Summary Table of Study Protocol	
Title	Temporal trends in pegloticase infusion reactions across the pre, intra, and post-COVID-19 vaccine eras in U.S. commercial insurance claims
Protocol version identifier	Version 1.0
Date of last version of the protocol	February 25, 2026
EU Post Authorization Study (PAS) Register No	NA
Active Substance	Pegloticase
Medicinal Product	Krystexxa
Device	NA
Product Reference	NA
Procedure Number	NA
Marketing authorization holder(s)	Amgen Inc.
Joint PASS	No

Research Question and Objectives	***Primary objective***: To quantify annual/era incidence rates of severe pegloticase infusion reactions across the pre-, intra-, and post-COVID-19 mass vaccination periods in patients with pegloticase with an immunomodulator co-therapy (primary) and those with pegloticase monotherapy (sensitivity analysis). ***Secondary objectives***: 1. *Negative control (contextualization)*: Using the same outcome definition and time-period framework, estimate annual/era-specific incidence rates of severe infusion reactions among rituximab initiators to evaluate whether there are broad secular changes in coding, detection, or infusion-care patterns unrelated to PEG exposure. 2. *PEG-containing infused comparators (contextualization)*: Using analogous design and outcome definitions, estimate annual/era-specific incidence rates of severe infusion reactions among initiators of pegaspargase and pegylated liposomal doxorubicin (PLD) to provide context on whether temporal patterns observed for pegloticase are consistent with other PEG-containing infused products. Comparator objectives are intended to support within-drug temporal trend interpretation (i.e., pre/intra/post changes within each drug) and are not intended for head-to-head drug–drug comparisons of incidence between pegloticase and comparator therapies.
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Marketing Authorization Holder (MAH)

MAH(s)	Amgen Inc.
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0	February 25, 2026	February 25, 2026

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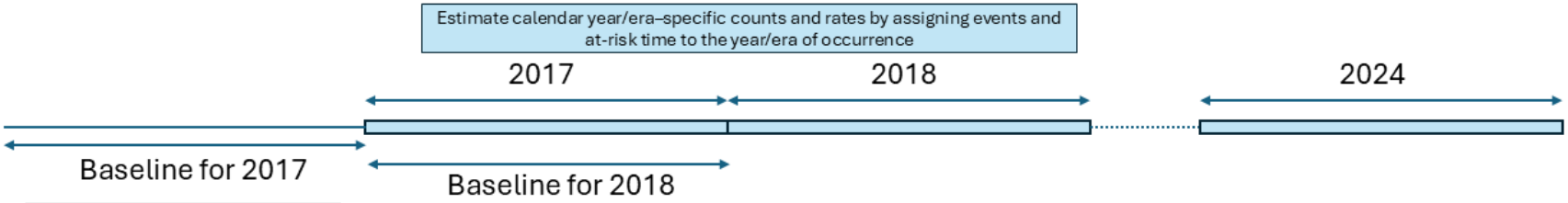
Signature	
Name of Investigator:	Date (DD Month YYYY):
Title: Name of Hospital/Site: Address/City/State/Country: Phone Number:	

Study Design Schema

Study design:

- A temporal trend analysis utilizing new-user cohorts and person-time denominators to assess incidence rates of severe infusion reactions.
- Rituximab: negative comparator (stable background rates); pegaspargase and pegylated liposomal doxorubicin: two *PEG-containing infused comparators for contextualization*.



- Identify new users of a product for 2017;
- Assess patient characteristics;

For each calendar year:

- ***Study cohort***: new users of each product (12-month wash-out);
- ***Follow-up start***: 1st pegloticase infusion in each calendar year (***index date***);
- ***Follow-up end***: earliest event of an outcome, death, disenrollment, pegloticase discontinuation;
- ***Study outcomes***: annual incidence rates of anaphylaxis/anaphylactoid reactions, cardiovascular events, heart failure, mortality

To assess IMM co-therapy status:

Index date (in each calendar year)

90 Days before index | 90 Days after index

Statistical analyses:

- ***Descriptive statistics*** for baseline characteristics;
- ***Generalized linear models*** with a Poisson distribution to calculate age- and sex-adjusted incidence rates (95% CIs) and to evaluate trends;
- ***Analyses will be conducted in patients with pegloticase+IMM (primary analysis) and those with pegloticase monotherapy (sensitivity analysis), separately.***

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2. List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	Anti-drug antibody
AMI	Acute myocardial infarction
ALL	Acute lymphoblastic leukemia
CARPA	Complement activation–related pseudoallergy
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRG	Chronic refractory gout
CVE	Cardiovascular event
ED	Emergency department
eGFR	Estimated glomerular filtration rate
FDA	U.S. Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IMM	Immunomodulator
IQR	Interquartile range
MTX	Methotrexate
NDC	National Drug Code
PAS	Post-Authorization Study
PEG	Polyethylene glycol
PLD	Pegylated liposomal doxorubicin
PY	Person-years
RCT	Randomized controlled trial
SD	Standard deviation
sUA	Serum uric acid
ULT	Urate-lowering therapy
US	United States

3. Responsible Parties

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4. Abstract

- Study Title: Temporal trends in pegloticase infusion reactions across the pre-, intra-, and post-COVID-19 vaccine eras in U.S. commercial insurance claims
- Study Background and Rationale

Gout affects nearly 12 million Americans, with about 2% developing chronic refractory gout unresponsive to conventional urate-lowering therapies. Pegloticase, a pegylated recombinant uricase, markedly lowers serum uric acid but its use may be associated with the occurrence of infusion reactions, such as severe hypersensitivity and anaphylaxis. Such events occur in 25–45% of patients receiving monotherapy but in only 0.1–6% when co-administered with immunomodulators such as methotrexate. Severe reactions are strongly linked to high anti-drug antibody titers directed against the polyethylene glycol (PEG) component of pegloticase.

mRNA COVID-19 vaccines contain PEG-lipid nanoparticles and have been reported to induce or amplify anti-PEG antibodies in some individuals. These antibodies may ***theoretically*** interact with PEGylated biologics like pegloticase, forming immune complexes that trigger complement activation and severe infusion reactions. Although some case reports suggest anti-PEG antibody development after COVID-19 vaccination, findings are not consistent. Only some descriptions in a medical forum (non-peer-reviewed) showed that some patients who received a mRNA COVID-19 vaccine and either an allergy immunotherapy or an omalizumab the next day developed reactions. There is no other direct clinical evidence (e.g., case reports/series) demonstrating that COVID-19 vaccination increases the risk of severe infusion reactions to biologic therapies.

This study evaluates whether the widespread implementation of COVID-19 vaccination coincided with any meaningful change in the real-world incidence of severe pegloticase-associated infusion reactions, with the a priori hypothesis that rates may remain stable across periods. Using commercial insurance claims data, we will evaluate temporal changes in the rates of severe infusion reactions among new users of pegloticase with an immunomodulator co-therapy. To contextualize observed trends, we will conduct independent comparator analyses using rituximab as a negative control and pegaspargase and pegylated liposomal doxorubicin (PLD) as PEG-containing contextual comparators. Both pegaspargase and PLD are PEGylated biologics administered by intravenous infusion. Because the number of adult patients treated with pegaspargase

may be limited (see Section 9.7.1.1), PLD will be included as an additional PEGylated contextual comparator to improve interpretability and robustness of this analysis. Results will provide an initial understanding of whether immune alterations during the COVID-19 era have influenced the risk of severe infusion reactions with pegloticase, supporting evidence-based management of patients with uncontrolled gout.

- Study Feasibility and Futility Considerations

This retrospective study will leverage a new in-house data resource at CfOR - Optum Market Clarity closed claims data source for which Amgen's data license will begin on January 1, 2026. Optum Market Clarity is a large, de-identified administrative claims dataset that has been commonly used in pharmacoepidemiologic research (Hankosky, Chinthammit et al. 2025, Li 2025). Definitions for comorbidities, medication use and health service utilization measures have been previously developed using a similar Optum data source (Optum Clinformatics data), included in Amgen studies 20240358 and 20240356. Methods for identifying new users of pegloticase have likewise been established in prior Amgen work (# 20240356), providing a strong methodological foundation for the current project.

The table below summarizes the number of newly identified pegloticase users from Optum Clinformatics data and the proportion receiving concomitant immunomodulators from 2017 to 2024. With the forthcoming addition of Optum Market Clarity closed claims to CfOR assets, the available sample size for pegloticase users is expected to increase significantly compared with the current Optum Clinformatics dataset. Market Clarity includes both open and closed claims; we will focus on the closed claims to maximize completeness of enrollment and healthcare utilization capture, thereby improving ascertainment of longitudinal medication use and outcome occurrence. Preliminary data review indicates that 3,434 pegloticase users were identified in Market Clarity closed claims as of March 31, 2025, demonstrating strong feasibility for achieving sufficient sample size to characterize infusion reactions across the pre-, intra- and post-COVID vaccine periods.

Table 1. Numbers of pegloticase new users in the Optum health claims data, by calendar year and immunomodulator co-therapy status.

Calendar year	# of pegloticase new users	# of new users of pegloticase PLUS an immunomodulator	% of new users with an immunomodulator
...2017	23	4	17.4

...2018	80	12	15.0
...2019	119	39	32.8
...2020	89	27	30.3
...2021	117	77	65.8
...2022	135	92	68.1
...2023	133	105	78.9
...2024	121	96	79.3
Total	817	452	55.3

- Research Question and Objective

Objectives	**Endpoints**
Primary	
To quantify annual incidence rates of severe pegloticase infusion reactions across the pre-, intra-, and post-COVID-19 mass vaccination periods in patients with pegloticase with an immunomodulator co-therapy (primary) and those with pegloticase monotherapy (sensitivity analysis).	• Anaphylaxis or anaphylactoid reactions • Acute cardiovascular events (CVE) including acute myocardial infarction (AMI) or stroke • Hospitalization for heart failure (HF) • All-cause mortality Each endpoint will be examined in a separate analysis.
Secondary	
Negative control (contextualization): Using the same outcome definition and time-period framework, estimate annual/era-specific incidence rates of severe infusion reactions among rituximab initiators to evaluate whether there are broad secular changes in coding, detection, or infusion-care patterns unrelated to PEG exposure.	• Same as above
PEG-containing infused comparators (contextualization): Using analogous design and outcome definitions, estimate annual/era-specific incidence rates of severe infusion reactions among initiators of pegaspargase and pegylated liposomal doxorubicin (PLD) to provide context on whether temporal patterns observed for pegloticase are consistent with other PEG-containing infused products.	• Same as above

- Hypothesis(es)/Estimation

*Pegloticase***:** We hypothesize that after accounting for secular changes in care, the incidence of severe pegloticase infusion reactions will remain stable across pre-, intra-, and post–COVID-19 vaccination periods.

