cystic fibrosis with other manifestations	277.0x Cystic fibrosis
Diagnosed as having or has received treatment for esophageal, gastric, pyloric channel, or duodenal ulceration		
Proton pump inhibitors	**Operationalization: NDC code**	**Operationalization: HCPCS code**
Omeprazole (Prilosec)	70515062501	-
Esomeprazole (Nexium)	00186504054, 00186504005, 00186504031	-
Lansoprazole (Prevacid)	64764054130, 64764054105, 64764054111, 64764054119	-
Rabeprazole (AcipHex)	62856024330	-
Pantoprazole (Protonix) HCPCS Source	00008092351, 00008092355, 00008092360	S0164 Injection, pantoprazole sodium, 40 mg
H2-blockers		
Famotidine (Pepcid AC, Pepcid Oral) HCPCS Source	16837087210, 16837087220, 16837087222, 16837087230, 16837087231,	J3490 Unclassified drugs

	16837087260, 16837087275, 16837087290	
Cimetidine (Tagamet, Tagamet HB)	63029022201, 63029022202, 63029022203, 63029022204, 63029022205, 63029022270	-
Ranitidine (Zantac, Zantac 75, Zantac Efferdose, Zantac injection, and Zantac Syrup) HCPCS Source	52565-102, 67751015101(for 150, max strength), 00173036238	J2780 Injection, ranitidine hydrochloride, 25 mg
Nizatidine Capsules (Axid AR, Axid Capsules, Nizatidine Capsules)	65726-144-15, 65726-145-10	-

9.4.3.3. Duration and dose of IV Pantoprazole

Duration of IV pantoprazole in days will be ascertained as follows: Date of last infusion during the observation period – date of first infusion during the observation period plus 1 day (minus treatment gaps, defined as a date with no record of infusion between the date of last infusion and date of first infusion; up to 7 days treatment gap between infusions will be allowed). Total daily dose of IV pantoprazole will be reported in mg/kg/day.

9.5. Data sources

The Optum EHR with Integrated Claims dataset from the US contains electronic health records data with prescriptions, diagnoses, and provider information as well as practice management data and claims information for deterministically-matched patients. The population of the dataset is made up of commercial health plan members and Medicare Advantage members, across all 50 states. The database currently encompasses the claims and EHR data of more than 95 million patients with approximately 1.9 million patients aged less than 2 years from 01 January 2007 through 31 December 2020. This dataset contains a combination of structured data (e.g. diagnoses, procedures, prescriptions) and information from unstructured data (e.g. drug rationale, provider notes) from the electronic health record and corresponding claims information for those instances. The claims are verified,

adjudicated, and adjusted by the relevant insurer, and de-identified by Optum prior to providing access to the database. Patients are only included in the database if they had both medical and prescription drug coverage, as well as the EHR information. Information is processed, normalized, and standardized across the continuum of care from both acute inpatient stays and outpatient visits. Optum® data elements include demographics, medications prescribed and administered, immunizations, allergies, lab results (including microbiology), vital signs and other observable measurements, clinical and inpatient stay administrative data and coded diagnoses and procedures.[1]

9.6. Study size

There are no a priori hypotheses specified, and therefore, sample size calculations are not applicable. All eligible patients meeting inclusion/exclusion criteria will be included in the study. Based on preliminary feasibility, it is anticipated that 7,489 infants aged 1 month to <1 year and 6,657 patients aged 1 to <2 years who have been treated with IV pantoprazole will be eligible for inclusion in the study. Table 5 below shows the 95% confidence intervals around varying hypothetical frequencies of outcomes given a 7,489 and 6,657 patient sample, calculated using the Wilson score interval.

Table 5. Precision estimates for varying frequencies of outcomes for given 7,489 and 6,657 patient samples

Sample size	Outcome Frequency	N Events*	Lower 95% Bound	Upper 95% Bound
7489	0.002	15	0.0012	0.0033
	0.005	37	0.0036	0.0068
	0.01	75	0.0080	0.0125
	0.05	374	0.0452	0.0551
	0.1	749	0.0934	0.1070
	0.2	1498	0.1911	0.2092
6657	0.002	13	0.0011	0.0033
	0.005	33	0.0035	0.0070
	0.01	67	0.0079	0.0128
	0.05	333	0.0450	0.0555

	0.1	666	0.0931	0.1075
	0.2	1331	0.1905	0.2097

*Note: Event counts are rounded to nearest whole number

9.7. Data management

De-identified Optum EHR data will be analyzed using the Aetion Evidence Platform (AEP). Data to be used for the proposed analysis have already been linked and uploaded into the AEP. The AEP is a data-handling technology, which allows for the analysis of large patient datasets by indexing patient data into a form that can be queried by an internal patient variable language and has been previously used.[3,4,5] Data are minimally transformed at the point of connection to the AEP, thus the original format of the raw Optum EHR data is preserved. At the point of data connection to the platform some discard rules are applied. Patient events are excluded if patient identification (ID) is missing and if the "start of enrollment" date is preceded by the "end of enrollment" date in the original data. Additionally, patient events are excluded if there are no dates associated with them, or if the start date of the event is preceded by the end date of the event (e.g. discharge date precedes admission date for an inpatient event). Aetion IDs are assigned to Optum EHR patient IDs and a crosswalk file is kept as a protected file available upon request to authorized parties. The data are at the individual patient level and will be analyzed within the AEP.

