| | |
|---|---|
| | ***NON-INTERVENTIONAL STATISTICAL ANALYSIS PLAN FOR SECONDARY DATA COLLECTION STUDY*** |

***VERSION HISTORY***

| ***Version*** | ***Effective Date*** | ***Change Type*** *(New, Revise, Admin)* | ***Summary of Revisions*** |
|---|---|---|---|
| *1.0* | *01-24-2022* | | |
| | | | |

**Non-Interventional Study Protocol**
**B1791096**

# 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

## Statistical Analysis Plan
## (SAP)

**Version**: 1.0

**Author**:
Taylor, Benjamin
Vice president, Science
Aetion, Inc.

**Date**: *01-24-2022*

**TABLE OF CONTENTS**

## LIST OF TABLES



## LIST OF FIGURES

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

N/A

## 2. INTRODUCTION

*Protonix® (pantoprazole sodium) IV for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE) [PROTONIX® I.V. (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 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 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 study as another strategy to address this post marketing requirement.*

### 2.1. STUDY DESIGN

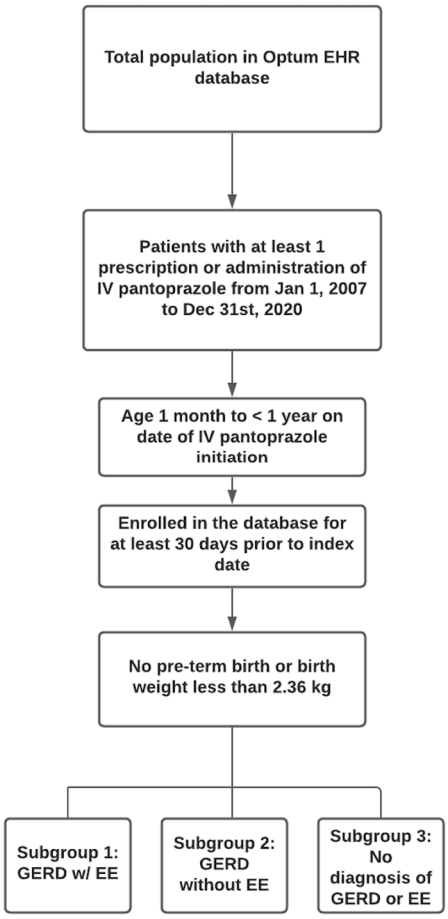
*This will be a retrospective cohort study without a comparator group. No a priori hypotheses are specified. Descriptive analyses, including an estimation of incidence rates, will be performed. This study will estimate the incidence of a number of outcomes of interest following the intravenous administration of pantoprazole sodium in infants for the treatment of GERD, with or without EE. Patients will enter the cohort on the date of first administration of pantoprazole sodium IV defined as the index date and will be followed for the occurrence of whichever of the following occurs first: any outcome of interest 90 days following the discontinuation of the first IV pantoprazole episode (a gap of <7 days between administrations will be considered one episode), initiation of a separate IV pantoprazole infusion within 90 days following the discontinuation of the first IV pantoprazole dispensing,*

*where a separate infusion is defined as the subsequent dispensing at least 7 days from the end of the previous infusion, death, end of enrollment in the database, end of study period (ie, December 31, 2020).*

### 2.1.1. Study population

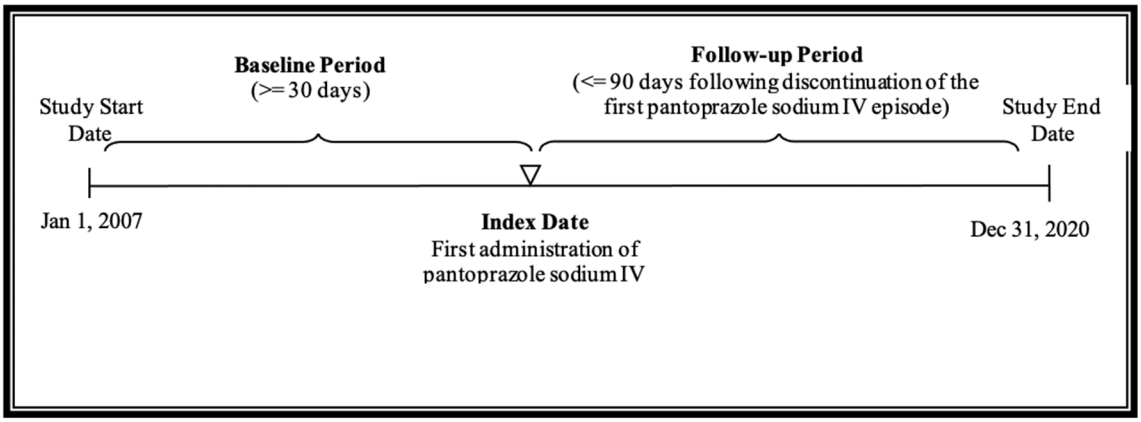
*Two separate cohorts of patients, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years will be identified. The study period will be defined from January 1, 2007 to December 31 2020.*

