Title: Drug Utilization Study to Describe the Pattern of Febuxostat Use in Relationship to Allopurinol Following Addition of the Boxed Warning and Modification of the Indication Based on the Results of the CARES Trial

EUPAS Number: 40179

Protocol Approve Date: 10 August 2020

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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TAKEDA PHARMACEUTICALS

NON-INTERVENTIONAL SAFETY STUDY

PROTOCOL

Study title: Drug Utilization Study to Describe the Pattern of Febuxostat Use in Relationship to Allopurinol Following Addition of the Boxed Warning and Modification of the Indication Based on the Results of the CARES Trial

Short title:	Febuxostat Drug Utilization Study		
Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	Febuxostat-5006		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	Febuxostat		
Date:	10 August 2020	**Amendment Number:**	2

Amendment History:

Date	Amendment Number	Amendment Type	Region
10 August 2020	2	Substantial	United States
27 February 2020	1.1	Nonsubstantial	United States
22 May 2019	Initial version	Not applicable	United States

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

Study title: Drug utilization study to describe the pattern of febuxostat use in relationship to allopurinol following addition of the boxed warning and modification of the indication based on the results of the CARES trial

Short title: Febuxostat drug utilization study

Study number: Febuxostat-5006

Amendment number: 2, 10 August 2020

Sponsor Signatory **Signature and date** (DD/Month/YYYY)

PPD

Investigator

PPD

1.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

2.0 LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADR	adverse drug reaction
AE	adverse event
CARES	Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities
CDM	Clinformatics DataMart
CV	cardiovascular
CVD	cardiovascular disease
DDI	drug-drug interaction
DSC	Drug Safety Communication
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, ninth revision, clinical modification
ICD-10	International Classification of Diseases, tenth revision
MACE	major adverse cardiac event
MI	myocardial infarction
NDC	National Drug Code
PI	Prescribing Information
PQI	product quality issue
SAE	serious adverse event
sNDA	supplemental New Drug Application
SOP	Standard Operating Procedure
SSR	special situation report
US	United States
ULT	urate lowering therapy
XO	xanthine oxidase

3.0 RESPONSIBLE PARTIES

Principal Investigator:

PPD

4.0 ABSTRACT

Title

Drug utilization study to describe the pattern of febuxostat use in relationship to allopurinol following addition of the boxed warning and modification of the indication based on the results of the CARES trial

Amendment 2, 10 August 2020

Rationale and Background

Gout is a complex, multifaceted metabolic disorder, and chronic condition. Control of hyperuricemia is the foundation of management of gout. Treatment options for hyperuricemia include xanthine oxidase (XO) inhibitors (allopurinol and febuxostat) that reduce uric acid production, uricosurics (probenecid) which increase uric acid excretion, and recombinant uricase (pegloticase) which metabolizes uric acid to the more soluble form allantoin and is usually reserved for patients with severe or treatment-refractory gout. In clinical practice in the United States (US), XO inhibitors are recommended first line urate lowering therapy (ULT), a role most often fulfilled with allopurinol, a purine analog.

Febuxostat, a non-purine XO inhibitor, was approved in February 2009 for the chronic management of hyperuricemia in patients with gout. A post-marketing cardiovascular outcomes study (CARES) found that, compared to allopurinol, febuxostat did not have an elevated risk for the primary endpoint of major adverse cardiac event (MACE) composite (cardiovascular [CV] death, nonfatal myocardial infarction [MI], nonfatal stroke, and unstable angina with urgent coronary revascularization) in patients with gout. However, CV mortality was more frequent in the febuxostat group than in the allopurinol group; the cause of CV mortality and the mechanism of action for this increased risk of CV death were not clear. Based on these results, on 21 February 2019, the US Food and Drug Administration (FDA) approved changes in febuxostat Prescribing Information (PI) and added a boxed warning on CV death and revised the indication to "patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable."

It is important to ensure prescribing of febuxostat is in accordance with the revised PI. Therefore, this drug utilization study examines the impact of changes to the PI on dispensing of febuxostat.

Research Question and Objectives

The research question of this cross-sectional non-interventional study is to evaluate the impact of the 2019 labeling changes (boxed warning and modified indication), based upon results of the CARES trial, on febuxostat utilization. The objectives of the study are:

1. To describe the number and proportion of patients initiating febuxostat as new users (ie, without previous allopurinol therapy) versus prevalent new users (ie, with previous allopurinol therapy) of ULT.
2. To describe the number and proportion of febuxostat users with established cardiovascular disease (CVD).

Study Design

Non-interventional cross-sectional descriptive study using 2 large US administrative claims databases.

Population

The study population is gout patients initiating febuxostat therapy on or after 01 June 2016. The date of initiating febuxostat is defined as the index fill date. Eligible patients must have filled at least one prescription for febuxostat, have at least one diagnosis of gout at any time in the patient's record, be age ≥21 years at index fill date, and have continuous enrollment for at least 12 months prior to the index fill date.

Variables

Exposure variable is initiation of febuxostat therapy. It is further categorized into new users (ie, without previous allopurinol therapy) of febuxostat, and prevalent new users (ie, with previous allopurinol therapy) of febuxostat.

Descriptive covariates are age group, sex, race, and selected established CVD including MI, unstable angina, hemorrhagic and ischemic strokes, transient ischemic attack, peripheral vascular disease, and diabetes mellitus with evidence of macrovascular or microvascular disease, and morbidities and selected medications of interest including XO substrates, ampicillin, amoxicillin, salicylates, dicumarol, probenecid, thiazide diuretics, chlorpropamide, cyclosporine, vidarabine, phenytoin, tolbutamide, and cytotoxic agents.