Rituximab (negative control): Severe infusion reaction rates will remain stable across calendar periods. This analysis is expected to help identify potential secular artifacts in detection/coding.

*Pegaspargase and PLD (PEG-containing contextual comparators)***:** We hypothesize no clinically meaningful increase in severe infusion reaction rates across periods. These analyses will be used to contextualize whether any pegloticase-related pattern aligns with broader patterns among PEG-containing infused products.

- Study Design/Type

This study is a retrospective temporal trend analysis utilizing annual new-user cohorts and corresponding person-time denominators to assess incidence rates of severe infusion reactions. Because co-administration of pegloticase with an immunomodulator (particularly methotrexate) is now recommended as a standard of care for patients with uncontrolled gout (label , FitzGerald, Dalbeth et al. 2020, Botson, Baraf et al. 2022) and because the increasing uptake of immunomodulator co-therapy may confound secular trends of infusion reaction rates (see Section 7.2), the primary analysis will estimate annual and era-specific incidence rates of severe infusion reactions among new users of pegloticase with an immunomodulator co-therapy, from January 1, 2017 through September 30, 2025. Temporal patterns will be summarized across three periods: pre–COVID-19 vaccine (2017–2020), intra–COVID-19 vaccine (2021–mid-2022), and post–COVID-19 vaccination (mid-2022–2025). The intention of this study is to detect population-level changes rather than estimate individual vaccine-associated risk. In a sensitivity analysis (section 9.7.2.3), we will apply the same methodology to a subgroup of patients with pegloticase monotherapy.

To estimate calendar year–specific (and era-specific) incidence rates, we will treat calendar year/era as a time-varying stratification variable and allocate each participant's at-risk follow-up time to the corresponding calendar year(s)/era(s). Severe infusion reactions will be attributed to the calendar year/era of occurrence, so participants may contribute person-time to more than one year/era if follow-up spans calendar boundaries.

To contextualize the interpretation of observed pegloticase trends, we will conduct parallel within-drug temporal trend analyses for rituximab (negative control) and for pegaspargase and PLD (PEG-containing infused comparators). These comparator analyses are intended to evaluate whether period-specific changes appear to be drug-specific versus reflective of broader secular trends, and are not intended for head-to-head drug–drug comparisons.

- Study Population or Data Resource

This study will include parallel new-user cohorts identified in Optum Market Clarity closed claims from January 1, 2017 through September 30, 2025: (1) pegloticase initiators with gout (primary cohort), (2) rituximab initiators with rheumatoid arthritis (negative control cohort), and (3) pegaspargase initiators and (4) PLD initiators (PEG-containing contextual comparator cohorts). Each cohort will be analyzed separately to estimate within-drug temporal trends (annual/era-specific incidence rates and incidence rate ratios (IRRs). We will not conduct head-to-head drug–drug comparisons across cohorts due to differences in treatment mechanisms, treated populations and care settings. New users of pegloticase will be identified in medical claims using the HCPCS J-code J2507. Co-administration of an immunomodulator will be determined using the 90 days before or after the pegloticase initiation date (Holladay, Mudano et al. 2024). An immunomodulator will include methotrexate, mycophenolate mofetil, azathioprine and leflunomide.

- Summary of Patient Eligibility Criteria

The inclusion criteria will include:

*Applies to all cohorts***:**

- Continuous commercial enrollment for 12 months prior to index date (i.e., baseline period, defined below)
- New-user design: no claims for the index drug during baseline

Pegloticase cohort (primary):

- Age ≥18 on index date (i.e., first observed pegloticase infusion)
- ≥1 gout diagnosis during baseline
- Pegloticase initiation identified by HCPCS J-code J2507

- Immunomodulator co-therapy defined by ≥1 dispensing/administration of methotrexate, mycophenolate mofetil, azathioprine, or leflunomide during the 90 days before or up to 90 days (or prior to a reaction date if it occurred earlier) after the pegloticase index date. Pegloticase monotherapy initiators will be evaluated in sensitivity analyses (see Section 9.7.2.3).

Rituximab cohort (negative control):

- Age ≥18 on index date
- ≥1 rheumatoid arthritis diagnosis during baseline
- Rituximab initiation identified by HCPCS codes: J9312, Q5115, Q5119, Q5123
- We will require methotrexate co-therapy in the 90 days before/after index to reflect typical RA use (FDALabeling)

Pegaspargase cohort (PEG-containing contextual comparator):

- Age ≥18 on the index date
- Evidence of acute lymphoblastic leukemia (ALL) during baseline using ICD-10 code C91.xx
- Pegaspargase initiation identified by HCPCS code: J9266
- No immunomodulator co-therapy requirement (FDALabeling)

PLD cohort (PEG-containing contextual comparator):

- Age ≥18 on index date
- Evidence of malignancy during baseline (ICD-10 codes: C00-C96)
- PLD initiation identified by HCPCS J codes: J9002, Q2050 and Q2049

  PLD does not require co-use of an immunomodulator as part of its labeled use or standard administration

- Observational period:

The index date is defined as the date of a patient's first observed pegloticase infusion during the study period. To identify new users, we will require a 365-day washout period with no evidence of pegloticase use prior to the index date; this period will serve as baseline.

During the follow-up, each study participant will be observed from the index date until the earliest occurrence of any of the following: death, the outcome of interest, pegloticase discontinuation (defined in Section 9.2.6) or the end of the study period (i.e., September 30, 2025).

While infusion reactions may occur at any point during treatment, prior evidence from the MIRROR trial indicates that the majority occur during the first or second infusion (Botson, Saag et al. 2023). Therefore, the definition of our study follow-up will effectively capture the majority, if not all, potential infusion reactions. This eight-year interval allows evaluation of temporal trends in severe infusion reactions associated with pegloticase across three distinct epidemiologic phases (rationale see Session 9.2.1).

- Pre-COVID vaccine period: January 1, 2017 – December 31, 2020
- Intra-COVID vaccine period: January 1, 2021 – June 30, 2022
- Post-COVID vaccine period: July 1, 2022 – September 30, 2025

Parallel follow-up definitions will be applied to rituximab, pegaspargase and PLD cohorts to ensure methodological consistency across the primary and comparator analyses.

- Variables

Primary outcomes

- *Severe infusion reactions* operationalized as anaphylaxis or anaphylactoid reaction, identified using validated claims-based algorithms based on a combination of International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes and relevant procedure/setting codes in the emergency department (ED) visit or hospitalization claims (see Section 9.3.2).
- *Timing (risk window)*: Because infusion reactions in KRYSTEXXA clinical trials were identified as events occurring during infusion or within 2 hours after infusion (Sundy, Baraf et al. 2011, Botson, Tesser et al. 2021), and claims data do not reliably capture hour-level timing, we will define a severe infusion reaction as one occurring on the infusion date (day 0) or within the subsequent 1 day (day 1) of an infusion/administration claim.

Secondary Safety Outcomes

- *CVE:* composite of AMI or stroke, identified using inpatient diagnosis codes (algorithm specified in Section 9.3.2).

- *Timing:* Primary definition will capture events occurring on day 0 through day 1 relative to an infusion, consistent with a peri-infusion acute safety window.

- *Hospitalization for HF:* inpatient hospitalization with a primary diagnosis of HF (ICD-10 codes: I50.xx. See Section 9.3.2).
  - *Timing:* assessed in the day 0–1 peri-infusion window.
- *All-cause mortality*: dates of mortality are reliably recorded in the Market Clarity closed claims data source.

All counts and rates will be reported by the calendar year (and by pre-/intra-/post-vaccination era) in which the event occurs, and denominators will reflect the corresponding at-risk person-time (or infusion-exposed time) accrued in those same calendar periods.

These outcomes will be examined in separate models.

Covariate(s)

- Demographics: age and gender at the index date
- Presence of a comorbidity during the baseline year, including type II diabetes, hypertension, hyperlipidemia, asthma, chronic obstructive pulmonary disease (COPD), and chronic kidney disease. All these conditions will be identified using the Centers for Medicare & Medicaid Services Chronic Condition Warehouse (CCW) algorithms (CMS-CCW).
- Baseline healthcare utilization, including the presence of all-cause inpatient or ED visits.
- Gout severity (pegloticase cohort only): number of flares (see Section 9.3.3), presence of tophi, gout-specific ED visits, gout-specific hospitalizations.

These characteristics are selected based on clinical relevance.

- Sample Size

Our preliminary analysis using Optum Clinformatics data identified 817 gout patients who are new users of pegloticase infusions and met the continuous enrollment. Table 1 shows a breakdown of sample sizes by immunomodulator co-administration status and calendar year from 2017 to 2024. The size of individuals covered by the new data source - Optum Market Clarity closed claims data is anticipated to be approximately three times larger than Optum claims data (according to personal communications with the DAC

team). Preliminary data review indicates that 3,434 pegloticase users were identified in Market Clarity as of March 31, 2025, demonstrating stronger feasibility for achieving sufficient sample size to characterize infusion reactions across the pre-, intra- and post-mass COVID-19 vaccine periods.

- Data Analysis

We will use descriptive statistics to describe patient characteristics during the 365-day baseline period preceding the index date. The mean (standard deviation [SD]), median, and interquartile range (IQR) of the number of pegloticase infusions during follow-up will be reported. To check the potential secular changes in care, we will compare the distribution of demographics, comorbidity burden, baseline health services utilization, number of infusions and immunomodulator type (methotrexate vs. others) across pre-, intra- and post-COVID-19 vaccination periods. If there are significant secular changes over time, we will include these covariables into the statistical models described below.

Calendar year/era-based outcome estimation:
For each outcome of interest, we will estimate calendar year–specific and era-specific event counts and incidence rates by attributing outcomes to the calendar year/era in which the event occurs and allocating each participant's at-risk follow-up time to the corresponding calendar year(s)/era(s). This approach allows participants to contribute person-time to multiple calendar years/eras if follow-up spans calendar boundaries.

