Summary Table of Study Protocol

Title	Burden of Illness Among Patients with Gout and Treated with Pegloticase
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EU Post Authorization Study (PAS) Register No	N/A
Active Substance	KRYSTEXXA® (pegloticase)
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Device	N/A
Product Reference	N/A
Procedure Number	
Joint PASS	NO
Research Question and Objectives	The study objectives are: • To describe patient characteristics of a sample of patients with gout who initiate pegloticase treatment • To examine treatment patterns among a sample of patients with gout pre- and post-pegloticase initiation • To assess rates of gout flares pre- and post-pegloticase initiation • To assess gout- and flare-related healthcare resource utilization and costs among a sample of patients pre- and post-pegloticase initiation
Country of Study	United States
Author	Amgen: PPD Inovalon: PPD AVP, HEOR, PPD PPD , Senior Director, HEOR, PPD PPD , Senior Manager, HEOR, PPD

Marketing Authorization Holder

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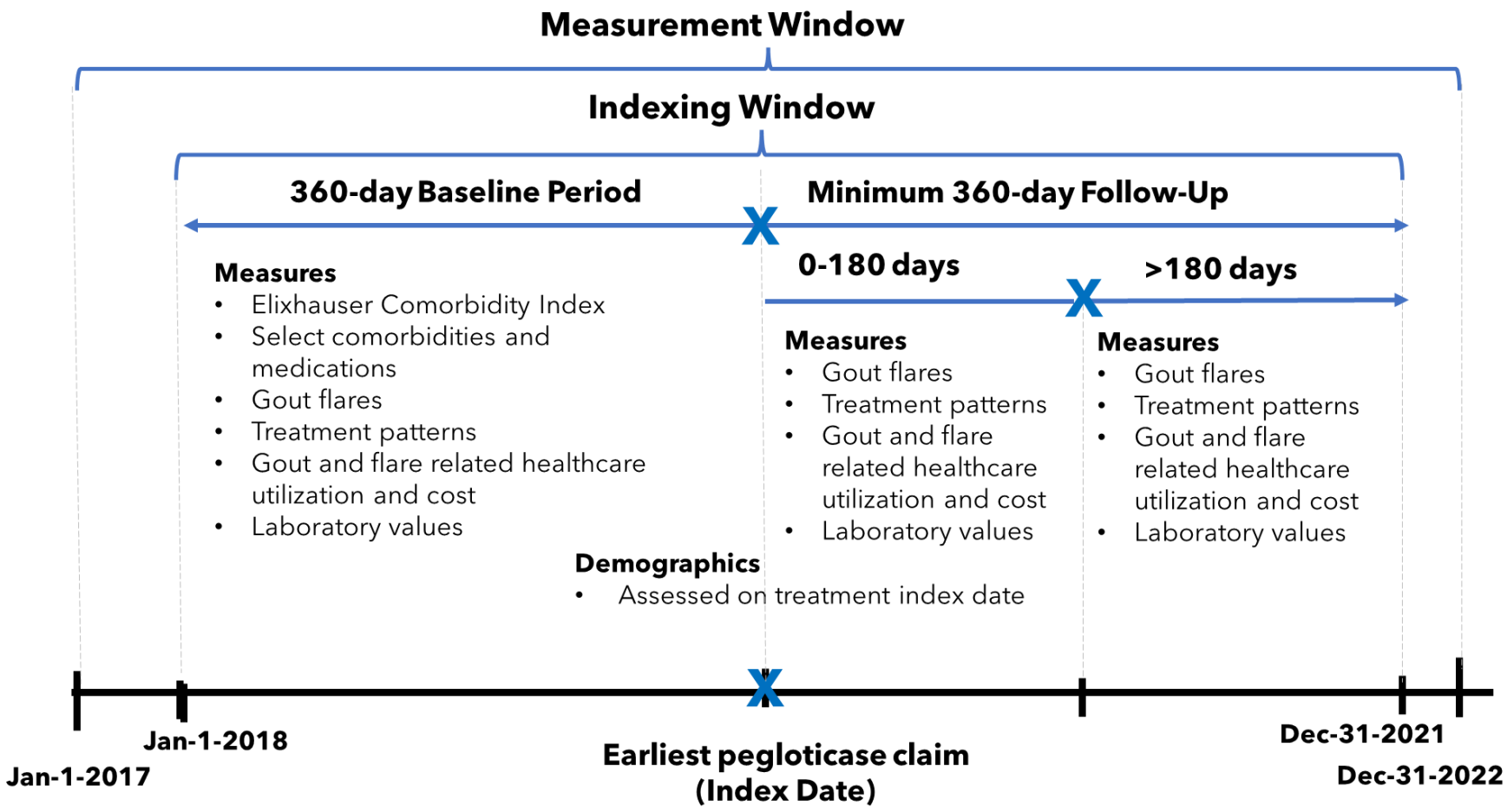
This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Proper Version Numbering and Dating