Data Sources

The Optum Clinformatics DataMart (CDM) including the Medicare Advantage administrative US claims database and the IQVIA PharMetrics Plus claims database.

Study Size

The study will include all patients in the claims databases who fulfill the inclusion criteria. Under a strict interpretation of the study inclusion criteria, which exclude patients who had use of febuxostat within 12 months prior to the index date, 11,683 patients who initiated febuxostat between June 2016 and September 2019 were identified in the IQVIA PharMetrics Plus database, of whom 4352 (37.2%) initiated febuxostat as new users and 7331 (62.8%) initiated

febuxostat as prevalent new users. Preliminary feasibility analysis of the Optum CDM identified 4268 patients initiating febuxostat between July 2016 and December 2017.

Data Analyses

Descriptive statistics (mean, standard deviation, median, range, temporal trends) will be used to describe the dispensing pattern of febuxostat. The analyses will examine dispensing in the following periods:

- Baseline period, covering the 18 months prior to FDA's Drug Safety Communication (DSC): 01 June 2016 to 15 November 2017.
- Intermediate period, from the DSC to the change in PI: 16 November 2017 to 21 February 2019.
- Post–labeling change period (final): 22 February 2019 to 30 April 2021.

5.0 PROTOCOL AMENDMENT 2 SUMMARY OF CHANGES

This section describes the changes in reference to the protocol incorporating Amendment 2. The primary reasons for this amendment are to:

- Add the IQVIA PharMetrics Plus claims database to the study in addition to the Optum CDM database (including the Medicare Advantage administrative US claims database).
- Update the preliminary feasibility analysis for the associated change to the overall sample size with the addition of the IQVIA PharMetrics Plus claims database.
- Correct the terminology for claims data information from "prescribing" to "dispensing" patterns; this drug utilization study will examine the impact of the changes to the PI on dispensing of febuxostat.
- Remove the post–labeling change period (interim), 22 February 2019 to 30 April 2020 (interim database refresh), and corresponding interim report.
- Revise Section 11.0 (Management and Reporting of Adverse Events) to align with updates to the sponsor's protocol template language.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol (v1.1, 27 February 2020)		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 4.0 Abstract Section 9.2 Setting Section 9.4 Data Sources Section 9.5 Study Size Section 9.9 Limitations of the Research Methods Section 10.0 Protection of Human Subjects	Addition of the IQVIA PharMetrics Plus claims database to the study with the previously included Optum CDM database (including the Medicare Advantage administrative US claims database).	To account for the low number of anticipated febuxostat initiators in the Optum CDM database (including the Medicare Advantage administrative US claims database), this study will also include the IQVIA PharMetrics Plus claims database. The overall sample size with both claims databases will provide adequate numbers of new initiators of febuxostat to allow stratification of results by age, sex, and race.
Section 4.0 Abstract Section 9.5 Study Size	Update to the preliminary feasibility analysis to include the anticipated number of febuxostat initiators (new users and prevalent new users) from the IQVIA PharMetrics Plus claims database.	This change is associated with the addition of the IQVIA PharMetrics Plus claims database *(see rationale above)*.

Footnotes on last page.

Protocol Amendment 2		
Summary of Changes Since the Last Version of the Approved Protocol (v1.1, 27 February 2020)		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 4.0 Abstract Section 7.0 Rationale and Background Section 9.7 Data Analysis	Correction of terminology for claims data information from "prescribing" to "dispensing" patterns.	Claims data provide information on dispensing patterns, and not prescribing patterns. The request to correct this error in terminology came from FDA.
Section 4.0 Abstract Section 6.0 Milestones Section 9.2.3 Study periods Section 9.5 Study Size Section 9.7 Data Analysis Section 12.0 Plans for Disseminating and Communicating Study Results Appendix B ENCePP Checklist	Removal of the post–labeling change period (interim), 22 February 2019 to 30 April 2020 (interim database refresh), and corresponding interim report.	Given the proximity of the timing of the protocol review and final study report due date, the sponsor has removed the interim report.
Section 11.0 Management and Reporting of AEs	Enhancement of language related to the management and reporting of AEs.	Modifications to align safety language with updates to the sponsor's protocol template.

AEs: adverse events; CDM: Clinformatics DataMart; FDA: Food and Drug Administration; US: United States.

6.0 MILESTONES

Milestone	Planned date
Draft protocol submission	May 2019
Final protocol submission	September 2019
Study completion date	February 2021
Final study report submission	June 2021

7.0 RATIONALE AND BACKGROUND

Gout is a complex, multifaceted metabolic disorder and chronic condition, where patients can experience several precipitating factors that can contribute to their symptoms of gout, particularly pain and other symptoms that can impact their quality of life. Based on the survey data from the National Health and Nutrition Examination Survey (NHANES) 2015 to 2016, approximately 9.2 million (3.9%) adults in the US are affected by gout, primarily middle-aged and older men and post-menopausal women [1]. The data from epidemiological studies suggest that the prevalence of gout has risen over the last few decades. While the incidence data are limited, data from the US suggests that the incidence of gout is also rising [2].

The diagnosis of gout is based on uric acid crystal accumulation in the joints, tissues, or body fluids, as well as on gouty attacks or flares characterized by intense pain, swelling, redness, and heat [3]. Hyperuricemia results from the accumulation of uric acid, the end product of purine metabolism, which possesses no physiological role. Hyperuricemia is defined as having a plasma or serum uric acid measurement ≥6.8 mg/dL, the limit of urate solubility, which signals a risk for gout through crystal formation and deposition.