Regression models for incidence rates and IRRs:
We will use generalized linear models with a Poisson distribution (with log link and the log of person-time as an offset) to estimate calendar year/era–specific incidence rates and corresponding 95% confidence intervals (CIs), as well as IRRs comparing periods (e.g., intra- vs pre-vaccine; post- vs pre-vaccine). Models will adjust for age and sex and, if meaningful secular changes in baseline characteristics are observed. If overdispersion is present, we will use robust (sandwich) standard errors and/or a negative binomial specification as appropriate.

Comparator cohorts: Parallel calendar year/era–based incidence estimation and modeling approaches will be applied separately to the rituximab, pegaspargase, and PLD cohorts to contextualize whether temporal patterns observed for pegloticase are drug-specific versus reflective of broader secular changes. Comparator analyses are

intended for within-drug temporal trend interpretation and are not intended as head-to-head comparisons across drugs.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data analysis	April 1, 2026
End of data analysis	May 15, 2026
Findings for ACR 2026 abstract submission	June 15th, 2026
Manuscript preparation	March 31st, 2027

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Gout is a chronic, systemic metabolic disorder driven by persistent hyperuricemia, which leads to supersaturation of serum urate and deposition of monosodium urate crystals within joints, tendons, bursae, and other soft tissues (Perez-Ruiz, Dalbeth and Bardin 2015, Asghari, Zahmatyar et al. 2024). Crystal deposition triggers recurrent episodes of acute inflammatory arthritis and, over time, may result in progressive joint damage, tophaceous burden, and functional impairment(Perez-Ruiz, Dalbeth and Bardin 2015). The prevalence of gout continues to rise in parallel with aging populations and increasing burdens of metabolic syndrome, CKD, and cardiovascular comorbidities(Dehlin, Jacobsson and Roddy 2020).

In the United States, approximately 12 million adults are affected by gout (Yokose, McCormick et al. 2023). Although most patients can achieve serum urate control using first-line urate-lowering therapies (ULTs) such as allopurinol or febuxostat, a subset—estimated at ~2%—progress to CRG(Botson, Baraf et al. 2022). CRG is defined by failure to attain target serum urate levels, ongoing flares, or persistent tophi despite appropriately dosed ULTs, often complicated by medication intolerance, diminished renal function, or heightened inflammatory burden (Botson, Baraf et al. 2022).

7.2 Rationale

Pegloticase, a pegylated recombinant uricase enzyme, is the only FDA-approved biologic therapy for patients with CRG. Pegloticase catalyzes the oxidation of uric acid into allantoin, a highly soluble metabolite readily cleared by the kidneys. Clinical trials have demonstrated its capacity for rapid and profound serum urate lowering, resolution of tophi, and meaningful improvements in patient-reported outcomes among responders (Sundy, Baraf et al. 2011, Becker, Baraf et al. 2013, Botson, Saag et al. 2023). However, the clinical utility of pegloticase is constrained by its immunogenicity. A substantial proportion of non-responders develop anti-drug antibodies—especially against the PEG moiety—leading to accelerated drug clearance, loss of urate-lowering efficacy, and heightened risk of infusion reactions, including severe hypersensitivity and anaphylaxis (Lipsky, Calabrese et al. 2014, Keenan, Botson et al. 2021).

In the pivotal Phase III randomized trials, infusion reactions were reported in 26% of patients receiving pegloticase every two weeks, compared with approximately 5% in the placebo group (Sundy, Baraf et al. 2011, Strand, Khanna et al. 2012). Among pegloticase-treated patients, about 5% experienced severe reactions later classified as anaphylaxis by the FDA (Sundy, Baraf et al. 2011, Strand, Khanna et al. 2012). A detailed pooled analysis identified 113 infusion-reaction events across 1,695 infusions: 6 met formal anaphylaxis criteria, 53 were classified as “hypersensitivity” (one feature of anaphylaxis), and 54 were “other” infusion reactions (no features of anaphylaxis) (Calabrese, Kavanaugh et al. 2017). In contrast, the MIRROR randomized controlled trial demonstrated that co-administration of methotrexate significantly reduces immunogenicity and infusion-reaction risk: through 6 months, infusion reactions occurred in 4.2% of patients receiving pegloticase with methotrexate versus 30.6% with pegloticase alone, with no new safety signals through 12 months and no infusion reactions reported after week 24 (Botson, Saag et al. 2023, Troum, Botson et al. 2025).

The COVID-19 pandemic introduced widespread, repeated population-level exposure to PEG through the use of PEGylated lipid nanoparticles in mRNA vaccines. Experimental and clinical studies have explored whether such exposure may induce or amplify anti-PEG antibody responses. While animal models have demonstrated PEG-associated immune responses (Wang, Wang et al. 2023), human data remain limited and inconsistent. In humans, only one case report posted in the American Academy of Allergy Asthma & Immunology Expert Forum described that patients who received a

mRNA COVID-19 vaccine and either an allergy immunotherapy or an omalizumab the next day developed reactions(Forum 2023). The allergy immunotherapy reaction included hypotension requiring ICU admission. One patient with Omalizumab experienced lymphadenopathy; the other patient with Omalizumab experienced dyspnea(Forum 2023). This report is not peer reviewed. There is no study that established a causal relationship with subsequent biologic infusion reactions.

Although mRNA COVID-19 vaccines contain PEG-lipid nanoparticles and have been associated with transient anti-PEG antibody responses in some studies, existing evidence is inconsistent and clinical consequences are still unclear(Guerrini, Gioria et al. 2022, Ju, Carreno et al. 2023, Omata, Kawahara et al. 2024). A Nature Reviews Immunology article states that anti-PEG antibodies can be induced by SARS-CoV-2 mRNA vaccines but emphasizes that the overall impact of these boosted anti-PEG antibodies remains unclear and requires further research(Ju, Carreno et al. 2023). In a cohort of patients who received three doses of COVID-19 vaccines, the presence of PEG in the formulation did not influence the level of antibodies generated upon vaccination or any serious adverse effects(Guerrini, Gioria et al. 2022). Importantly, no direct clinical evidence currently links COVID-19 vaccination to an altered risk of infusion reactions with pegloticase.

As a result, it remains unclear whether population-level COVID-19 vaccination campaigns translated into clinically meaningful changes in real-world rates of severe pegloticase infusion reactions. Evaluating temporal trends across the pre-, intra-, and post-COVID-19 vaccination periods is therefore clinically relevant. Because individual COVID-19 vaccination status and timing are not reliably captured in commercial claims, this study provides a population-level temporal trend assessment rather than a direct evaluation of infusion reactions conditional on documented vaccination. We will interpret findings as evidence about population-level stability or change in real-world infusion reaction incidence over calendar time, and we will avoid causal statements about vaccination effects in individuals.

7.3 Feasibility and Futility Considerations

This retrospective study will leverage a new in-house data resource at CfOR - Optum Market Clarity closed claims for which Amgen’s data license has begun on January 1, 2026. Optum Market Clarity is a large de-identified integrated claims dataset that has

been commonly used in pharmacoepidemiologic research (Hankosky, Chinthammit et al. 2025, Li 2025). Market Clarity includes both open and closed claims; we will focus on the closed claims data to maximize completeness of enrollment and healthcare utilization capture, thereby improving ascertainment of longitudinal medication use and outcome occurrence. Definitions for comorbidities, medication use and health service utilization measures have been previously developed using a similar Optum data source (Optum Clinformatics data), included in Amgen studies 20240358 and 20240356. Methods for identifying new users of pegloticase have likewise been established in prior Amgen work (# 20240356), providing a strong methodological foundation for the current project.

7.4 Statistical Inference (Estimation or Hypothesis[es])

Primary hypothesis (Pegloticase + immunomodulator; primary cohort):

We hypothesize that calendar year– and era-specific incidence rates of severe safety outcomes among pegloticase initiators receiving concomitant immunomodulator therapy will remain clinically stable across the pre–COVID-19 vaccine (January 1, 2017–December 31, 2020), intra–COVID-19 vaccine (January 1, 2021–June 30, 2022), and post–COVID-19 vaccination (July 1, 2022–September 30, 2025) periods, after accounting for secular changes in case mix and care patterns.

Comparator hypotheses (contextualization; within-drug temporal patterns):

Comparator analyses are intended to support within-drug temporal trend interpretation and are not intended for causal/mechanistic inference via between-drug comparisons. We hypothesize that rituximab (negative control) will show stable incidence rates across periods, suggesting no major secular artifact in outcome capture, and that pegaspargase and PLD (PEG-containing contextual comparators) will likewise show no clinically meaningful increases across periods, providing context for the pegloticase findings.

8. Research Question and Objectives

8.1 Primary

Primary objective:

To quantify annual/era incidence rates of severe pegloticase infusion reactions across the pre-, intra-, and post-COVID-19 vaccination periods in patients with pegloticase with an immunomodulator co-therapy (primary) and those with pegloticase monotherapy (sensitivity analysis).

Secondary objectives:

1. *Negative control (contextualization)*: Using the same outcome definition and time-period framework, estimate annual/era-specific incidence rates of severe infusion reactions among rituximab initiators to evaluate whether there are broad secular changes in coding, detection, or infusion-care patterns unrelated to PEG exposure.
2. *PEG-containing infused comparators (contextualization)*: Using analogous design and outcome definitions, estimate annual/era-specific incidence rates of severe infusion reactions among initiators of pegaspargase and PLD to provide context on whether temporal patterns observed for pegloticase are consistent with other PEG-containing infused products.

9. Research Methods

9.1 Study Design

This is a retrospective observational cohort study with a temporal trend analysis design using large-scale U.S. commercial claims data. The primary analysis will estimate annual and era-specific incidence rates of severe infusion reactions among new users of pegloticase with an immunomodulator co-therapy, from January 1, 2017 through September 30, 2025. Temporal patterns will be summarized across three periods: pre–COVID-19 vaccine (2017–2020), intra–COVID-19 vaccine rollout (2021–mid-2022), and post–COVID-19 vaccination (mid-2022–September 30, 2025).