**Figure 1. Flow Diagram of Patient Selection for Cohort 1***




** Footnotes:*
*1. Cohort 2 will have the same patient selection process, but will be for patients aged 1 to <2 years.*
*2. During the analysis phase, patients with a specific outcome of interest prior to the index date will be excluded from the incidence rate calculation of that outcome. These patients will be included in the incidence rate calculation of all other outcomes.*

**Figure 2. Flow Diagram of Key Study Time Points**




### 2.1.2. Data source

*The study will be conducted using Optum's longitudinal integrated EHR from the US.*[1] *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 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 January 1, 2007 through Dec 31, 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.*

### 2.1.3. Treatment/cohort labels

Cohort 1: Infants aged 1 month to <1 year, who were treated with IV pantoprazole

Cohort 2: Patients aged 1 to <2 years, who were treated with IV pantoprazole

## 2.2. STUDY OBJECTIVES

*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*
- *Hypertrigliceridema*
- *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*
- *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 the start of IV pantoprazole (ie, index date) through 90 days of 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).*

## 3. HYPOTHESES AND DECISION RULES

### 3.1. STATISTICAL HYPOTHESES

N/A

### 3.2. STATISTICAL DECISION RULES

N/A

## 4. ANALYSIS SETS/POPULATIONS

*Two separate cohorts of patients, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years will be identified. Patients will enter the study on their index date, given that they meet all inclusion criteria and exclusion criterion described in Section 4.1.*

*Exposure to IV pantoprazole will be identified from inpatient procedure and drug codes including any of the following National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes shown in Table 1. Only the first treatment episode during the study period will be of interest. Any subsequent infusion occurring within 7 days after the end of the previous infusion will be considered one treatment episode.*

**Table 1. NDC and HCPCS Codes Indicating IV Dispensing 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* |

**Table 1. NDC and HCPCS Codes Indicating IV Dispensing of pantoprazole**

| ***Code*** | ***Description*** |
|---|---|
| *0008-4001-01* | *40mg/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* |

## 4.1. FULL ANALYSIS SET (FAS)

*Two separate cohorts of patients, ie, infants aged 1 month to <1 year and patients aged 1 to <2 years will be identified. Patients will enter the study on their index date, given that they meet all inclusion criteria and exclusion criterion below:*

***Inclusion Criteria***

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 prescription or 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 the minimum of 30-days of baseline enrollment, patients will be further excluded based on the occurrence of a history of outcomes of interest identified in Section 5.2 occurring prior to the index date.*

#### 4.1.1. Exclusion criteria

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 3rd 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.*

### 4.2. SAFETY ANALYSIS SET

The safety analysis set is the same as the full analysis set.

### 4.3. OTHER ANALYSIS SET

No additional analysis sets.

### 4.4. SUBGROUPS

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

*(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 2 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 2.*

*(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 2.*

*(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 2 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 2:*

**Table 2. 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.*

## 5. ENDPOINTS AND COVARIATES

The baseline period is defined as a period of minimum 30 days prior to index date (patients may have a baseline period greater than 30 days depending upon data availability prior to the index date). All comorbidities and exclusion criteria will be determined during this time period.

### 5.1. EFFICACY/EFFECTIVENESS ENDPOINT(S)

There will be no efficacy/effectiveness endpoints measured.

### 5.2. SAFETY ENDPOINTS

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 an inpatient or outpatient setting during the follow-up period.