Control of hyperuricemia is the foundation of gout management [4,5]. Treatment and prevention of gout traditionally involved anti-inflammatory medication for acute attacks (such as colchicine, corticosteroids, or nonsteroidal anti-inflammatory drugs), and ULT for long-term management of hyperuricemia and prevention of urate crystal-induced damage. To achieve the optimum treatment goals for gout, the American College of Rheumatology (ACR) gout guidelines recommend that a ULT include a target serum urate goal of <6.0 mg/dL for most gout patients, with a goal of <5.0 mg/dL in patients with tophaceous disease or more severe gout [6].

Overall, there are few ULTs available: XO inhibitors (allopurinol and febuxostat), uricosuric therapies (probenecid, sulfinpyrazone, and lesinurad), and uricase products (pegloticase). XO inhibitors reduce uric acid production and are consensus first line ULT per the ACR, a role most often fulfilled with allopurinol. Allopurinol has been on the market since the 1960s for management of patients with signs and symptoms of primary or secondary gout at a dose range of 100 to 800 mg daily. Febuxostat, a structurally unrelated non-purine XO inhibitor, went on market in February 2009 for chronic management of hyperuricemia in patients with gout at doses of 40 and 80 mg once daily (QD) [6,7]. Uricosuric therapies increase urinary acid excretion and uricase products break down uric acid. These therapies are considered second line treatments and have known safety concerns that limit their use. Uricase products in particular are reserved for patients who are refractory to conventional therapy.

In February 2009, febuxostat was approved with a Warning and Precaution for CV events in the PI, based on the numerical imbalance observed in the pooled analysis of the randomized phase 3 studies (APEX, FACT, and CONFIRMS). Upon approval of febuxostat, the FDA required a post-marketing (PMR 811-1) CV outcomes study to evaluate the CV safety of febuxostat.

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, was conducted to assess if febuxostat was noninferior to allopurinol for the primary endpoint of the MACE composite (CV death, nonfatal MI, nonfatal

stroke, and unstable angina with urgent coronary revascularization) in subjects with gout and a high CV risk profile. It was initiated in 2010 and completed in 2017. The study had a prespecified noninferiority margin of 1.3 for the hazard ratio (HR) for the primary endpoint. For the primary endpoint of MACE composite, CARES showed that febuxostat was noninferior to allopurinol (HR: 1.03; 95% CI: 0.87-1.23). When analyzing the individual components of MACE as secondary endpoints, the rate of CV death was higher with febuxostat compared with allopurinol (HR: 1.34; 95% CI: 1.03-1.73), whereas the individual rates for nonfatal MI, nonfatal stroke, and urgent revascularization for unstable angina did not differ between febuxostat and allopurinol. All-cause mortality was also higher with febuxostat than allopurinol due to the higher rate of CV deaths (HR: 1.22; 95% CI: 1.01-1.47).

A summary of the key dates and results associated with the CARES trial are provided below:

On 15 November 2017, FDA issued a DSC to inform prescribers and the public that preliminary results from a safety clinical study (CARES) show an increased risk of heart-related death with febuxostat (Uloric) compared with allopurinol.

On 19 January 2018, Takeda filed the supplemental New Drug Application (sNDA) 21856/S-013 with the FDA to provide the CARES clinical study report and update the US PI based on the results of CARES.

On 12 March 2018, the primary and secondary endpoint study results of the CARES study were published in the *New England Journal of Medicine* and presented at the American College of Cardiology congress to facilitate scientific exchange of the data and ensure that the latest information is publicly available.

On 11 January 2019, FDA convened a Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the sNDA 21856/S-013, which included the CARES results.

- The committees held a widely varied discussion, which included the interpretation/strength of the potential CV mortality signal, the biological plausibility, appropriate patient population, and potential regulatory actions.
- The members of the committees voted 19 to 2, with 1 abstention that, based on the available data, the benefit-risk profile for febuxostat is favorable for certain patients for the treatment of hyperuricemia in patients with gout.

On 21 February 2019, the FDA approved updates to the PI for febuxostat and added a boxed warning to febuxostat for CV death [8]. In addition, the indication for febuxostat was revised "for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol or for whom treatment with allopurinol is not advisable." The FDA also required Takeda (PMC 3579-1) to conduct this drug utilization study to describe the impact of these labeling changes on the dispensing patterns for febuxostat.

8.0 RESEARCH QUESTION AND OBJECTIVES

The research question of this cross-sectional non-interventional study is to evaluate the impact of the 2019 labeling changes (boxed warning and modified indication), based upon results of the CARES trial, on febuxostat utilization.

The study objectives are:

1. To describe the number and proportion of patients initiating febuxostat as new users (ie, without previous allopurinol therapy) versus prevalent new users (ie, with previous allopurinol therapy) of ULT.
2. To describe the number and proportion of febuxostat users with established CVD.

9.0 RESEARCH METHODS

9.1 Study Design

This study will be a descriptive non-interventional cross-sectional study.

9.2 Setting

The study setting is 2 large national administrative claims databases from 2 insurers in the US. Details of the databases are provided in Section 9.4.

9.2.1 Study population

The study population is gout patients initiating febuxostat therapy on or after 01 June 2016. The date of initiating febuxostat is defined as the index fill date.

9.2.2 Inclusion criteria

To be included in the analyses, patients must meet each of the following criteria:

1. Index fill date on or after 01 June 2016.
2. Having at least one diagnosis for gout (identified with diagnosis codes, International Classification of Diseases [ICD]-9-CM: 274.x or ICD-10: M10.x) at any time in the patient's record.
3. Age ≥21 years at index fill date.
4. Continuously enrolled for at least 12 months prior to index fill date.