To contextualize the interpretation of observed pegloticase trends, we will conduct parallel within-drug temporal trend analyses for rituximab (negative control) and for pegaspargase and PLD (PEG-containing infused comparators). These comparator analyses are intended to evaluate whether period-specific changes appear to be drug-specific versus reflective of broader secular trends, and are not intended for head-to-head drug–drug comparisons.

9.2 Setting and Study Population

9.2.1 Study Period

The study observation window will extend from January 1, 2017, through September 30, 2025, corresponding to the period covered by the Optum Market Clarity closed claims database. This eight-year interval allows evaluation of temporal trends in severe infusion reactions across three epidemiologic phases defined by the timing of COVID-19 vaccine authorization and population uptake:

- Pre-COVID vaccine period: January 1, 2017 – December 31, 2020 (The FDA first granted emergency use authorization to the Pfizer-BioNTech vaccine on December 11, 2020.)

- Intra-COVID vaccine period: January 1, 2021 – June 30, 2022 (COVID-19 vaccines became widely available for individuals aged 16 years or older in the US by April 19, 2021 and vaccination coverage increased substantially through 2021 (Hall, Mahon and Peacock 2024, Oliver, Wallace et al. 2024))
- Post-COVID-19 vaccine period: July 1, 2022 – September 30, 2025 (Although COVID-19 vaccination coverage continued after 2022, the period since mid-2022 reflects a post–mass vaccination phase characterized by stabilized uptake and seasonal booster campaigns rather than initial mass vaccine rollout. CDC coverage estimates indicate ongoing vaccination coverage into 2023–2025, including updated 2024–25 and 2025–26 vaccines)(CDC).

To support calendar year–specific and era-specific estimation, outcomes will be attributed to the calendar year/era in which they occur, and participants' at-risk follow-up time will be allocated to the corresponding calendar year(s)/era(s). Participants may therefore contribute person-time to more than one calendar year/era if their follow-up spans calendar boundaries.

9.2.2 Selection and Number of Sites

Not applicable

9.2.3 Subject/Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

The inclusion criteria are:

*Applies to all cohorts (unless otherwise noted)***:**

- Continuous commercial enrollment for 12 months prior to index date (baseline period)
- New-user design: no claims for the index drug during baseline

Pegloticase cohort (primary):

- Age ≥18 on index date
- ≥1 gout diagnosis during baseline (ICD-9: 274.x; ICD-10: M10.x or M1A.x)
- Pegloticase initiation identified by HCPCS J-code J2507
- Immunomodulator co-therapy defined by ≥1 dispensing/administration of methotrexate, mycophenolate mofetil, azathioprine, or leflunomide during the 90 days before or up to 90 days (or prior to the study end if it occurred earlier) after the

pegloticase index date. Pegloticase monotherapy initiators will be evaluated in sensitivity analyses (see Section 9.7.2.3).

Rituximab cohort (negative control):

- Age ≥18 on index date
- ≥1 rheumatoid arthritis diagnosis during baseline
- Rituximab initiation identified by HCPCS codes: J9312, Q5115, Q5119, Q5123
- We will require methotrexate co-therapy in the 90 days before/after index to reflect typical RA use (FDALabeling)

Pegaspargase cohort (PEG-containing contextual comparator):

- Age ≥18 on the index date
- Evidence of ALL during baseline using ICD-10 code C91.xx
- Pegaspargase initiation identified by HCPCS code: J9266
- No immunomodulator co-therapy requirement (FDALabeling)

PLD cohort (PEG-containing contextual comparator):

- Age ≥18 on index date
- Evidence of malignancy during baseline (ICD-10 codes: C00-C96)
- PLD initiation identified by HCPCS J codes: J9002, Q2050 and Q2049
- PLD does not require co-use of an immunomodulator as part of its labeled use or standard administration

9.2.4 Matching

Not applicable

9.2.5 Baseline Period

The baseline period will be defined as the 365 days immediately preceding the index date, which is the date of the first observed pegloticase infusion during the study period. A 365-day washout with no evidence of pegloticase use will be required prior to the index date to identify new users.

9.2.6 Study Follow-up

The follow-up period will begin on the index date and continue until the earliest occurrence of any of the following:

- Pegloticase discontinuation, defined by a gap of >90 days between infusions to maximize specificity and reduce misclassification(Holladay, Mudano et al. 2024);
- Insurance disenrollment (loss of continuous medical or pharmacy coverage);
- Death;
- Study end (September 30, 2025).

To support calendar year–specific and era-specific estimation of event counts and incidence rates, each participant's at-risk follow-up time will be allocated to the calendar year(s)/era(s) in which it occurs, and outcomes will be attributed to the calendar year/era of occurrence.

Parallel baseline and follow-up definitions will be applied to the rituximab, pegaspargase, and PLD comparator cohorts to ensure methodological consistency across analyses, with drug-specific discontinuation rules selected to reflect typical dosing intervals and reduce misclassification of planned treatment gaps as discontinuation. More specifically, for rituximab (RA), where retreatment commonly occurs in courses separated by 6 months, discontinuation will be defined as a gap of >270 days without a subsequent rituximab administration after the last observed infusion (sensitivity analyses: >365 days). For PLD, which is generally administered often every 3–4 weeks, discontinuation will be defined as a gap of >60 days after the last administration (sensitivity analyses: >90 days). For pegaspargase, which is typically administered every 2–3 weeks as part of multi-agent ALL regimens, discontinuation will be defined as a gap of >45 days without a subsequent administration (sensitivity analyses: >60 days).

9.3 Variables

9.3.1 Exposure Assessment

Exposure will be defined using medical and pharmacy claims for administration of the index therapies. For the primary cohort, pegloticase exposure will be identified via HCPCS J2507. The primary analysis will focus on the co-therapy of an immunomodulator, assessed using pharmacy claims and defined as at least one dispensing of oral methotrexate, mycophenolate mofetil, azathioprine, or leflunomide during the 90 days before or after the pegloticase index date; these products will be identified using NDCs.

For comparator cohorts, exposure will be defined analogously based on the first observed administration of the index therapy during the study period. Rituximab administrations will be identified using HCPCS codes for rituximab products (e.g., J9312 and biosimilar Q-codes Q5115, Q5119, Q5123). Pegaspargase administrations will be identified using HCPCS J9266. PLD administrations will be identified using HCPCS codes for liposomal doxorubicin products (e.g., J9002, and where applicable Q2049/Q2050). Comparator cohorts will not require immunomodulator co-therapy per labelling.

Exposure definitions are product-based and not indication-specific; therefore, disease-based cohort restrictions are applied separately in the eligibility criteria.

9.3.2 Outcome Assessment

Primary outcomes:

Anaphylaxis or anaphylactoid reaction occurring in the peri-infusion window (day 0–1). Events will be identified using a validated claims-based algorithm for anaphylaxis (Table 2) (Walsh, Cutrona et al. 2013), using diagnosis and procedure codes from ED or inpatient claims. ICD-9 codes from prior FDA Mini-Sentinel study will be mapped to ICD-10-CM using CMS General Equivalence Mappings as needed (CMS).

*Exploratory supportive marker (not part of the primary endpoint definition)***:** Because not all clinically significant reactions captured in real-world data are coded as anaphylaxis, we will descriptively assess the ordering of tryptase testing on day 0 through day 1 of the infusion date as an additional signal consistent with suspected hypersensitivity/mast cell activation, as used in prior claims-based work (Chen, Liu and Kim 2020).

Table 2. Claims-based algorithm for the identification of anaphylaxis.

Criterion A:	T78.2xxA, T78.2xxD, T78.2xxS [anaphylactic shock, unspecified (initial, subsequent, sequela)], T80.52xA, T80.52xD, T80.52xS [anaphylactic shock due to serum (initial, subsequent, sequela)] in the ED or hospitalization claims (primary diagnosis)
OR	
Criterion B:	T78.2xxA, T78.2xxD, T78.2xxS [anaphylactic shock, unspecified (initial, subsequent, sequela)], T80.52xA, T80.52xD, T80.52xS [anaphylactic shock due to serum (initial, subsequent, sequela)] in the ED or hospitalization claims (in any diagnostic field) **PLUS** a code for one of the

	following symptoms/procedures/treatment on the same day or within 1 day before or after the diagnosis codes: Bronchospasm (J98.01) or Stridor (R06.1) or Hypotension (I95.9) or Epinephrine (HCPCS J0171 and J0170) or Injection of diphenhydramine (procedure J1200) or CPR (CPT procedure 92950 or ICD-10 procedure code 5A12012)
OR	
Criterion C	T78.40xA, T7840xD, T78.40xS [allergy, unspecified], T50.905A, T50905D, T50.905S [adverse effect of unspecified drug/med/biological substance], T36-T50 [Drugs/medicinal and biological substances causing adverse effects] in the inpatient or ED claim (in any diagnostic field), **PLUS** a code for one of the following symptoms/procedures/treatments: Bronchospasm (J98.01) or Stridor (R06.1) or Injection of diphenhydramine (procedure J1200) **And ALSO** a code for one of the following symptoms/procedures/treatments: Hypotension (I95.9) or Epinephrine (HCPCS J0171 and J0170) or CPR (CPT procedure 92950 or ICD-10 procedure code 5A12012)

Secondary safety outcomes*:*

CVE: hospitalization for AMI or stroke, identified using inpatient primary diagnosis codes.

Hospitalization for HF: inpatient hospitalization for heart failure, identified using inpatient diagnosis codes.

*All-cause mortality***:** as captured in the Optum Market Clarity closed claims data source.

For each endpoint, an incident ("new") event will be defined as the absence of the same endpoint during the 365-day baseline period prior to the index date. This incident-event definition will be used for outcome-specific analyses to reduce inclusion of prevalent/recent events. Because infusion reactions in KRYSTEXXA clinical trials were identified as events occurring during infusion or within 2 hours after infusion (Sundy, Baraf et al. 2011, Botson, Tesser et al. 2021), and claims data do not reliably capture hour-level timing, we will define a severe infusion reaction as one occurring on the infusion date (day 0) or within the subsequent 1 day (day 1) of an infusion/administration claim.

9.3.3 Covariate Assessment

- Demographics: age and gender at the index date
- Presence of comorbidities during the baseline year, including type II diabetes, hyperlipidemia, cardiovascular diseases, heart failure, asthma, COPD, and chronic kidney disease. All these conditions will be identified using the Centers for Medicare & Medicaid Services CCW algorithms (CMS-CCW).
- Baseline healthcare utilization, including the presence of all-cause inpatient or ED visits, and the number of outpatient visits.
- Gout severity (pegloticase cohort only): number of flares, presence of tophi, gout-specific ED visits, gout-specific hospitalizations.