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| *Agranulocytosis* | *D70.2 Other drug-induced agranulocytosis*<br><br>*D70.1 Agranulocytosis secondary to cancer chemotherapy* | *288.03 Drug induced neutropenia* |
| *Thrombocytopenia* | *D69.3 Immune thrombocytopenic purpura*<br>*D69.59 Other secondary thrombocytopenia*<br>*D69.6 Thrombocytopenia, unspecified*<br>*D69.41 Evans syndrome*<br>*D69.49 Other primary thrombocytopenia* | *287.31 Immune thrombocytopenic purpura*<br>*287.49 Other secondary thrombocytopenia*<br>*287.5 Thrombocytopenia, unspecified*<br>*287.32 Evans' syndrome*<br>*287.39 Other primary thrombocytopenia* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| | | |
| *Leukopenia* | *D72.810 Lymphocytopenia*<br>*D72.818 Other decreased white blood cell count*<br>*D72.819 Decreased white blood cell count, unspecified*<br>*D70.8 Other neutropenia*<br>*D70.9 Neutropenia, unspecified* | *288.51 Lymphocytopenia*<br>*288.59 Other decreased white blood cell count*<br>*288.50 Leukocytopenia, unspecified*<br>*288.09 Other neutropenia*<br>*288.00 Neutropenia, unspecified* |
| *Pancytopenia* | *D61.811 Other drug-induced pancytopenia*<br>*D61.818 Other pancytopenia* | *284.12 Other drug-induced pancytopenia*<br>*284.19 Other pancytopenia* |
| *Hypersensitivity (including anaphylactic reactions and anaphylactic shock)* | *K52.2x Allergic and dietetic gastroenteritis and colitis*<br>*M31.0 Hypersensitivity angiitis*<br>*T78.2x Anaphylactic shock, unspecified*<br>*T78.4x Other and unspecified allergy*<br>*M36.4 Arthropathy in hypersensitivity reactions classified elsewhere* | *558.3 Allergic gastroenteritis and colitis*<br>*446.20 Hypersensitivity angiitis, unspecified*<br>*446.21 Goodpasture's syndrome*<br>*446.29 Other specified hypersensitivity angiitis*<br>*995.0 Other anaphylactic reaction, NEC*<br>*995.3 Allergy, unspecified, NEC*<br>*713.6 Arthropathy associated with hypersensitivity reaction* |
| *Hyperlipidemia* | *E78.49 Other hyperlipidemia*<br>*E78.5 Hyperlipidemia, unspecified* | *272.4 Other and unspecified hyperlipidemia* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| *Hypertriglyceridema* | *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*<br>*R11.11 …… without nausea*<br>*R11.12 Projectile vomiting*<br>*R11.13 Vomiting of fecal matter*<br>*R11.2 Nausea with vomiting, unspecified* | *536.2 Persistent vomiting*<br>*0 78.82 Epidemic vomiting syndrome*<br>*787.03 Vomiting alone*<br>*569.87 Vomiting of fecal matter*<br>*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*<br>*K72x Hepatic failure, not elsewhere classified*<br>*K72.00 Acute and subacute hepatic failure without coma*<br>*K72.01 Acute and subacute hepatic failure with coma*<br>*K72.10 Chronic hepatic failure without coma*<br>*K72.11 Chronic hepatic failure with coma* | *572.2 Hepatic encephalopathy.*<br>*572.8 Other sequelae of chronic liver disease*<br>*571.41 Chronic persistent hepatitis*<br>*571.49 Other chronic hepatitis*<br>*571.4 Chronic hepatitis*<br>*571.5 Cirrhosis of liver without mention of alcohol*<br>*571.6 Biliary cirrhosis*<br>*573.3 Hepatitis, unspecified*<br>*571.42 Autoimmune hepatitis* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| | *K72.90 Hepatic failure, unspecified without coma*<br>*K72.91 Hepatic failure, unspecified with coma*<br>*K73x Chronic hepatitis*<br>*K73.0 Chronic persistent hepatitis, not elsewhere classified*<br>*K73.1 Chronic lobular hepatitis, not elsewhere classified*<br>*K73.2 Chronic active hepatitis, not elsewhere classified*<br>*K73.8 Other chronic hepatitis, not elsewhere classified*<br>*K73.9 Chronic hepatitis, unspecified*<br>*K74 Fibrosis and cirrhosis of the liver*<br>*K74.00 Hepatic fibrosis, unspecified*<br>*K74.01 Hepatic fibrosis, early fibrosis*<br>*K74.02 Hepatic fibrosis, advanced fibrosis*<br>*K74.1 Hepatic sclerosis*<br>*K74.3 Primary biliary cirrhosis*<br>*K74.4 Secondary biliary cirrhosis*<br>*K74.5 Biliary cirrhosis, unspecified*<br>*K74.60 Unspecified cirrhosis of liver*<br>*K74.69 Other cirrhosis of liver*<br>*K75x Other