Protocol Version	Date of Protocol	Page Header Date
Original, Version 1.0		

Confidentiality Notice

Study Design Schema



1. Table of Contents

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2. List of Abbreviations

ED	Emergency department
eGFR	Estimated glomerular filtration rate
FDA	US Food and Drug Administration
FFS	Fee-for-Service
GC	Glucocorticoid
HCPCS	Healthcare Common Procedure Coding System
HCRU	Healthcare resource utilization
ICJME	International Committee of Medical Journal Editors
LOS	Length of stay
NDC	National Drug Codes
PDD	Prednisone-equivalent daily dose
QC	Quality control
SD	Standard deviation

3. Responsible Parties

Amgen:

PPD

Inovalon:

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4. Abstract

Study Title

Burden of Illness Among Patients with Gout and Treated with Pegloticase

Study Background and Rationale

In the United States, recent estimates indicate that up to 5.2% of the adult population is affected by gout[1,2] with a rise in prevalence occurring due to increasing obesity rates, dietary factors, and metabolic syndrome.[3] Annual healthcare costs for gout patients

range from $11,839 (patients with 0-1 flares) to $14,842 (patients with 3+ flares), with costs driven primarily by ambulatory and inpatient costs.[4]

Long-term management aims to prevent painful flares and complications by maintaining serum urate levels below the saturation point for crystal formation.[5] This is achieved through urate-lowering therapies (ULT).[6] Adherence to ULT is critical for effective gout management, but many patients struggle with medication adherence due to side effects, complex dosing regimens, and misconceptions about the chronic nature of the disease.[7] Patients who do not respond to traditional ULT have the option of pegloticase (KRYSTEXXA®) as a third-line treatment for severe, treatment-refractory, chronic gout.[8]

To support both the ongoing value of pegloticase given the scarcity of recent data on gout and flare-related healthcare utilization and costs, this retrospective database study will leverage Inovalon's MORE^2 Registry®, the 100% Medicare Fee-for-Service (FFS) claims database, and the Norstella Laboratory database.

Study Feasibility and Futility Considerations

A feasibility analysis identified 4,526 patients with gout and at least one pegloticase pharmacy claim in the 100% Medicare FFS and Inovalon MORE^2 Registry® databases since 1 January 2017. An overlap analysis revealed that approximately 50% of pegloticase-treated gout patients identified in the MORE^2 Registry or Medicare FFS database had at least one estimated glomerular filtration rate (eGFR) test result in the Norstella laboratory database.

Research Question and Objective(s)

Objectives	Endpoints
Primary	
• To describe patient characteristics of a sample of patients with gout who initiate pegloticase treatment	• Descriptive analysis of patient demographics (e.g. age, gender, race/ethnicity) and baseline clinical characteristics (e.g. Elixhauser Comorbidity Score [ECI], comorbid conditions, and concurrent medications) • Laboratory values (serum urate and eGFR) in the pegloticase baseline (pre-pegloticase initiation) period, pegloticase follow-up period 1 and pegloticase follow-up period 2 (see Table 2 for details)
• To examine treatment patterns among a sample of patients and compare select treatment patterns (opioid use, glucocorticoid use, and prednisone equivalent daily dose) pre- and post-pegloticase initiation	• Treatment patterns during the pegloticase baseline period (pre-pegloticase initiation), pegloticase follow-up period 1 and pegloticase follow-up period 2 (see Table 2 for details): o Opioid use o Glucocorticoid use o Prednisone equivalent daily dose (PDD) • Other treatment patterns: o Duration of pegloticase treatment o Total number of pegloticase claims o Patients who receive monotherapy o Patients who receive any combination therapy o Patients who receive methotrexate combination therapy
• To assess rates of gout flares pre- and post-pegloticase initiation	• Total number of flares and the count and proportion of patients with 1 flare, 2 flares and 3+ flares in the pegloticase baseline (pre-pegloticase initiation) period, pegloticase follow-up period 1 and pegloticase follow-up (post-pegloticase initiation) period 2 (see Table 2 for details) • Time from treatment index date to first observed flare • Rate of flares per person-time over the pegloticase baseline (pre-pegloticase initiation) period, pegloticase follow-up period 1 and pegloticase follow-up (post-pegloticase initiation) period 2 (see Table 2 for details)

• To assess gout- and flare-related healthcare resource utilization and costs among a sample of patients pre- and post-pegloticase initiation	• Gout- and flare-related estimates of healthcare resource use (HCRU) and associated costs will be reported overall and by service use categories in the pegloticase baseline (pre-pegloticase initiation) period, pegloticase follow-up period 1 and pegloticase follow-up period 2 (see Table 2 for details)

Hypothesis(es)/Estimation

This retrospective study will be descriptive in nature and will include a pre/post comparison of outcomes (gout flares, laboratory values, and HCRU and cost) between pre-and post- pegloticase periods (see Table 2 for details). Non-parametric tests for paired data (e.g., Wilcoxan signed rank) will be used to compare the number of gout flares, person-time gout flare rate, number of HCRU visits and cost between the pegloticase baseline and pegloticase follow-up periods (see Table 2 for details). McNemar's tests will be used to compare the count of patients with gout flare and the count of patients with at least one HCRU visit between pre- and post- pegloticase periods (see Table 2 for details).