We will use the same methodology/algorithms that were used in our previous studies (Amgen # 20240358, #20240357 and #20240355). Gout flare will be defined according to the presence of 1 or more of the following: an outpatient or ED visit or a hospitalization with a diagnosis for gout as the primary diagnosis in combination with a prescription of NSAIDs, opioid or colchicine (Appendix B) dispensed within 7 days; or an outpatient or ED visit or a hospitalization for joint pain in combination with a pharmacy claim or medical claim with a procedure code for oral or injectable colchicine within 7 days. Similar algorithms have been used in the literature.(Rothenbacher, Primatesta et al. 2011, Cipolletta, Tata et al. 2022) In a study based on data from 3.6 million people registered with the Kaiser Permanente Southern California database, a definition of gout flare using physician consultation and prescription and/or procedure codes yielded a positive predictive value of 95% (Zheng, Rashid et al. 2014). Because gout flares typically last for 1 to 2 weeks, gout-related consultations and prescriptions within 14 days of the initial observed flare claim will be considered part of the same flare.

We will use diagnostic codes to identify tophi (see Appendix C).

These characteristics are selected based on clinical relevance.

9.3.4 Validity and Reliability

Optum Market Clarity closed claims data is a large, nationally representative, longitudinal U.S. healthcare database that integrates multiple data assets to support real-world evidence generation. It includes medical and pharmacy claims from a large, geographically diverse, commercially insured U.S. population, enhancing generalizability to similar patient groups. Outpatient infusion services are reliably captured through

procedure codes, allowing accurate identification of pegloticase administrations and follow-up. Coding systems (ICD-10-CM, CPT, HCPCS) remained stable during the study period, supporting consistent measurement across calendar years.

Limitations.

Market Clarity does not provide physician notes or clinical charts to extract infusion reactions. Claims lack a specific code for the primary infusion reactions, requiring algorithm-based identification that may under- or over-ascertain events, particularly milder reactions occurring solely in infusion centers. Claims also record service dates rather than exact clinical timestamps, limiting granularity in determining same-day versus delayed reactions. Pandemic-related disruptions in healthcare access and coding practices could influence detection of less severe events; however, severe reactions requiring ED care or hospitalization—our primary outcomes—are less affected by shifts to outpatient or telehealth settings. Clinical details such as antibody titers, the exact time of COVID vaccine administration, are unavailable, limiting control of certain confounders.

Reliability.

Pegloticase is a high-cost infused therapy, which incentivizes accurate billing and enhances the reliability of exposure capture. Overall, while clinical depth is limited, the large, stable, and longitudinal structure of Optum Market Clarity closed claims data makes it well suited for assessing relative changes in severe infusion reaction rates over time when paired with transparent outcome algorithms and appropriate sensitivity considerations.

9.4 Data Sources

The study will use data from the Optum Market Clarity closed claims data (January 1, 2016 – September 30, 2025) data, which captures comprehensive enrollment information, medical claims and outpatient pharmacy records.

Market Clarity includes information for more than 80 million covered individuals and preserves continuous person-level tracking across years, making it particularly well suited for studying temporal trends across the pre-COVID vaccine (2017-2020)**,** intra-COVID vaccine (2021 to mid-2022)**,** and post-COVID vaccine (mid-2022 to 2025)**.** The database captures detailed information on outpatient and inpatient encounters, infusion services, coded diagnoses and procedures, emergency department visits, and pharmacy dispensing claims. This comprehensive data structure allows for accurate identification

of infusion episodes, characterization of infusion reactions and associated clinical management, and assessment of temporal changes in utilization patterns, patient characteristics, and clinical outcomes surrounding the COVID-19 pandemic. Because Market Clarity closed claims data supports person-level linkage across sites and years, it facilitates the evaluation of secular trends, changes in clinical practice, and potential shifts in patient risk profiles across the 2017–2025 study window.

In addition, the breadth of demographic and clinical information available in Market Clarity closed claims allows for assessment of baseline comorbidities, risk factors for infusion reactions, and post-infusion outcomes, making the dataset well suited for safety-focused observational research in patients receiving pegloticase.

9.5 Study Size

Our preliminary analysis identified 817 gout patients who are new users of pegloticase infusions in the Optum Clinformatics data and met our inclusion criteria. The new data resource—Optum Market Clarity closed claims data—has been available in CfOR in Q1 2026. Based on preliminary data review, more than 3,000 pegloticase users had been identified in the Market Clarity dataset as of March 31, 2025, indicating strong feasibility for achieving sufficient sample size.

9.6 Data Management

9.6.1 Obtaining Data Files

Not applicable

9.6.2 Linking Data Files

Not applicable

9.6.3 Review and Verification of Data Quality

This is secondary data analysis. The Optum Market Clarity closed claims data are constructed through collection and standardization of raw data from the appropriate payers and linking files across time and data type to create a comprehensive and efficient set of database tables. Enhancements are made to improve the data quality and efficiency, for example: updating diagnosis and procedure codes to reflect changes in codes over time if necessary; creating a common synthetic patient identifier that enables patients to be tracked over time and across data types; integrating benefit plan characteristics, enrollment, outpatient pharmaceutical claims, and medical/surgical data.

This Optum data has been maintained internally by Amgen. Any relevant limitations due to the database and adjustments for bias are documented in Section 9.9.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Analysis/Analyses

Using the FDA Sentinel analytic module, we generated preliminary annual incidence rates of severe infusion-related outcomes for rituximab (negative control) and pegaspargase (PEG-containing contextual comparator) using the Optum Clinformatics claims data from 2017–2024. These results provide contextual information to support interpretation of temporal trends in pegloticase infusion reactions (Appendix B).

Rituximab (Negative Control)

Across approximately eight years, rituximab users demonstrated generally stable incidence rates of allergy/adverse events and cardiovascular events, with no clear, sustained systematic increases during the COVID-19 era.

- *Allergy/adverse event rates* remained within a relatively narrow range over time (5.7–11.3 per 100 PYs), with the highest rate observed in 2020 (11.31 per 100 PYs) and the lowest in 2022 (5.73 per 100 PYs).
- *Cardiovascular event rates* likewise fluctuated modestly (7.2–11.0 per 100 PYs) without consistent directional changes corresponding to pre-, intra-, or post-COVID periods.
- *Anaphylaxis or anaphylactoid reactions* were extremely rare, with only 0–3 cases per year. Several years (e.g., 2020) had no reported cases. Rates remained ≤0.36 per 100 PYs across all years.

These patterns suggest that background coding practices and healthcare utilization did not shift in a way that would artifactually raise infusion reaction detection during the COVID-19 timeframe, supporting the use of rituximab as a negative control.

*Pegaspargase (*PEG-containing infused comparators*)*

Among pegaspargase-treated patients, sample sizes were extremely small across all years, resulting in very limited person-time and substantial statistical instability.

- Reported allergy or adverse event rates fluctuated widely (approximately 31–55 per 100 PYs in most years), but these estimates were driven by very small numerators and denominators, making them unreliable.

- Cardiovascular events and anaphylaxis were rare or absent in nearly all years, again reflecting insufficient sample size rather than true clinical patterns.

Given these constraints, pegaspargase data cannot be used to infer meaningful temporal trends.

We expect Optum Market Clarity to capture a larger number of new users of pegaspargase and will also include PLD as a second mechanistic comparator. In preliminary analyses using Optum Clinformatics data, more than 10,000 patients received PLD between 2016 and 2025. This sample size should allow us to estimate annual incidence rates of infusion reactions with sufficient precision to assess clinical meaningful temporal patterns.

9.7.1.2 Primary Analysis

The primary analysis will quantify calendar year–specific and era-specific incidence rates of severe infusion reactions among new users of pegloticase in Optum Market Clarity closed claims from January 1, 2017 through September 30, 2025, spanning the pre-, intra-, and post–COVID-19 mass vaccination periods. New users will be identified based on the first observed pegloticase infusion during the study period following a 365-day washout with continuous enrollment.

To support calendar-time estimation, outcomes will be attributed to the calendar year/era of occurrence, and each participant's at-risk follow-up time will be allocated to the corresponding calendar year(s)/era(s) if follow-up spans calendar boundaries. Incidence rates will be estimated for four prespecified severe outcomes occurring on the infusion date or within the subsequent one day:

1. anaphylaxis or anaphylactoid reactions;
2. acute cardiovascular events;
3. hospitalization for heart failure; and
4. all-cause mortality.

Primary analyses will be conducted among patients receiving pegloticase with immunomodulator co-therapy. Recognizing that immunomodulator co-therapy is expected to modify risk, we will conduct a complementary/sensitivity analysis applying the same methodology among pegloticase monotherapy initiators. Results will be summarized as calendar year–specific and era-specific incidence rates with 95%

confidence intervals, and corresponding incidence rate ratios comparing eras where specified.

Parallel calendar year/era–based incidence estimation will be conducted separately in the rituximab (negative control) and pegaspargase and PLD (PEG-containing contextual comparator) cohorts to contextualize observed pegloticase temporal patterns, with inference focused on within-drug trends rather than head-to-head comparisons.

9.7.2 Planned Method of Analysis

Baseline demographic and clinical characteristics will be summarized using descriptive statistics for each cohort, based on the 365-day baseline period preceding the index date. Means (SD) or medians (IQR) will be reported for continuous variables, and counts/percentages for categorical variables. Baseline healthcare utilization measures and comorbidities will be described and compared across the pre-, intra- and post-COVID-19 vaccination eras to characterize potential secular changes in case mix and care patterns.

Incidence Rate Estimation (calendar year/era-based)

For each outcome, we will estimate calendar year–specific and era-specific event counts and incidence rates. Participants' at-risk follow-up time will be allocated to the calendar year(s)/era(s) in which it occurs, and outcomes will be attributed to the calendar year/era of occurrence. Person-time will accrue from the index date until the earliest of the first occurrence of the outcome, insurance disenrollment, death, discontinuation of the index therapy (drug-specific definition), or study end, whichever occurs first.