inflammatory liver diseases* | *571.8 Other chronic nonalcoholic liver disease*<br>*573 Other disorders of the liver*<br>*573.0 Chronic passive congestion of liver*<br>*573.8 Other specified disorders of liver*<br>*570 Acute and subacute necrosis of liver*<br>*573.4 Hepatic infarction*<br>*572.3 Portal hypertension*<br>*572.4 Hepatorenal syndrome*<br>*573.5 Hepatopulmonary syndrome*<br>*571.8 Other chronic nonalcoholic liver disease*<br>*571.9 Unspecified chronic liver disease without mention of alcohol*<br>*573.9 Unspecified disorder of liver*<br>*782.4 Jaundice, unspecified, not of newborn* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| | *K75.2 Nonspecific reactive hepatitis*<br>*K75.3 Granulomatous hepatitis, not elsewhere classified*<br>*K75.4 Autoimmune hepatitis*<br>*K75.81 Nonalcoholic steatohepatitis (NASH)*<br>*K75.89 Other specified inflammatory liver diseases*<br>*K75.9 Inflammatory liver disease, unspecified*<br>*K76x Other diseases of the liver*<br>*K76.0 Fatty (change of) liver, not elsewhere classified*<br>*K76.1 Chronic passive congestion of liver*<br>*K76.2 Central hemorrhagic necrosis of liver*<br>*K76.3 Infarction of liver*<br>*K76.4 Peliosis hepatis*<br>*K76.5 Hepatic veno-occlusive disease*<br>*K76.6 Portal hypertension*<br>*K76.7 Hepatorenal syndrome*<br>*K76.81 Hepatopulmonary syndrome*<br>*K76.89 Other specified diseases of liver*<br>*K76.9 Liver disease, unspecified*<br>*K77 Liver disorders in diseases classified elsewhere*<br>*K71.6 Toxic liver disease with hepatitis, not elsewhere classified* | |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| | *K71.2 Toxic liver disease with acute hepatitis*<br>*K71.3 Toxic liver disease with chronic persistent hepatitis*<br>*K71.4 Toxic liver disease with chronic lobular hepatitis*<br>*K71.50 Toxic liver disease with chronic active hepatitis without ascites*<br>*K71.51 Toxic liver disease with chronic active hepatitis with ascites*<br>*R17 Unspecified jaundice* | |
| *Urticaria* | *L50.0 Allergic urticaria*<br>*L50.1 Idiopathic urticaria*<br>*L50.8 Other urticaria*<br>*L50.9 Urticaria, unspecified* | *708.0 Allergic urticaria*<br>*708.1 Idiopathic urticaria*<br>*708.8 Other specified urticaria*<br>*708.9 Urticaria, unspecified* |
| *Angioedema* | *T78.3XXA Angioneurotic edema initial encounter*<br>*T78.3XXD Angioneurotic edema subsequent encounter*<br>*T78.3XXS Angioneurotic edema sequela* | *995.1 Angioneurotic edema, not elsewhere classified* |
| *Stevens- Johnson syndrome* | *L51.1 Stevens-Johnson syndrome*<br>*L51.3 Stevens-Johnson syndrome -toxic epidermal necrolysis overlap syndrome* | *695.13 Stevens-Johnson syndrome*<br>*695.14 Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome* |
| *Lyell syndrome* | *L51.2 Toxic epidermal necrolysis [Lyell]* | *695.15 Toxic epidermal necrolysis* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| *Erythema multiforme* | *L51.0 Nonbullous erythema multiforme*<br>*L51.8 Other erythema multiforme*<br>*L51.9 Erythema multiforme, unspecified* | *695.10 Erythema multiforme, unspecified*<br>*695.11 Erythema multiforme minor*<br>*695.12 Erythema multiforme major*<br>*695.19 Other erythema multiforme* |
| *Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)* | *D72.12 Drug rash with eosinophilia and systemic symptoms syndrome* | |
| *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*<br>*N14.2 Nephropathy induced by unspecified drug, medicament or biological substance*<br>*N14.4 Toxic nephropathy, not elsewhere classified*<br>*N15.8 Other specified renal tubulo-interstitial diseases*<br>*N15.9 Renal tubulo-interstitial disease, unspecified* | *583x Nephritis and nephropathy not specified as acute or chronic* |
| *Photosensitivity* | *L56.0 Drug phototoxic response*<br>*L56.1 Drug photoallergic response*<br>*L56.2 Photocontact dermatitis [berloque dermatitis]*<br>*L56.4 Polymorphous light eruption*<br>*L56.8 Other specified acute skin changes due to ultraviolet radiation* | *692.72 Acute dermatitis due to solar radiation*<br>*692.79 Other dermatitis due to solar radiation* |