9.2.3 Study periods

Febuxostat utilization will be assessed in the following separate periods:

- Baseline period, covering the 18 months prior to FDA's DSC: 01 June 2016 to 15 November 2017.
- Intermediate period, from the DSC to the change in PI: 16 November 2017 to 21 February 2019.

- Post–labeling change period (final): 22 February 2019 to 30 April 2021.

9.3 Variables

9.3.1 Initiation of febuxostat

The study inclusion criteria require patients to have at least 12 months of enrollment in the database prior to first febuxostat prescription, thereby limiting the study to patients newly initiating febuxostat. Identification of patients initiating febuxostat will be based on outpatient dispensed prescriptions in pharmacy claims and recorded medication use in medical claims records.

The study will include branded Uloric and generic versions of febuxostat. National Drug Codes (NDCs) are listed in Appendix A. Any new NDC for generic versions of febuxostat will be included in the analyses of the study datasets.

9.3.2 Line of ULT

Patients initiating febuxostat therapy will be categorized into one of 2 mutually exclusive groups:

- **New users** of febuxostat: febuxostat users who were naïve to allopurinol, defined as no record of allopurinol use in all historic pharmacy or medical claims at any time [9] prior to initiation of febuxostat.
- **Prevalent new users** of febuxostat: febuxostat users who had used allopurinol and switched, defined as at least one record of allopurinol use in all historic pharmacy or medical claims at any time prior to initiation of febuxostat.

NDCs for allopurinol are listed in Appendix A. Any new NDCs for allopurinol will be included in the analyses of the study datasets.

9.3.3 Established CVD

Each patient initiating febuxostat will be categorized as having (Yes/No) each of the following morbidities at any time prior to initiation of febuxostat:

- MI
- Unstable angina
- Stroke (hemorrhagic and ischemic)
- Transient ischemic attack
- Peripheral vascular disease
- Diabetes mellitus with evidence of macrovascular or microvascular disease

Presence of a disease is defined as any of the following in the patient's claims record:

- Having at least one inpatient or outpatient diagnosis code in any diagnosis field, or
- Having at least one procedural code (listed in Table 9.a)

Table 9.a Procedural Codes for CVDs of Interest

		Algorithm and codes		
#	CVD of interest	ICD-9-CM Diagnostic code	ICD-10 Diagnostic code	CPT Procedural code
1	MI	410.x, 412.x	I21.x, I22.x, I25.2	N/A
2	Unstable angina	411.1	I20.0	N/A
3	Hemorrhagic stroke	431.x, 430.x	I61.9, I60.9	N/A
4	Ischemic stroke	433.x, 434.x, 436	I63.x, I65.x, I66.09, I66.19, I66.29, I66.9, I67.89	N/A
5	Transient ischemic attack	435.x	G45.x	N/A
6	Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	N/A
7	Diabetes mellitus	250.x	E09–E13	N/A
8	Diabetic nephropathy	250.4x	E10.2x, E11.2x, E13.2x	N/A
9	Diabetic retinopathy	250.5x	E10.3x, E11.3x, E13.3x	N/A
10	Diabetic neuropathy	250.6x	E10.4x, E11.4x, E13.4x	N/A
11	Diabetes with peripheral circulatory disorders	250.7x	E10.5x, E11.5x, E13.5x, E10.61x, E11.61x, E13.61x	N/A
12	Ischemic heart disease	410.x–414.x	I20.x–I22, I24, I25	N/A
13	Cerebrovascular disease	362.34, 430.x–438.x	G45.x, G46.x, H34.0, I60.x–I69.x	N/A
14	Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0	N/A
15	Coronary artery bypass surgery	N/A	N/A	36.10–36.16, 36.19
16	Percutaneous transluminal angioplasty	N/A	N/A	36.01, 36.05
17	Diabetes mellitus with evidence of macrovascular diseases	#11 OR [#7 AND (6# OR #12 OR #13 OR #15 OR #16)]		

Table 9.a Procedural Codes for CVDs of Interest

#	CVD of interest	Algorithm and codes		
		ICD-9-CM Diagnostic code	ICD-10 Diagnostic code	CPT Procedural code
18	Diabetes mellitus with evidence of microvascular diseases		#8 OR #9 OR #10	

Source: [10-13]

CPT: Current Procedural Terminology; CVD: cardiovascular disease; ICD-9-CM: International Classification of Diseases, ninth revision, clinical modification; ICD-10: International Classification of Diseases, tenth revision; MI: myocardial infarction.

9.3.4 Morbidities of interest

This exploratory analysis intends to gain insight into morbidities that may be potential reasons for initiating febuxostat. New users and prevalent new users of febuxostat will be analyzed separately.

Adverse reactions to allopurinol will be restricted to prevalent new users of febuxostat who had previously used allopurinol and then switched to febuxostat. We are only able to assess certain adverse events (AEs) that can be captured in claims databases. It should be noted the results of this exploratory investigation will only describe how many prevalent new users of febuxostat may have experienced AEs including hypersensitivity before febuxostat initiation. As AEs and hypersensitivity to allopurinol may be reasons for initiating febuxostat, we will explore related morbidities to gain insight into the following events: allergic and hypersensitivity conditions, skin rash, hypersensitivity, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Other AEs including, but not limited to, elevation in liver enzymes, decline in renal function, or bone marrow suppression are difficult to ascertain in claims databases in the absence of laboratory test results, and thus have not been included in the protocol. Indicators of liver injury (eg, liver function tests), decline in renal functions (eg, serum creatinine, blood urea nitrogen, and estimated glomerular filtration rate), or bone marrow suppression (blood cell parameters) are usually not available in claims databases because laboratory test results are not recorded for reimbursement purposes. Other potential reasons for discontinuing allopurinol such as gastric irritation are also challenging to identify in claims databases because there are no ICD-9/10 diagnosis codes for these specific clinical events.