We will fit generalized linear models to estimate incidence rates and IRRs comparing eras and/or calendar years, using the log of person-time as an offset. We will assess overdispersion for each outcome. If mild overdispersion is present, we will use Poisson regression with robust (sandwich) standard errors to account for any residual within-person correlation induced by splitting follow-up into multiple year/era segments. If substantial overdispersion is observed, we will use negative binomial regression. For each outcome, we will report:

- Calendar year–specific incidence rates and era-specific incidence rates and 95% CIs
- IRRs comparing prespecified periods (e.g., intra- vs pre-vaccine; post- vs intra-vaccine)

Models will adjust for age and sex, and additional covariates will be included if there are meaningful secular changes in baseline characteristics (e.g., comorbidity burden, baseline utilization, immunomodulator type).

Comparator analyses:

Parallel calendar year/era-based incidence estimation and modeling will be conducted separately for rituximab (negative control) and pegaspargase and PLD (PEG-containing contextual comparators) to contextualize observed pegloticase temporal patterns. Comparator analyses will be interpreted as within-drug temporal trends and will not be used for head-to-head comparisons across therapies.

9.7.2.1 Descriptive Analysis

9.7.2.1.1 Description of Study Enrollment

Study enrollment will identify new-user cohorts of patients initiating the index therapies between January 1, 2017, and September 30, 2025, in the Optum Market Clarity closed claims data. Detailed inclusion criteria are summarized in Section 9.2.3.

9.7.2.1.2 Description of Patient Characteristics

Baseline patient characteristics will be summarized for each cohort. Variables include:

- Demographics: Age (mean ± SD), gender distribution.
- Clinical Comorbidities: Hypertension, diabetes, heart failure, coronary artery disease, CKD, asthma, COPD.
- Healthcare Utilization: Presence of inpatient or ED encounters in baseline year.
- Gout severity (pegloticase cohort only): number of flares, presence of tophi, gout-specific ED visits, gout-specific hospitalizations.

Descriptive statistics (means, medians, proportions) will be presented. Between group comparisons will use t-tests, Wilcoxon rank-sum tests, or χ^2 tests, as appropriate.

To check the potential secular changes in care, we will compare the distribution of demographics, comorbidity burden, baseline health services utilization, number of infusions and IMM type (MTX vs. others) across pre-, intra- and post-mass COVID-19 vaccination periods. If there are significant secular changes over time, we will include these covariables into the statistical models described below.

9.7.2.2 Analysis of the Endpoints

Overall, analyses will focus on estimating calendar year-specific and era-specific incidence rates and corresponding 95%CIs across the study period. Interpretation will emphasize the magnitude and precision of observed differences rather than statistical significance alone. Calendar-year incidence rates will be reported in addition to era-specific estimates to provide a higher-resolution description of secular trends in severe infusion-related outcomes. Annual rates help identify gradual or non-linear changes over time—such as shifts in infusion practices and site of care, and broader pandemic-related changes in healthcare utilization—that may not align precisely with the pre/intra/post era cut points and could be obscured by pooling. Calendar-year estimates therefore complement era-level comparisons by improving interpretability, facilitating visualization of temporal patterns, and supporting sensitivity checks for transient disruptions within the broader eras.

For each year, we will compute event counts and incidence rates per 1,000 person-years, attributing events to the calendar year/era in which they occur and allocating each participant's at-risk follow-up time to the corresponding calendar year/era if follow-up spans calendar boundaries. Both crude and age- and sex-adjusted incidence rates will be estimated for each calendar year and vaccination era.

Overdispersion will be assessed for each outcome, using the ratio of the Pearson chi-square statistic to its degrees of freedom. When little overdispersion is observed, generalized linear models with a Poisson distribution (log link) will be used to estimate incidence rates and 95% CIs, with robust (sandwich) standard errors applied to account for residual overdispersion. If substantial overdispersion is detected, negative binomial regression models will be considered. In addition to rates, we will estimate IRRs comparing prespecified vaccination eras (e.g., intra- vs pre-vaccine; post- vs intra-vaccine), and, where informative, adjacent calendar years.

Parallel endpoint analyses will be conducted separately for the rituximab, pegaspargase, and PLD comparator cohorts to contextualize pegloticase temporal patterns; inference will focus on within-drug trends rather than head-to-head comparisons across therapies.

9.7.2.3 Sensitivity Analysis

As described in Section 7.2, pegloticase monotherapy is associated with higher rates of infusion reactions (Sundy, Baraf et al. 2011, Becker, Baraf et al. 2013), and the introduction of routine co-administration with an immunomodulator beginning around 2022 has led to a substantial reduction in these events (Botson, Tesser et al. 2021). Despite this shift in clinical practice, a small subset of patients in recent years continue to receive pegloticase without an IMM. Because this changing treatment landscape may influence temporal trend estimates, it is important to evaluate whether the primary findings are robust to variations in IMM use over time.

To assess the rigor and stability of our results, we will conduct a sensitivity analysis focused specifically on pegloticase monotherapy users. Using the same new-user cohort design, person-time construction, and analytic methods as in the primary analysis, we will estimate annual incidence rates of severe infusion reactions among individuals receiving pegloticase without any concomitant IMM. This analysis will allow us to examine how infusion reaction rates evolved across the pre-, intra-, and post-mass COVID vaccine periods, independent of the confounding influence introduced by increasing IMM co-use.

By comparing temporal trends in the monotherapy cohort with those observed in the primary pegloticase + IMM cohort, this sensitivity analysis will help determine whether observed changes in infusion reaction rates reflect true shifts in risk over time versus changes in prescribing patterns or evolving standards of care. Consistency in findings across analyses would strengthen the validity of our conclusions, whereas divergence may provide important insights into treatment selection, immune modulation, and COVID-era clinical practice dynamics.

Whether reactions shift earlier (1st/2nd) in certain eras/products. To characterize the timing of severe reactions, we will describe the distribution of the infusion number at first event (1st, 2nd, >2 administrations) by calendar year/era for each product.

Prevent reverse-causation in IMM and premedication classification. To avoid misclassifying patients as receiving immunomodulator (IMM) co-therapy when IMM initiation occurs after pegloticase initiation (and potentially in response to an early infusion reaction), we will evaluate alternative exposure definitions that ensure the co-

therapy (or prophylaxis proxy) is present before the infusion being evaluated. we will re-define IMM co-therapy using pre-index exposure only, requiring evidence of IMM dispensing/administration during days −90 through 0 relative to the pegloticase index date (inclusive).

9.7.2.3.1 Subgroup Analysis

Not available.

8.7.2.3.2 Stratified Analysis

We will stratify patients by the following covariates:

1. Age (<65 and 65 years of age and older)
2. Gender (male vs. female)
3. We will descriptively summarize the use of corticosteroids and antihistamines as peri-administration 'premedication proxies' for each product and calendar period. Premedication proxies will be defined using claims for systemic corticosteroids and/or antihistamines on day −7 or day 0 relative to each pegloticase infusion administration date. We will report the proportion of administrations with evidence of steroid use, antihistamine use, and both, by calendar year and vaccination era. If there are significant changes in the utilization patterns of systemic corticosteroids and/or antihistamine, we will stratify patients by the status of premedication.

9.7.2.3.2 Sensitivity Analysis for Residual Confounding and Bias

Not applicable

9.7.2.3.3 Other Sensitivity Analysis

Not applicable

9.7.3 Analysis of Safety Endpoints

As described in Section 9.3.2, the safety endpoints include:

- Annual incidence rates of anaphylaxis or anaphylactoid reactions, which will be identified using validated claims algorithms, based on a combination of International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes and procedure codes in inpatient and/or ED visits claims (details in Section 9.3.2).
- Annual incidence rates of CVE, which will be a composite outcome including AMI or stroke. These events will be identified using inpatient diagnosis codes.

- Annual incidence rates of hospitalization for heart failure.
- All-cause mortality.

For each of these end points, we will calculate IRRs to compare prespecified periods (e.g., intra- vs pre-vaccine; post- vs intra-vaccine).

Details on the analysis of these safety outcomes have been outlined in ***Section 9.7.2***.

9.8 Quality Control

Programs will be developed and maintained, and output will be verified in accordance with current quality control procedures. Statistical analyses of this project will be conducted by two biostatisticians and crosschecked for quality assurance.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

This retrospective analysis relies on administrative claims data, which are subject to potential misclassification due to coding inaccuracies. Specific considerations include:

Exposure Misclassification: Pegloticase, rituximab, pegaspargase and PLD will be identified via HCPCS J-codes; miscoding is unlikely but possible.

Outcome Misclassification: Diagnostic-code–based identification of anaphylaxis and cardiovascular events in claims data is subject to misclassification, particularly for milder events or those managed exclusively in outpatient settings. In a Mini-Sentinel validation study, physician adjudicators confirmed 77 true anaphylaxis cases among 122 medical records flagged by ICD-9-CM diagnosis and procedure codes, yielding a positive predictive value (PPV) of 63.1% (95% CI: 53.9–71.7%) (Walsh, Cutrona et al. 2013). A systematic review of validated anaphylaxis algorithms in administrative data likewise reported modest performance; for example, the most specific ICD-9-CM code—995.0 (“anaphylactic shock”)—demonstrated PPVs of approximately 55–57% across studies (Schneider, Kachroo et al. 2012). Taken together, prior evidence suggests that claims-based definitions generally achieve moderate validity (PPV ~55–65%) for identifying anaphylaxis. While this reflects the best available approach for large-scale observational research, some degree of outcome misclassification is expected and will be considered when interpreting study findings.

Only inpatient or ED-coded severe reactions will be considered to enhance specificity. However, severe infusion reactions are our main interests, and the identification is based

on published claims-based algorithms (i.e., the FDA Sentinel definitions), which ensures the validity of our case definition of severe reactions.

Timing Accuracy: Infusion reaction timing may be misaligned if infusion and reaction claims are billed on separate service dates. We will use a 0–2-day window to mitigate this.

9.9.1.2 Information Bias

Information bias may occur if clinical monitoring intensity or coding practices changed during the pandemic period. However, substantial shifts in coding sensitivity for anaphylaxis or pegloticase administration are not expected, as these events are typically captured consistently across care settings. As described in our methodology, we will use rituximab as a negative-control comparator to detect background shifts in infusion-related reporting or coding unrelated to pegloticase. In addition, we will examine temporal trends in unrelated infusion-reaction diagnoses to identify any systematic changes in coding behavior over time. Our primary outcome definition relies on hospital and emergency department encounters for acute events, which are less vulnerable to differential coding by era and therefore reduce the risk of information bias.