**Table 3. Outcomes of Interest**

| ***Outcome of interest*** | ***Operationalization: ICD-10-CM code*** | ***Operationalization: ICD-9-CM code*** |
|---|---|---|
| | | |
| *Peripheral edema* | *R60.0 Localized edema*<br>*R60.9 Edema, unspecified* | *782.3 Edema* |
| *Injection site thrombophlebitis* | *I80.8 Phlebitis and thrombophlebitis of other sites*<br>*I80.9 Phlebitis and thrombophlebitis of unspecified site*<br>*T80.1 Vascular complications following infusion, transfusion and therapeutic injection*<br>*T80.81 Extravasation of vesicant agent*<br>*T80.90 Unspecified complication following infusion and therapeutic injection* | *451.89 Phlebitis and thrombophlebitis of other sites*<br>*451.9 Phlebitis and thrombophlebitis of unspecified site*<br>*999.2 Other vascular complications of medical care, NEC*<br>*909.3 Late effect of complications of surgical and medical care*<br>*999.82 Extravasation of another vesicant agent*<br>*V58.89 Other specified aftercare*<br>*999.88 Other infusion reaction* |

## 5.3. OTHER ENDPOINTS

The frequency of the 25 most common diagnostic codes (ICD-9-CM/ICD-10-CM) occurring within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) through within 90 days of 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).

## 5.4. KEY VARIABLES OF INTEREST

### 5.4.1. 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 reported as last recorded value on index date.

### 5.4.2. Comorbidities

The following comorbidities will be identified based on the presence of at least one International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)/International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code or NDC/HCPCS codes identified using all available data during the baseline period and are operationalized in the table below.

**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*<br>*K22.5 Diverticulum of esophagus, acquired*<br>*K31.5 Obstruction of duodenum*<br>*Q39.3 Congenital stenosis and stricture of esophagus*<br>*Q39.4 Esophageal web* | *530.3 Stricture and stenosis of esophagus*<br>*537.3 Other obstruction of duodenum*<br>*530.6 Diverticulum of esophagus, acquired*<br>*562 Diverticula of intestine*<br>*750.3 Congenital tracheoesophageal fistula, esophageal atresia and stenosis* |
| *Gastrointestinal strictures of any kind* | *K56.69x Other intestinal obstruction*<br>*K50 Crohn's Disease* | *555 Regional enteritis*<br>*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*<br>*Z85.01 Personal history of malignant neoplasm of esophagus*<br>*K31.84 Gastroparesis*<br>*K91.1 Postgastric surgery syndromes* | *150 Malignant neoplasm of esophagus*<br>*530 Diseases of esophagus*<br>*787.1 Heartburn*<br>*V10.03 Personal history of malignant neoplasm of esophagus*<br>*536.3 Gastroparesis* |

**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*** |
|---|---|---|
| | *K20 Esophagitis*<br>*K21 Gastro-esophageal reflux disease*<br>*K22 Other diseases of esophagus*<br><br>*R12 Heartburn*<br><br>*K30 Functional dyspepsia*<br><br>*K23 Disorders of esophagus in diseases classified elsewhere*<br><br>*Q39 Congenital malformations of esophagus* | *564.2 Postgastric surgery syndromes*<br>*750.3 Congenital tracheoesophageal fistula, esophageal atresia and stenosis*<br>*750.4 Other specified congenital anomalies of esophagus*<br>*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*<br><br>*K26 Duodenal ulcer*<br><br>*K27.x Peptic ulcer, site unspecified*<br><br>*K28 Gastrojejunal ulcer* | *531 Gastric ulcer*<br><br>*532 Duodenal ulcer*<br><br>*533 Peptic ulcer site unspecified*<br><br>*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* |