Despite these limitations, we propose this exploratory analysis for pre-existing liver and renal diseases before febuxostat initiation that may have contributed to their choice of therapy. This exploratory analysis is also descriptive and non-inferential and the findings will be inconclusive. A patient with a record of hepatic or renal morbidities of interest at any time prior to febuxostat initiation is considered to have pre-exiting liver or renal disease. Pre-exiting liver and renal diseases will be assessed for new users and prevalent new users of febuxostat, respectively.

Each patient initiating febuxostat will be classified as having or not having (Yes/No) each of the morbidities listed below. Presence of a morbidity is defined as having at least one inpatient or outpatient diagnosis code in any diagnosis field (listed in Table 9.b).

Table 9.b Procedural Codes for Morbidities of Interest

Morbidities of interest	ICD-9-CM Diagnostic code	ICD-10 Diagnostic
Allergic and Hypersensitivity conditions	287.0, 995.0–995.3, 974.7, V58.89, 999.2, 999.9, E994.7, 478.8, 713.6, 695.1x, 695.2	D69.0, T78.2x, T78.3x, T78.4x, T78.8x, T78.9x, T88.6x–T88.9x, T80.1x, T80.8x, T80.9x, T50.4X5, J39.3, M36.4, L51.x–L52.x
Skin rash	691.8, 693.0, 693.8, 693.9, 782.1, 708.x, 695.1x, 695.2	L20.8x, L20.9x, L27.0, L27.1, L27.8, L27.9, R21, L50.x, L51.x, L52
Toxic epidermal necrolysis	695.15	L51.2
Stevens-Johnson syndrome	695.13	L51.1
Liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	456.0–456.2, 572.2–572.8
Renal disease	250.4x, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0–583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	E10.2x, E11.2x, E13.2x, I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2

ICD-9-CM: International Classification of Diseases, ninth revision, clinical modification; ICD-10: International Classification of Diseases, tenth revision.

9.3.5 Concomitant medications

As drug-drug interactions (DDI) or avoiding potential DDIs are other potential reasons for initiating febuxostat, we intend to explore the exposure to medications that have the potential for DDI with allopurinol.

This analysis will examine both new users and prevalent new users of febuxostat and look at concomitant drug exposure with allopurinol in the 12 months prior to initiating of febuxostat. These analyses will provide insight into the proportion of switchers who were at risk of an allopurinol DDI; however, it is challenging to ascertain whether a DDI was the potential reason for initiating febuxostat. Concomitant medications will be analyzed in new users and prevalent new users of febuxostat separately. Within each group, medications of interest will be studied within 12 months prior to initiating febuxostat.

Each patient initiating febuxostat will be classified as having or not having (Yes/No) each of the medications listed below at any time in the 12 months prior to initiating febuxostat:

- XO substrate drugs, including mercaptopurine, azathioprine, theophylline

- Ampicillin
- Amoxicillin
- Salicylates, including aspirin alone and combination drugs containing aspirin, magnesium salicylate alone and combination with choline salicylate, salsalate, diflunisal
- Dicumarol
- Probenecid
- Thiazide diuretics, including chlorothiazide (oral or sodium injection), chlorthalidone, indapamide, hydrochlorothiazide, methyclothiazide, metolazone
- Chlorpropamide
- Cyclosporine
- Vidarabine
- Phenytoin
- Tolbutamide
- Cytotoxic Agents, including cyclophosphamide, doxorubicin, bleomycin, procarbazine, mechlorethamine

9.3.6 Demographic variables

Demographic variables include patient age (21-44, 45-64, and 65+ years), sex, and race.

9.4 Data Sources

Optum's CDM and IQVIA's PharMetrics Plus will be used for this drug utilization study. An important advantage of claims databases is complete data from a large number of subjects, which provides the capability to study medication utilization longitudinally [14].

CDM is a large administrative health claims database that is geographically diverse and includes patients from all 50 states in the US. It comprises administrative health claims for patients with a health insurance plan provided by United HealthCare; a large, national provider of health care insurance including Medicare Supplement coverage. This database encompasses 17 to 19 million lives annually and a total of approximately 57 million unique lives over the 10-year period from 2007 to 2017. The database contains statistically de-identified data in compliance with the Health Insurance Portability and Accountability Act (HIPAA), including demographic, diagnostic, and procedural information in the medical claims, and outpatient dispensed medications in the pharmacy claims.

The IQVIA PharMetrics Plus database is the largest claims database of integrated medical and pharmacy claims in the US. As of February 2018, the aggregated database was comprised of adjudicated claims for over 140 million unique enrollees (covered individuals) across the US. Over 70 national and sub-national health plans and self-insured employer groups submit data

(ie, enrollment dates and fully adjudicated medical and pharmacy claims of their enrollees) to the database. Data are available from 2006 onwards with a typical 6-month lag due to claims' adjudication. PharMetrics Plus data have diverse representation of geography, employers, payers, providers, and therapy areas, with a majority of the 3-digit ZIP codes in the US covered and reported. Patients in the PharMetrics Plus database are similar to the national, commercially-insured population in terms of age and sex for individuals aged ≤65 years. The data are also longitudinal, with more than 48 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment.