9.9.1.3 Selection Bias

Selection bias may arise if the characteristics of patients initiating pegloticase changed over time, particularly in relation to COVID-19–related disruptions in healthcare access. However, there is no evidence to suggest that patients initiating pegloticase during the pandemic differed meaningfully in gout severity compared with earlier periods. A more relevant concern is the evolving use of immunomodulators: following FDA approval in 2022 of methotrexate co-therapy with pegloticase, increasing adoption of immunomodulator use after 2020 could confound temporal trends in infusion-reaction rates. To address this, we will stratify analyses into two cohorts as described in the study design—pegloticase with immunomodulator co-therapy versus pegloticase monotherapy—allowing us to isolate time-related changes in patient selection from treatment-related effects.

9.9.1.4 Confounding

Because this study compares incidence rates of severe infusion reactions across calendar periods, potential confounding may arise from factors that vary over time and are independently associated with outcomes. However, meaningful shifts in the underlying characteristics of patients eligible for pegloticase are not expected, as the

indication and clinical profile of refractory gout have remained stable over the study period. Additionally, although healthcare utilization changed during the COVID-19 pandemic, pegloticase is administered exclusively in infusion centers, and the severe outcomes of interest—anaphylaxis, cardiovascular events, and heart-failure–related hospitalizations—require emergency or inpatient care, for which access and coding practices have remained relatively consistent.

The primary time-varying factor relevant to confounding is the increasing adoption of immunomodulator co-therapy, which substantially reduces infusion-reaction risk and could influence temporal patterns. To address this, as described in our study design and methodology, we will focus on patients with pegloticase + IMM co-therapy for the primary analysis, and those with pegloticase monotherapy for the sensitivity analysis. Standard baseline covariates (demographics, comorbidities, medication use, and prior healthcare utilization) will also be measured to account for any residual differences across periods. Comparator analyses with rituximab, pegaspargase and PLD will help contextualize whether observed trends are specific to pegloticase or reflect broader secular patterns.

An important unmeasurable confounding factor relates to COVID-19 vaccination details. Prior evidence suggests that the risk of infusion reactions may be higher when vaccination occurs closer to the infusion date; however, the exact timing of COVID-19 vaccination relative to infusion is not captured in our data. Moreover, administrative claims data alone have been shown to substantially under-capture COVID-19 vaccine administrations particularly in 2021 and early 2022, as many doses are delivered in settings that do not generate insurance claims. For example, the Centers for Medicare & Medicaid Services (CMS) reported that Medicare claims data reflect only approximately half of actual COVID-19 vaccine receipt when compared with CDC vaccination counts ((CMS) 2021).

9.9.2 External Validity of Study Design

Our study will utilize Optum Market Clarity data only. Results from this study will reflect the experience of Optum enrollees with gout who received a ULT. Our findings may not generalize to other populations (e.g., those who are uninsured or those with public health insurance).

9.9.3 Analysis Limitations

The main limitation of this study is that exposure to COVID-19 vaccination is not directly measured, and the era-based approach is therefore subject to ecologic exposure misclassification. As a result, observed differences (or lack of differences) across eras cannot be interpreted as definitive evidence for or against an individual-level causal effect of vaccination on infusion reaction risk. Any true association could be diluted by incomplete vaccination uptake, heterogeneity in vaccine type and timing relative to infusion, and temporal changes in case mix, infusion practices, and outcome capture.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Limitations are not anticipated.

9.10 Other Aspects

Not applicable.

10. Protection of Human Subjects

The data used for this study will not involve the interaction with or interview of any subjects and the data does not include any individually identifiable data. All database records are de-identified and fully compliant with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

Research materials for this study will include de-identified claims data. Data to be collected includes information on patient demographics and medical care received in the past. All data will be maintained on secure servers. No data will be downloaded to local computers or removable media for any reason. Individual project folder access is limited to individuals who are approved to access the data.

As mentioned above, this study will only use de-identified data and comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omit subject identification.

10.1 Informed Consent

This is a retrospective cohort study using secondary data housed in CfOR. Since no primary data collection will occur, informed consent is not required.

10.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

This is a retrospective cohort study using secondary data housed in CfOR. Since no primary data collection will occur, Institutional Review Board approval is not required.

10.3 Patient Confidentiality

All data to be used in this study are de-identified and fully HIPAA compliant.

10.4 Participants Decision to Withdraw

Not applicable.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints (PCs)

This study is analyzing secondary data from the Optum Market Clarity closed claims data housed by Amgen CfOR. The outcomes that are listed in section Outcome Assessment 9.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as annual incidence rates and incidence rate ratios when comparing calendar years. See section Outcome Assessment 9.3.2 for outcomes and definitions.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. Amgen reserves the right to terminate the study at any time.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

We will submit this work for peer-reviewed publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

1. Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the

work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Not applicable

15. References

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16. Appendices

[Do not include the Declaration of Helsinki. Provide applicable regulations and guidelines separately to the investigating staff.]

Appendix A. List of Stand-alone Documents

None.

Appendix B. Summary of Preliminary Data Analysis of Annual Infusion Reaction Rates of Rituximab and Pegaspargase using Sentinel Module

Allergy or adverse event incidence rates among patients treated with Rituximab enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort by Year	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
2017	2,521	54	585	9.23 (6.77,11.69)
2018	2,939	58	697	8.33 (6.18,10.47)
2019	3,289	76	744	10.21 (7.91,12.50)
2020	3,111	77	681	11.31 (8.78,13.83)
2021	3,306	50	766	6.52 (4.72,8.33)
2022	3,507	47	821	5.73 (4.09,7.36)
2023	3,703	71	872	8.14 (6.25,10.03)
2024	4,184	93	962	9.67 (7.70,11.63)

Cardiovascular event incidence rates among patients treated with Rituximab enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort by Year	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
2017	2,378	46	558	8.24 (5.86,10.62)
2018	2,752	53	656	8.08 (5.91,10.26)
2019	3,065	64	698	9.17 (6.92,11.42)
2020	2,895	71	648	10.95 (8.40,13.50)
2021	3,087	73	722	10.12 (7.80,12.44)
2022	3,251	56	776	7.22 (5.33,9.11)
2023	3,428	79	811	9.75 (7.60,11.90)
2024	3,807	86	893	9.636 (7.599,11.672)

Anaphylaxis or anaphylactoid reaction incidence rates among patients treated with Rituximab enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort by Year	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
Any care setting				
2017	2,556	1	602	0.166 (0.015,0.775)
2018	2,998	1	719	0.139 (0.013,0.649)
2019	3,317	1	762	0.131 (0.012,0.612)
2020	3,163	0	705	--
2021	3,337	1	783	0.128 (0.012,0.596)
2022	3,552	3	839	0.358 (0.099,0.954)
2023	3,752	2	893	0.224 (0.045,0.718)
2024	4,228	2	987	0.203 (0.040,0.649)

Allergy or adverse event incidence rates among patients treated with Pegaspargase enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
2017	74	6	12	50.9 (21.2,105.0)
2018	72	8	15	54.7 (25.8,103.2)
2019	70	5	13	38.5 (14.6,84.5)
2020	85	6	19	31.6 (13.1,65.1)
2021	69	5	13	39.4 (14.9,86.3)
2022	56	3	9	33.2 (9.2,88.5)
2023	15	0	2	--
2024	7	0	2	--

Cardiovascular event incidence rates among patients treated with Pegaspargase enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
2017	78	1	14	7.32 (0.66,34.12)
2018	73	2	15	13.38 (2.67,42.90)
2019	71	3	14	20.9 (5.8,55.7)
2020	84	0	20	--
2021	73	0	14	--
2022	58	1	10	9.88 (0.90,46.06)
2023	18	0	2	--
2024	8	0	2	--

Anaphylaxis or anaphylactoid reaction incidence rates among patients treated with Pegaspargase enrolled in Optum 01/01/2017 – 12/31/2024				
Cohort	**Eligible Members**	**Members with Diagnosis**	**Person-Years**	**Rate (95% CI) per 100 PYs**
Any care setting				
2017	79	0	14	--
2018	76	0	16	--
2019	75	1	16	6.19 (0.56,28.88)
2020	90	0	21	--
2021	76	0	15	--
2022	60	0	10	--
2023	18	0	2	--
2024	8	0	2	--

Appendix C. Summary of ICD-10-CM Codes for Tophi

ICD-10	M1A00X1	Idiopathic chronic gout, unspecified site, with tophus (tophi)
ICD-10	M1A0111	Idiopathic chronic gout, right shoulder, with tophus (tophi)
ICD-10	M1A0121	Idiopathic chronic gout, left shoulder, with tophus (tophi)
ICD-10	M1A0191	Idiopathic chronic gout, unspecified shoulder, with tophus (tophi)
ICD-10	M1A0211	Idiopathic chronic gout, right elbow, with tophus (tophi)
ICD-10	M1A0221	Idiopathic chronic gout, left elbow, with tophus (tophi)
ICD-10	M1A0291	Idiopathic chronic gout, unspecified elbow, with tophus (tophi)
ICD-10	M1A0311	Idiopathic chronic gout, right wrist, with tophus (tophi)
ICD-10	M1A0321	Idiopathic chronic gout, left wrist, with tophus (tophi)
ICD-10	M1A0391	Idiopathic chronic gout, unspecified wrist, with tophus (tophi)
ICD-10	M1A0411	Idiopathic chronic gout, right hand, with tophus (tophi)
ICD-10	M1A0421	Idiopathic chronic gout, left hand, with tophus (tophi)
ICD-10	M1A0491	Idiopathic chronic gout, unspecified hand, with tophus (tophi)
ICD-10	M1A0511	Idiopathic chronic gout, right hip, with tophus (tophi)
ICD-10	M1A0521	Idiopathic chronic gout, left hip, with tophus (tophi)
ICD-10	M1A0591	Idiopathic chronic gout, unspecified hip, with tophus (tophi)
ICD-10	M1A0611	Idiopathic chronic gout, right knee, with tophus (tophi)
ICD-10	M1A0621	Idiopathic chronic gout, left knee, with tophus (tophi)
ICD-10	M1A0691	Idiopathic chronic gout, unspecified knee, with tophus (tophi)
ICD-10	M1A0711	Idiopathic chronic gout, right ankle and foot, with tophus (tophi)
ICD-10	M1A0721	Idiopathic chronic gout, left ankle and foot, with tophus (tophi)
ICD-10	M1A0791	Idiopathic chronic gout, unspecified ankle and foot, with tophus (tophi)
ICD-10	M1A08X1	Idiopathic chronic gout, vertebrae, with tophus (tophi)
ICD-10	M1A09X1	Idiopathic chronic gout, multiple sites, with tophus (tophi)
ICD-10	M1A10X1	Lead-induced chronic gout, unspecified site, with tophus (tophi)
ICD-10	M1A1111	Lead-induced chronic gout, right shoulder, with tophus (tophi)
ICD-10	M1A1121	Lead-induced chronic gout, left shoulder, with tophus (tophi)
ICD-10	M1A1191	Lead-induced chronic gout, unspecified shoulder, with tophus (tophi)
ICD-10	M1A1211	Lead-induced chronic gout, right elbow, with tophus (tophi)
ICD-10	M1A1221	Lead-induced chronic gout, left elbow, with tophus (tophi)