**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*** |
|---|---|---|
| *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*<br><br>*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* | *NA** |
| *Esomeprazole (Nexium)* | *00186504054, 00186504005, 00186504031* | *NA* |
| *Lansoprazole (Prevacid)* | *64764054130, 64764054105, 64764054111, 64764054119* | *NA* |
| *Rabeprazole (AcipHex)* | *62856024330* | *NA* |

**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*** |
|---|---|---|
| *Pantoprazole (Protonix)*<br><br>*HCPCS Source* | *00008092351, 00008092355, 00008092360* | *S0164 Injection, pantoprazole sodium, 40 mg* |
| ***H2-blockers*** | | |
| *Famotidine (Pepcid AC, Pepcid Oral)*<br><br>*HCPCS Source* | *16837087210, 16837087220, 16837087222, 16837087230, 16837087231, 16837087260, 16837087275, 16837087290* | *J3490 Unclassified drugs* |
| *Cimetidine (Tagamet, Tagamet HB)* | *63029022201, 63029022202, 63029022203, 63029022204, 63029022205, 63029022270* | *NA* |
| *Ranitidine (Zantac, Zantac 75, Zantac Efferdose, Zantac injection, and Zantac Syrup)*<br><br>*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* | *NA* |

**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*** |
|---|---|---|

*NA = not available

### 5.4.3. 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.

## 6. HANDLING OF MISSING VALUES

*Patient events are excluded if patient identification (ID) attributed by Aetion 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).*

No imputation for missing values will be performed.

## 7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 7.1. STATISTICAL METHODS

*All statistical analyses 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 Aetion's platform[3], AEP version 4.2. Analyses 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 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 as shown in table shells 1a-1d. Mean, median, minimum and maximum values, interquartile range (IQR), and standard deviation will be*

*provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data.*

*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 the first IV pantoprazole infusion (a gap of <7 days between administrations will be considered one episode)*
- *Initiation of a separate IV pantoprazole infusion within 90 days following 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, December 31, 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, χ2v,a is the chi-square quantile for upper tail probability on v 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 subgroups 1 and 2. These results will be displayed as shown in table shells 2a-2c. Within the overall cohort and in the subgroups, incidence rates will be calculated by duration of IV pantoprazole treatment (<4 days, ≥ 4 days) as shown in table shells 3a-3c. For the analysis of the secondary objective 1, incidence rates will be*

*estimated for the overall population in each cohort (table shell 2d) and by duration of IV pantoprazole treatment (<4 days, ≥ 4 days) within each cohort (table shell 3d). 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) and within 90 days of last treatment with IV pantoprazole in the subsets of patients with a diagnosis of GERD regardless of EE status (ie, subgroups 1 and 2 combined) will be generated. These results will be displayed in table shell 4a for cohort 1 and 4b for cohort 2). For each patient, reoccurring codes within 30 days prior to starting or on the date of start of IV pantoprazole (ie, index date) and within 90 days of last treatment with IV pantoprazole will be counted once.*

## 7.2. STATISTICAL ANALYSES

*See Section 7.2.3*

### 7.2.1. Safety Analyses

*N/A*

### 7.2.2. Sensitivity Analyses

The following sensitivity analyses will be conducted. The results from the first sensitivity analysis will be displayed in table shell 5a and results from the second sensitivity analysis will be displayed as shown in table shell 5b.

**Table 5. 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 | Perform analysis in both cohorts, stratified by those patients identified via | ICD-9-CM coding for subgroup identification is less specific than ICD-10-CM based on |

**Table 5. Sensitivity Analyses**

| Sensitivity Analysis | Description | Rationale |
|---|---|---|
| for subgroup classification. | ICD-9-CM codes versus ICD-10-CM codes, respectively. | Lopushinsky et al. 2007[2]. Stratifying incidence rates and comparing incidence estimates between strata will allow us to understand comparability between patient cohorts identified using different coding schemes and any potential heterogeneity in patients and incidence rates of outcomes of interest. |

### 7.2.3. Summary of Analyses

**Table 6. Summary of Analyses**

| Outcome | Analysis Set | Supports Protocol Objective Number | Subgroup | Statistical method | Table Shell Number | Covariates/ Strata | Missing Data |
|---|---|---|---|---|---|---|---|
| Each of 27 outcomes of interest described in Section 5.2 | FAS | Primary Objective 1 | Subgroups 1 and 2 | Descriptive Statistics; Incidence Rate per 1,000 Person-Years | Table 1a-1c; Tables 2a-2c, 3a-3c | N/A | Excluded |
| Each of 27 outcomes of interest described in Section 5.2 | FAS | Secondary Objective 1 | Subgroup 3 | Descriptive Statistics; Incidence Rate per 1,000 | Table 1d; Tables 2d, 3d | N/A | Excluded |