9.5 Study Size

The study will include all patients that meet the inclusion criteria listed in Section 9.2.2. A preliminary analysis of the Optum CDM study database has identified 8389 patients as having initiated febuxostat therapy from July 2016 to June 2019, of whom 2859 (34.1%) initiated febuxostat as new users and 5530 (65.9%) initiated febuxostat as prevalent new users. Under a strict interpretation of the study inclusion criteria, which exclude patients who had use of febuxostat within 12 months prior to the index date, 11,683 patients who initiated febuxostat between June 2016 and September 2019 were identified in the IQVIA PharMetrics Plus database, of whom 4352 (37.2%) initiated febuxostat as new users and 7331 (62.8%) initiated febuxostat as prevalent new users. The study datasets are expected to provide adequate numbers of new initiators of febuxostat to allow stratification of results by age, sex, and race.

9.6 Data Management

Patient attrition will be assessed by applying the full inclusion criteria for the study population. The operational definition, including diagnostic and procedural codes as well as NDCs for cohort identification, medical histories, and exploratory analysis are provided in the protocol. Detailed data specifications will be developed providing the precise operational definitions for all study variables, including coding for categorical variables and the time window in which variables are to be measured. These files will be used to construct analytical datasets from the raw data extract, which will contain all study variables. All analytical datasets generated will be saved on a secure company shared drive.

9.7 Data Analysis

Cross-sectional analysis to describe dispensing patterns will be conducted at the study start and after the final study period (post–labeling change period: 22 February 2019 to 30 April 2021).

Variables will be summarized descriptively through tabular displays of mean, median, ranges, and standard deviations of continuous variables and frequency distributions of categorical variables. Data will be separately presented for the baseline, intermediate, and post–labeling change periods described in Section 9.2.3.

The number and proportion of unique patients who initiated febuxostat will be used to describe the utilization of febuxostat across the study periods: baseline, intermediate, and post-labeling change. Analyses of patients initiating febuxostat as new users or prevalent new users, and

occurrence of established CVD will be presented overall, and stratified by age, sex, and race to achieve study objectives. Sensitivity analysis will be conducted for established CVD using a more stringent case definition, which requires a patient to meet at least one of the following criteria:

- Having at least one hospitalization diagnosis code in any diagnosis field, or
- Having at least 2 outpatient claims with diagnosis codes (matched to first 3 digits) in any diagnosis field at least 30 days apart, or
- Having at least one procedural code (listed in Table 9.a).

For exploratory analyses of potential reasons for initiating febuxostat as either new user or prevalent new user, pre-existing morbidities of interest at any time prior to initiating febuxostat, and concomitant medications with DDI potential to allopurinol in the 12 months prior to initiating febuxostat will also be presented overall, and stratified by age, sex, and race.

This study is not a hypothesis testing study. Study results are non-inferential and will only demonstrate temporal trends. All analyses will be descriptive and will be conducted using SAS statistical software (version 9.3 or newer).

9.8 Quality Control

All study investigators are trained according to all applicable standard operating procedures (SOPs) and will carry out the study in compliance with recommended real-world data study guidelines. Data-cleaning procedures will be followed with the aim of removing errors and inconsistencies in the data that would otherwise affect the analysis, reporting aims, or credibility of the final study report. The study data will be stored and accessed on secure servers by username/password combination only and available only to authorized personnel. For the analysis, all programming will be reviewed independently by a different analyst with oversight by a manager. All key study documents, such as the study protocol, statistical analysis plan, and study reports will undergo reviews according to applicable sponsor SOPs.

9.9 Limitations of the Research Methods

The study has some limitations:

- The study's data sources represent populations of patients with health insurance. Patient populations such as the uninsured are underrepresented in this database, which may limit the generalizability of study findings. Nevertheless, data from the CDM and PharMetrics Plus databases are geographically representative of the commercially insured US population. The age distribution of the CDM database is also representative of the general US population; and patients in the PharMetrics Plus database are similar to the national, commercially-insured population in terms of age and sex for individuals aged ≤65 years.
- The data are based on diagnosis codes and procedure codes used for insurance billing, which may not fully align with the physician's diagnosis.

- A patient's line of ULT is subject to potential misclassification by left censoring. No information on prescriptions filled is recorded in claims databases prior to a patient's joining the claims database. It is possible some patients will be incorrectly categorized as new users of febuxostat when they are truly prevalent new users, but prior allopurinol use was before the start of their database enrollment. This study's inclusion criteria require at least 12 months of database membership before initiation of febuxostat to minimize this misclassification.
- Certain ethnic groups such as Korean, Han Chinese, or Thai are associated with severe hypersensitivity reactions (eg, allopurinol hypersensitivity syndrome [AHS]) during allopurinol treatment and could serve as potential reasons for initiating febuxostat as a new user to prevent such reactions or as a prevalent new user subsequent to a reaction. However, racial information recorded (White, Black, Hispanic, Asian) in the claims database is not able to distinguish between patients of East Asian (eg, Han Chinese) and South Asian (eg, Indian sub-continent) descent. However, study results will be stratified on known race as suggested by the FDA.
- Adverse drug reactions (ADRs) associated with allopurinol resulting in a switch to febuxostat cannot be examined in a claims database. Instead this study looks at selected morbidities (such as hypersensitivity) and their temporal relation to discontinuation of febuxostat. While no firm conclusions can be drawn from such data, this approach may provide useful insight into reasons for switching to febuxostat.
- Data on DDIs as a reason for discontinuation of allopurinol and switching to febuxostat cannot be examined in a claims database as reasons for change in medication is not recorded. Instead, this study looks at concomitant medications likely to cause a DDI with allopurinol prior to starting febuxostat. A few other potential reasons for switching from allopurinol to febuxostat such as hepatic toxicity cannot be captured by the claims database due to the absence of laboratory testing results in the database. While no firm conclusions can be drawn from such data, this approach may provide useful insight into reasons for switching to febuxostat.