ICD-10	M1A1291	Lead-induced chronic gout, unspecified elbow, with tophus (tophi)
ICD-10	M1A1311	Lead-induced chronic gout, right wrist, with tophus (tophi)
ICD-10	M1A1321	Lead-induced chronic gout, left wrist, with tophus (tophi)
ICD-10	M1A1391	Lead-induced chronic gout, unspecified wrist, with tophus (tophi)
ICD-10	M1A1411	Lead-induced chronic gout, right hand, with tophus (tophi)
ICD-10	M1A1421	Lead-induced chronic gout, left hand, with tophus (tophi)
ICD-10	M1A1491	Lead-induced chronic gout, unspecified hand, with tophus (tophi)
ICD-10	M1A1511	Lead-induced chronic gout, right hip, with tophus (tophi)
ICD-10	M1A1521	Lead-induced chronic gout, left hip, with tophus (tophi)
ICD-10	M1A1591	Lead-induced chronic gout, unspecified hip, with tophus (tophi)
ICD-10	M1A1611	Lead-induced chronic gout, right knee, with tophus (tophi)
ICD-10	M1A1621	Lead-induced chronic gout, left knee, with tophus (tophi)
ICD-10	M1A1691	Lead-induced chronic gout, unspecified knee, with tophus (tophi)
ICD-10	M1A1711	Lead-induced chronic gout, right ankle and foot, with tophus (tophi)
ICD-10	M1A1721	Lead-induced chronic gout, left ankle and foot, with tophus (tophi)
ICD-10	M1A1791	Lead-induced chronic gout, unspecified ankle and foot, with tophus (tophi)
ICD-10	M1A18X1	Lead-induced chronic gout, vertebrae, with tophus (tophi)
ICD-10	M1A19X1	Lead-induced chronic gout, multiple sites, with tophus (tophi)
ICD-10	M1A20X1	Drug-induced chronic gout, unspecified site, with tophus (tophi)
ICD-10	M1A2111	Drug-induced chronic gout, right shoulder, with tophus (tophi)
ICD-10	M1A2121	Drug-induced chronic gout, left shoulder, with tophus (tophi)
ICD-10	M1A2191	Drug-induced chronic gout, unspecified shoulder, with tophus (tophi)
ICD-10	M1A2211	Drug-induced chronic gout, right elbow, with tophus (tophi)
ICD-10	M1A2221	Drug-induced chronic gout, left elbow, with tophus (tophi)
ICD-10	M1A2291	Drug-induced chronic gout, unspecified elbow, with tophus (tophi)
ICD-10	M1A2311	Drug-induced chronic gout, right wrist, with tophus (tophi)
ICD-10	M1A2321	Drug-induced chronic gout, left wrist, with tophus (tophi)
ICD-10	M1A2391	Drug-induced chronic gout, unspecified wrist, with tophus (tophi)

ICD-10	M1A2411	Drug-induced chronic gout, right hand, with tophus (tophi)
ICD-10	M1A2421	Drug-induced chronic gout, left hand, with tophus (tophi)
ICD-10	M1A2491	Drug-induced chronic gout, unspecified hand, with tophus (tophi)
ICD-10	M1A2511	Drug-induced chronic gout, right hip, with tophus (tophi)
ICD-10	M1A2521	Drug-induced chronic gout, left hip, with tophus (tophi)
ICD-10	M1A2591	Drug-induced chronic gout, unspecified hip, with tophus (tophi)
ICD-10	M1A2611	Drug-induced chronic gout, right knee, with tophus (tophi)
ICD-10	M1A2621	Drug-induced chronic gout, left knee, with tophus (tophi)
ICD-10	M1A2691	Drug-induced chronic gout, unspecified knee, with tophus (tophi)
ICD-10	M1A2711	Drug-induced chronic gout, right ankle and foot, with tophus (tophi)
ICD-10	M1A2721	Drug-induced chronic gout, left ankle and foot, with tophus (tophi)
ICD-10	M1A2791	Drug-induced chronic gout, unspecified ankle and foot, with tophus (tophi)
ICD-10	M1A28X1	Drug-induced chronic gout, vertebrae, with tophus (tophi)
ICD-10	M1A29X1	Drug-induced chronic gout, multiple sites, with tophus (tophi)
ICD-10	M1A30X1	Chronic gout due to renal impairment, unspecified site, with tophus (tophi)
ICD-10	M1A3111	Chronic gout due to renal impairment, right shoulder, with tophus (tophi)
ICD-10	M1A3121	Chronic gout due to renal impairment, left shoulder, with tophus (tophi)
ICD-10	M1A3191	Chronic gout due to renal impairment, unspecified shoulder, with tophus (tophi)
ICD-10	M1A3211	Chronic gout due to renal impairment, right elbow, with tophus (tophi)
ICD-10	M1A3221	Chronic gout due to renal impairment, left elbow, with tophus (tophi)
ICD-10	M1A3291	Chronic gout due to renal impairment, unspecified elbow, with tophus (tophi)
ICD-10	M1A3311	Chronic gout due to renal impairment, right wrist, with tophus (tophi)
ICD-10	M1A3321	Chronic gout due to renal impairment, left wrist, with tophus (tophi)
ICD-10	M1A3391	Chronic gout due to renal impairment, unspecified wrist, with tophus (tophi)
ICD-10	M1A3411	Chronic gout due to renal impairment, right hand, with tophus (tophi)
ICD-10	M1A3421	Chronic gout due to renal impairment, left hand, with tophus (tophi)
ICD-10	M1A3491	Chronic gout due to renal impairment, unspecified hand, with tophus (tophi)

ICD-10	M1A3511	Chronic gout due to renal impairment, right hip, with tophus (tophi)
ICD-10	M1A3521	Chronic gout due to renal impairment, left hip, with tophus (tophi)
ICD-10	M1A3591	Chronic gout due to renal impairment, unspecified hip, with tophus (tophi)
ICD-10	M1A3611	Chronic gout due to renal impairment, right knee, with tophus (tophi)
ICD-10	M1A3621	Chronic gout due to renal impairment, left knee, with tophus (tophi)
ICD-10	M1A3691	Chronic gout due to renal impairment, unspecified knee, with tophus (tophi)
ICD-10	M1A3711	Chronic gout due to renal impairment, right ankle and foot, with tophus (tophi)
ICD-10	M1A3721	Chronic gout due to renal impairment, left ankle and foot, with tophus (tophi)
ICD-10	M1A3791	Chronic gout due to renal impairment, unspecified ankle and foot, with tophus (tophi)
ICD-10	M1A38X1	Chronic gout due to renal impairment, vertebrae, with tophus (tophi)
ICD-10	M1A39X1	Chronic gout due to renal impairment, multiple sites, with tophus (tophi)
ICD-10	M1A40X1	Other secondary chronic gout, unspecified site, with tophus (tophi)
ICD-10	M1A4111	Other secondary chronic gout, right shoulder, with tophus (tophi)
ICD-10	M1A4121	Other secondary chronic gout, left shoulder, with tophus (tophi)
ICD-10	M1A4191	Other secondary chronic gout, unspecified shoulder, with tophus (tophi)
ICD-10	M1A4211	Other secondary chronic gout, right elbow, with tophus (tophi)
ICD-10	M1A4221	Other secondary chronic gout, left elbow, with tophus (tophi)
ICD-10	M1A4291	Other secondary chronic gout, unspecified elbow, with tophus (tophi)
ICD-10	M1A4311	Other secondary chronic gout, right wrist, with tophus (tophi)
ICD-10	M1A4321	Other secondary chronic gout, left wrist, with tophus (tophi)
ICD-10	M1A4391	Other secondary chronic gout, unspecified wrist, with tophus (tophi)
ICD-10	M1A4411	Other secondary chronic gout, right hand, with tophus (tophi)
ICD-10	M1A4421	Other secondary chronic gout, left hand, with tophus (tophi)
ICD-10	M1A4491	Other secondary chronic gout, unspecified hand, with tophus (tophi)
ICD-10	M1A4511	Other secondary chronic gout, right hip, with tophus (tophi)

ICD-10	M1A4521	Other secondary chronic gout, left hip, with tophus (tophi)
ICD-10	M1A4591	Other secondary chronic gout, unspecified hip, with tophus (tophi)
ICD-10	M1A4611	Other secondary chronic gout, right knee, with tophus (tophi)
ICD-10	M1A4621	Other secondary chronic gout, left knee, with tophus (tophi)
ICD-10	M1A4691	Other secondary chronic gout, unspecified knee, with tophus (tophi)
ICD-10	M1A4711	Other secondary chronic gout, right ankle and foot, with tophus (tophi)
ICD-10	M1A4721	Other secondary chronic gout, left ankle and foot, with tophus (tophi)
ICD-10	M1A4791	Other secondary chronic gout, unspecified ankle and foot, with tophus (tophi)
ICD-10	M1A48X1	Other secondary chronic gout, vertebrae, with tophus (tophi)
ICD-10	M1A49X1	Other secondary chronic gout, multiple sites, with tophus (tophi)
ICD-10	M1A9XX1	Chronic gout, unspecified, with tophus (tophi)