**Table 6. Summary of Analyses**

| Outcome | Analysis Set | Supports Protocol Objective Number | Subgroup | Statistical method | Table Shell Number | Covariates/ Strata | Missing Data |
|---|---|---|---|---|---|---|---|
| | | | | Person-Years | | | |
| Most Common ICD codes | FAS | Secondary Objective 2 | Subgroups 1 and 2 | Descriptive Statistics | Tables 4a-4b | N/A | Excluded |
| Each of 27 outcomes of interest described in Section 5.2 | FAS | Sensitivity Analysis 1 | None | Incidence Rate per 1,000 Person-Years | Table 5a | N/A | Excluded |
| Each of 27 outcomes of interest described in Section 5.2 | FAS | Sensitivity Analysis 2 | None | Incidence Rate per 1,000 Person-Years | Table 5b | N/A | Excluded |

## 8. LIST OF TABLES AND TABLE SHELLS

**Table 7. List of Table Shells**

| | |
|---|---|
| Table 1a | Baseline Characteristics of Main Study Cohorts |
| Table 1b | Baseline Characteristics of Subgroup 1: GERD with EE |
| Table 1c | Baseline Characteristics of Subgroup 2: GERD without EE |
| Table 1d | Baseline Characteristics of Subgroup 3: No Dx of GERD/EE |
| Table 2a | Incidence of Outcomes of Interest During the Follow-Up Period Among Main Study Cohorts |
| Table 2b | Incidence of Outcomes of Interest During the Follow-Up Period Among Subgroup 1: GERD with EE |
| Table 2c | Incidence of Outcomes of Interest During the Follow-Up Period Among Subgroup 2: GERD without EE |
| Table 2d | Incidence of Outcomes of Interest During the Follow-Up Period Among Subgroup 3: No Dx of GERD/EE |
| Table 3a | Incidence of Outcomes of Interest During the Follow-Up Period Among the Study Cohorts Stratified By Duration of pantoprazole Treatment |
| Table 3b | Incidence of Outcomes of Interest During the Follow-Up period Among Subgroup 1: GERD with EE Stratified By Duration of pantoprazole Treatment |
| Table 3c | Incidence of Outcomes of Interest During the Follow-Up Period Among Subgroup 2: |

**Table 7. List of Table Shells**

| | |
|---|---|
| | GERD without EE Stratified By Duration of pantoprazole Treatment |
| Table 3d | Incidence of Outcomes of Interest During the Follow-Up Period Among Subgroup 3: No Dx of GERD/EE Stratified By Duration of pantoprazole Treatment |
| Table 4a | Top 25 Diagnostic Codes Among Cohort 1: Infants Aged 1 Month - <1 Year |
| Table 4b | Top 25 Diagnostic Codes Among Cohort 2: Infants Aged 1 Year - <2 Years |
| Table 5a (Sensitivity Analysis 1) | Incidence of Outcomes of Interest During the Follow-Up Period Among Main Study Cohorts, Sensitivity Analysis 1: No Requirement for Minimum 30 Day Baseline Period |
| Table 5b (Sensitivity Analysis 2) | Incidence of Outcomes of Interest During Follow-Up Period Among Main Study Cohorts, Sensitivity Analysis 2: ICD9 vs ICD10 Coding |

## 9. REFERENCES

1. Optum® de-identified Electronic Health Record dataset (2007-2019)

2. Lopushinsky, S.R., Covarrubia, K.A., Rabeneck, L. et al. Accuracy of administrative health data for the diagnosis of upper gastrointestinal diseases. Surg Endosc 21, 1733–1737 (2007).

3. Aetion Evidence Platform. Aetion. Accessed January 12, 2022. https://aetion.com/platform/

# 10. APPENDICES

## 10.1. APPENDIX 1: DATA DERIVATION DETAILS

*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.*

### 10.1.1. Definition and use of visit windows in reporting

*N/A*

### 10.1.2. Further definition of endpoints

## 10.2. APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

*N/A*

### 10.2.1. Further Details of the Statistical Methods

## 10.3. APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

*N/A*