9.8. Data analysis

All statistical analysis will be performed in the two cohorts of interest, ie, infants aged 1 month to < 1 year and patients aged 1 to <2 years, separately using the AEP version 4.2. Analysis combining the two cohorts of interest will not be performed.

Descriptive statistics will be presented for key variables of interest i.e., demographic characteristics, comorbidities and duration and dose of IV pantoprazole, listed in Section 9.4.3 to characterize the overall cohort treated with IV pantoprazole and in the 3 subgroups defined based on the presence or absence of GERD and EE and listed under Section 9.3.3. These will include counts and percentages for categorical data and statistics such as mean, median, standard deviation, and range for continuous variables.

For analyses of estimation of incidence rates of the outcomes of interest during follow-up, each analysis will be restricted to patients without a history of outcome of interest prior to the index date (ie baseline period); thus, for each analysis of a given specified outcome, a distinct sub-cohort will be used (i.e. for the estimation of the incidence of hepatitis, only patients with prevalent cases of hepatitis in the baseline period will be excluded from follow-up and will not contribute to person-time at risk).

For each outcome of interest, patients will be followed from the index date to whichever of the following occurs first (follow-up period):

- Occurrence of an outcome of interest,
- 90 days following the discontinuation of IV pantoprazole administration,
- Initiation of a separate IV pantoprazole infusion within 90 days following the discontinuation of IV pantoprazole administration, where a separate infusion is defined as the subsequent administration at least 7 days from the end of the previous infusion,
- Death,
- End of enrollment in the database,
- End of study period (ie, 31 December 2020).

Incidence rates of each prespecified outcome of interest will be estimated as the number of patients with a specific outcome of interest during the follow-up period divided by the total person-time at risk and reported as incidence per 1,000 person-years with associated 95% CIs, assuming a Poisson distribution. Exact Poisson confidence limits for the estimated rate are found as the Poisson means, for distributions with the observed number of events and probabilities relevant to the chosen confidence level, divided by time at risk.

$$Y_l = \frac{\chi^2_{2Y,\ \alpha/2}}{2}$$

$$Y_u = \frac{\chi^2_{2(Y+1),\ 1-\alpha/2}}{2}$$

- where Y is the observed number of events, Yl and Yu are lower and upper confidence limits for Y respectively, $\chi 2\nu,a$ is the chi-square quantile for upper tail probability on ν degrees of freedom.

For the analysis of the primary objective, incidence rates for all outcomes of interest will be estimated in the overall cohort and in the 2 subgroups, i.e., patients with GERD and EE and patients with GERD, but without EE. Within the overall cohort and in the 2 subgroups, incidence rates will be calculated by duration of IV pantoprazole treatment (<4 days, ≥ 4 days). For the analysis of the secondary objective 1, incidence rates will be estimated for the subgroup of patients treated with IV pantoprazole without a diagnosis of GERD or EE in each cohort and by duration of IV pantoprazole treatment (<4 days, ≥ 4 days) within each cohort. For the analysis of the secondary objective 2, counts of the 25 most common diagnostic codes occurring within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) through 90 days of discontinuation with IV pantoprazole in the subsets of patients with a diagnosis of GERD with or without EE will be generated. For each patient, reoccurring codes within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) and through 90 days of discontinuation with IV pantoprazole will be counted once.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained

by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8.1. Sensitivity Analyses

Two sensitivity analyses will be performed as outlined in Table 6.

Table 6. Sensitivity analyses

Sensitivity Analysis	Description	Rationale
Sensitivity to enforced 30-day enrollment period prior to the index date	Perform analysis in both cohorts without exclusion criteria of at least 30-day enrollment prior to the index date.	Given the age of the study population, patients may not be enrolled in the database for greater than 30 days prior to the index date and it will be important to include such patients in the analysis and examine the incidence rates of outcomes of interest.
Sensitivity to ICD-9-CM versus ICD-10-CM coding for subgroup classification.	Perform analysis in both cohorts, stratified by those patients identified via ICD-9-CM codes versus ICD-10-CM codes, respectively.	ICD-9-CM coding for subgroup identification is less specific than ICD-10-CM based on Lopushinsky et al. 2007[2]. Stratifying incidence rates and comparing incidence estimates between strata will allow to understand comparability between patient cohorts identified using different coding schemes and any potential heterogeneity in patients and incidence rates of outcomes of interest.