Study Design/Type

This retrospective cohort study will describe patient characteristics and treatment patterns and compare gout flares, laboratory measures, and HCRU and cost between the pre- and post- pegloticase initiation periods (see Table 2 for details) among gout patients in a real-world setting using administrative claims data from the MORE^2 Registry® and the 100% Medicare FFS database.

Study Population or Data Resource

Adults diagnosed with gout who were treated with pegloticase between January 1, 2018 and December 31, 2021 will be included. The date of the first pegloticase claim during the identification period will be set as the treatment index date.

Summary of Patient Eligibility Criteria

Inclusion criteria:

- Patients with an ICD-10-CM diagnosis code for gout (M10.0*[a]) in the primary position on ≥ 1 inpatient claim or any position on ≥ 2 outpatient claims (> 30 days apart) within 360 days between January 1, 2018 and December 31, 2021

[a] Includes all ICD-10-CM diagnosis codes that start with M10.0

- ≥1 claim with an NDC or HCPCS for pegloticase following the first observed diagnosis for gout between January 1, 2018 and December 31, 2021
    - The earliest pegloticase claim will be set as the treatment index date
- Use of pegloticase for a minimum of 6 infusions (approximately 90 days)
    - If sample size permits, the minimum time on pegloticase may be increased to 12 or 24 infusions *(approximately 180 to 360- days)*
- ≥360 days of continuous enrollment with clinical and pharmacy benefits preceding the treatment index date
- ≥360 days of continuous enrollment with clinical and pharmacy benefits following the treatment index date
- Age ≥ 18 years on the treatment index date

Measurement Periods

The measurement periods to compare treatment patterns, gout flares, laboratory values, and gout and flare related HCRU and cost will be the pre- and post- pegloticase initiation periods (see Table 2 for details). Treatment patterns, gout flares, and laboratory values will also be measured during the pegloticase follow-up period (see Table 2 for details).

Variables

Outcome Variables

To meet the primary objectives, baseline patient characteristics, treatment patterns (opioid use, glucocorticoid use, prednisone equivalent daily dose [PDD], and other gout related treatments), gout flares, laboratory values and economic outcomes (HCRU and cost) will be described across all time periods (see Table 2 for details). Additionally, gout flares, laboratory values, gout- and flare related economic outcomes will be compared between pre- and post- pegloticase baseline and pegloticase follow-up periods (see Table 2 for details).

All clinical characteristics, gout flares, and treatments will be identified using a combination of ICD-10 diagnosis codes, NDC or HCPCS drug codes, ICD-10-PCS procedure codes, and CPT codes. Additionally, laboratory results (e.g. serum urate, eGFR) will be assessed among a subset of patients for whom data is available. Details of outcome definitions may be found in Sections 8.3.2 and 8.3.3.2.

Exposure Variables

Initiators of pegloticase therapy identified using NDC and HCPCS codes (see Appendix A for details) will be considered exposed.

Other Covariates

Patient demographics (e.g. age, sex) will be measured on the index date. Clinical characteristics (e.g. comorbidities) will be measured during the 360-day pegloticase baseline period. Details of covariates are described in Section 8.3.3 and specific codes can be found in Appendix A.

Study Sample Size

Please refer to the feasibility results presented under Section 6.3 “Study Feasibility and Futility Considerations”.

Data Analysis

All outcomes will be evaluated for the overall cohort and by payer (sample size permitting) for the pegloticase baseline and pegloticase follow-up periods (see Table 2 for details). This will be a descriptive analysis using administrative claims and laboratory databases. Summary statistics for continuous variables (mean, standard deviation (SD) and median) will be calculated. For categorical variables, the frequency and percentage will be provided. Laboratory results will be analyzed and presented based on their availability in the Norstella laboratory database. Only a subset of the total study cohort will have an available link to the Norstella laboratory database. Comparative statistics will be calculated when comparing outcomes (gout flares, economic outcomes, and laboratory values) between pre- and post- pegloticase initiation periods (see Table 2 for details) and will include non-parametric paired tests for continuous variables and McNemar’s tests for categorical variables.