Notwithstanding the above limitations, the use of administrative claims databases has substantial advantages:

- Claims data include important details about all medications. Databases contain complete information for every fill/refill of a prescription, date of prescription fill, and quantity of medication dispensed.
- Claims databases reflect real-life healthcare provision. These data include the collection of complete data on large groups of patients, including groups that are typically more difficult to observe through primary data collection such as off-label use, pediatric populations, and severely ill individuals.
- Real-world data from such databases are generating real-world evidence and playing an increasing role in health care decisions. Claims databases and other real-world data have been used by the FDA for post-marketing surveillance and regulatory decisions. The health

care community uses claims databases to support coverage decisions and to develop guidelines for clinical practice. The pharmaceutical industry uses claims databases to support clinical trial designs and generate innovative, new treatment approaches.

10.0 PROTECTION OF HUMAN SUBJECTS

This non-interventional study only involves the use of de-identified and anonymized data from Optum's CDM database and IQVIA's PharMetrics Plus database. Optum implemented policies and processes to address important guidelines for protecting individual health care information, as described in the Final Privacy Rule of HIPAA, 1996. These rules were further amended by the American Recovery and Reinvestment Act (ARRA) of 2009. PharMetrics Plus data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are HIPAA-compliant to protect patient privacy. The researchers will not have any access to named or identifiable patient information, nor make any attempt to identify individual patients. The study results will be in an aggregated format without individual patient information. This study does not require separate ethics approval from an external Research Ethics Committee.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

11.0 MANAGEMENT AND REPORTING OF AES

11.1 Definitions

11.1.1 AEs

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for a serious adverse event (SAE).
- A laboratory test result that requires the subject/patient to receive specific corrective therapy.

- A laboratory abnormality that leads to discontinuation of therapy.
- A laboratory abnormality that the health care provider considers to be clinically significant.

11.1.2 SAEs

An SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the health care provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.1.3 ADRs

An ADR is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

11.1.4 Product quality issues

A product quality issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

11.1.5 Special situation reports

A special situation report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnant patient is exposed to a Takeda product or in which a female patient or female partner of a male patient becomes pregnant following treatment with a Takeda product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk.
- Overdose: All information of any accidental or intentional overdose.

- Drug abuse, misuse, or medication error: All information on medicinal product abuse, misuse, or medication error (potential or actual).
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda product.
- Accidental/Occupational exposure.
- Use outside the terms of the marketing authorization, also known as "off-label".
- Use of falsified medicinal product.
- Use of counterfeit medicinal product.
- DDIs and drug-food interactions.
- Inadvertent or accidental exposure with or without an AE.
- Unintended benefit.

An SSR should be reported even if there is no associated AE.

11.2 Collection and Reporting of AEs, SAEs, ADRs, PQIs, SSRs to Takeda Pharmacovigilance

11.2.1 AEs, SAEs, ADRs, PQIs, and SSRs in the healthcare records or other applicable source data that are part of the study objectives or endpoints

Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

11.2.2 AEs, SAEs, ADRs, PQIs, and SSRs in the healthcare records or other applicable source data that are NOT part of the study objectives or endpoints

Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

12.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information on the study, including a synopsis of aggregated study results for endpoints, will be disclosed on the company website (www.takeda.com) within 12 months following the final study report. The study will also be registered at clinicaltrials.gov, which is a public website, within 12 months following the final study report.

Takeda intends to submit study results to the International Conference of Pharmacoepidemiology and Risk Management.

The final study report will be submitted to the FDA.

13.0 REFERENCES

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14.0 APPENDICES

Appendix A NDCs for Febuxostat and Allopurinol

NDCs for Febuxostat	NDCs for Allopurinol
55154515808	43063077430
55154515908	43063077490
64764067711	43063079320
64764067713	43063079360
64764067719	43063079390
64764067730	00378013701
64764091811	00378013710
64764091818	00378018101
64764091830	55154475000
64764091890	55154545400
43353030560	55154553400
	63187046330
	55154205600
	60760011490
	71335011201
	71335011202
	71335011203
	71335011204
	55111072901
	55111072910
	55111073001
	55111073005
	53489015601
	53489015602
	53489015605
	53489015610
	53489015701
	53489015702
	53489015705
	53489015707
	63629640501
	63629650801
	63629650802
	63629650803
	63629650804
	55700003530

NDCs for Febuxostat	NDCs for Allopurinol
	60760011890
	60760013490
	60760013990
	66267022430
	66267022460
	66267022490
	66267066530
	66267066560
	50090376004
	53002482000
	00378018105
	70518157301
	70518167800
	43063093401
	43063007930
	43063007960
	43063007990
	53489015710
	33261059730
	33261059760
	33261059790
	33261081030
	33261081060
	33261081090
	55111073010
	70934007230
	70518140700
	71205004930
	71205004960
	71205004990
	55700054030
	55700054090
	55700003560
	55700003590
	00603211521
	00603211528
	00603211532
	00603211621
	00603211628
	00603211632

NDCs for Febuxostat	NDCs for Allopurinol
	68788060301
	68788060303
	68788211501
	68788211503
	68788211509
	68788983101
	68788983103
	43353018660
	68071413103
	68071413106
	68071413109
	68788983201
	68788983203
	68788983209
	68788632301
	68788632303
	68788738303
	68788738306
	68788738309
	00615159205
	00615159239
	00615159305
	00615159339
	70518157600
	58118115608
	62584071301
	62584098801
	53002482003
	60429018001
	60429018010
	60429018018
	60429018090
	60429018101
	60429018105
	60429018190
	68788933101
	68788933103
	16729013401
	16729013416
	16729013501