9.9. Quality control

Aetion will build measures for cohort inclusion, outcomes and covariates based on codes and algorithms described in this protocol, which were collaboratively agreed upon with Pfizer. All measures created, cohorts developed, statistical analyses implemented, and tables completed will undergo quality control review by at least one additional analyst or scientist under the supervision of the Science Lead. All analyses will separately be doubly implemented by an independent team. Results of single and double implementations will be compared, and any discrepancies will be adjudicated by a third-party senior science team

member not involved in either implementation. Furthermore, the Science Lead will review all results tables to confirm accuracy, logical flow, and appropriate format. This protocol will be strictly followed when conducting the analysis of this study.

The data were subject to quality control procedures. The data provider was contacted to help rectify any problems identified during the quality control procedures, including if the files received appeared to be incomplete or the data values were implausible. The data are loaded into the Aetion Evidence Platform after minimal processing into patient longitudinal timelines to enable representation of the original data and without any data loss. Events are required to have a valid start date. Record counts are cross-checked for validation and compared to the original data counts.

9.10. Strengths and limitations of the research methods

This study has several strengths. It is a population-based study, and while the use of IV pantoprazole in infants aged 1 month to <1 year and patients aged 1 to <2 years is rare, this database includes a relatively large number of IV pantoprazole users in these age groups, facilitating generation of precise incidence rates. Given the age of the study population, it is less likely that patients will seek health care outside of the Optum EHR system during the baseline period, and therefore, it is less likely that an outcome of interest occurring during the baseline period will be missed; thus prevalent conditions are unlikely to be mistaken for incident events. Similarly, given the relatively short follow up time, it is less likely that patients will seek care outside of the Optum EHR system during this period, and therefore, that incidence events will be missed.

The study also has several limitations. As is the case in any administrative claims-based study without outcome validation/adjudication, outcome misclassification is a possibility. Diagnosis codes may be incorrect, or may be included as part of the diagnostic rule-out process rather than an indication of diagnosis itself. Conditions not requiring treatment or office visits tend to be systematically undercoded in such databases. It is possible that this study will only capture severe manifestations of such disorders. However, this limitation is likely to be applicable to two outcomes of interest -vomiting and diarrhea as patients experiencing these symptoms may not always visit a physician for care. Another well-recognized limitation of claims database analysis is that the gap between disease onset and date of diagnosis. However, in an incidence analysis, the time at risk begins on the date of IV pantoprazole administration (ie index date), not at disease onset. For outcome events, as only the incidence of new events is considered that occur after the initiation of IV pantoprazole, the impact of this limitation is expected to be minimal, as complications arising in infants would almost certainly be captured in the inpatient setting. Additionally, this would result in underestimating the incidence rate as time at risk would be inflated.

More sensitive algorithms will be employed (i.e. algorithms based only on diagnostic codes, rather than more specific algorithms employing procedure and treatment codes in addition to diagnostic codes) for capturing outcomes to ensure safety events of interest are not missed.

However, the limitation of this approach is that , the incidence of some outcomes may be overestimated. Infants with a diagnosis of GERD with EE may be misclassified as those without EE. This is because a confirmed diagnosis of GERD with EE may not be available in infants due to reluctance of healthcare professionals to seek a confirmation via endoscopy. Also, those with a presumptive diagnosis of EE may be classified into the subset of infants with GERD alone. Prior to October 2015, ICD-9-CM codes were exclusively used to identify eligible patients, and GERD is not explicitly captured under this coding schema. ICD-10-CM codes provide additional granularity, but a validated code for erosive esophagitis and GERD is not available, nor well-established or validated in the literature. However, including patients identified using both coding schemes is important to increase sample size of this small population of pediatric patients with a rare condition and exposure. To examine the impact of different coding systems, a sensitivity analysis stratified by those patients identified via ICD-9-CM codes versus ICD-10-CM codes, respectively is planned. The counts of the top 25 most common conditions occurring within 30 days prior to or on the index date through 90 days of the last treatment with IV pantoprazole may include prevalent/comorbid conditions and not just conditions emerging following IV pantoprazole administration. This will however help generate hypotheses about unsuspected safety events in this patient population. Furthermore, a pre-planned sensitivity analysis stratifying by each code type will be performed for the analysis to understand if significant heterogeneity exists in this patient population with respect to the incidence of these outcomes following administration of IV pantoprazole. Finally, the study results may not be generalizable to infants aged 1 month to <1 year and patients aged 1 to <2 years outside of the commercially insured population.

9.11. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

As this study involves anonymized structured data IRB/IEC review is not required; no IRB waiver was received.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment[6], Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE)[7], and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.[8]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study results will be presented as a final study report describing the two cohorts of interest separately. The study may potentially lead to manuscripts that will be submitted to peer-reviewed scientific journals.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

None

1. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

2. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

3. ANNEX 3. ADDITIONAL INFORMATION

Not applicable

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