NDCs for Febuxostat	NDCs for Allopurinol
	16729013516
	52959031100
	52959031104
	52959031130
	52959031160
	52959031184
	00591554301
	00591554310
	00591554401
	00591554405
	71335059901
	71610023160
	50742013501
	43353008860
	00904657161
	00904657261
	71610019780
	50090375803
	50090004203
	50090004204
	51079020520
	51079020620
	71335046701
	71335046702
	70710120900
	70710120901
	70710121000
	70710121001
	70710121005
	71610019460
	63739079610
	70771112600
	50742013505
	50742013510
	50742013601
	50742013605
	50742013610
	71610019760
	63187024030
	71610006460

NDCs for Febuxostat	NDCs for Allopurinol
	70771112601
	70771112700
	70771112701
	70771112705
	67544073660
	67544073680
	63629178101
	63629178102
	63629178103
	63629178104
	70518180600
	63629167501
	63629167502
	63629167503
	63629167504
	63629167505
	63629167506
	53808092901
	53808102602
	55289001001
	61919047130
	67046000830
	67046002230
	70518157300
	53002482006
	43063093501
	68788642201
	68788642203
	66267066590
	51655003852
	50268006315
	50268006415
	63739041010
	53217018700
	53217018730
	53217018760
	53217018790
	71335046703
	71335046704
	71335046705

NDCs for Febuxostat	NDCs for Allopurinol
	71335046706
	55289001003
	55289001030
	55289001090
	71335059902
	71335059903
	71335059904
	70518167801
	16714004107
	16714004110
	16714004112
	16714004207
	16714004210
	16714004211
	70785002105
	70785002130
	70785002205
	70785002230
	70199001605
	70199001690
	70199001590
	67046068130

Appendix B ENCePP Checklist

ENCePP Checklist for Study Protocols (Revision 3)

Study title: Drug utilization study to describe the pattern of febuxostat use in relationship to allopurinol following addition of the boxed warning and modification of the indication based on the results of the CARES trial

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.0
1.1.2 End of data collection[2]	☒	☐	☐	6.0
1.1.3 Study progress report(s)	☒	☐	☐	6.0
1.1.4 Interim progress report(s)	☐	☒	☐	6.0
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6.0

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8.0
2.1.2 The objective(s) of the study?	☒	☐	☐	8.0
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

This study intends to assess the impact of labeling changes on febuxostat utilization. No formal hypothesis testing is planned.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (eg, incidence rate, absolute risk)	☐	☐	☒	N/A

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.0

Comments:

This study intends to assess the impact of labeling changes on febuxostat utilization. No measures of occurrence and association are planned.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				9.2
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☒	☐	☐	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	9.7, 9.9
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Study is limited to current user of one single medication.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3, 9.7, 9.9

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

Drug utilization study. No Health Technology Assessment component.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (eg, healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.9

Comments:

Febuxostat is the only drug being investigated. Confounding by indication does not apply.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

No effect measurement.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Appendix 1
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

No linkage between data sources.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.2.5, 9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.0

Comments:

Study results will be communicated with FDA and published in peer-reviewed journal.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.0
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	11.0
13.3 Have data protection requirements been described?	☒	☐	☐	10.0

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.0

Comments:

Appendix C Protocol History

Date	Amendment Number	Amendment Type	Region
10 August 2020	2	Substantial	United States
27 February 2020	1.1	Nonsubstantial	United States
22 May 2019	Initial version	Not applicable	United States

Rationale for Amendment 1.1

The primary reason for this amendment was to:

- Update the protocol in response to the FDA's Request for Information on 25 November 2019 (details outlined below).

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only; this includes an update to the study title for clarity and brevity.

Changes in Amendment 1.1

1. Global clarification of the terminology and definitions for line of ULT, to prevent potential misclassification of febuxostat use (Sections 4.0, 8.0, 9.3.2, 9.3.4, 9.3.5, 9.5, 9.7, and 9.9):

   New users of febuxostat: febuxostat users who were naïve to allopurinol defined as no record of allopurinol use in all historic pharmacy or medical claims at any time prior to initiation of febuxostat.

   Prevalent new users of febuxostat: febuxostat users who had used allopurinol and switched, defined as at least one record of allopurinol use in all historic pharmacy or medical claims at any time prior to initiation of febuxostat.

2. Clarification in Section 9.7 (Data Analysis) that both the number and proportion of patients that used febuxostat will be reported.
3. Removal of the sensitivity analysis for concomitant medication use in the 24 and 36 months prior to initiating febuxostat in Section 9.7 (Data Analysis).
4. Update to the post–labeling change period in Sections 6.0 (Milestones) and 9.2.3 (Study Period) to end on the last available day of final database refresh for the interim and final study reports. The end of study period will be determined by the last day of available database refresh. Additionally, these sections were updated to include the April 2020 database refresh for the June 2020 interim study report submission, and to use the April 2021 database refresh for the June 2021 final study report submission to the Agency.
5. Clarification that pre-existing liver and renal diseases will be assessed for new users and prevalent new users, respectively, in Section 9.3.4 (Morbidities of Interest).
6. Specification that only one code for hypersensitivity and other morbidities will be used (Section 9.3.4 – Morbidities of Interest).

7. Inclusion of at least one inpatient or outpatient diagnosis to identify CVD covariates in Section 9.3.3 (Established CVD) and to conduct a sensitivity analysis for CVD covariates using previous definitions in Section 9.7 (Data Analysis).
8. Enhancement of the feasibility analysis for the CDM claims database from July 2016 to June 2019 in Section 9.5 (Study Size) to demonstrate the robust size of anticipated numbers of febuxostat initiators (new users and prevalent new users).