NON-INTERVENTIONAL POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL PS0038 AMENDMENT 1

COHORT STUDY ON THE SAFETY OF BIMEKIZUMAB IN PATIENTS WITH PLAQUE PSORIASIS, PSORIATIC ARTHRITIS, OR AXIAL SPONDYLOARTHRITIS: A NON-INTERVENTIONAL POST AUTHORIZATION STUDY

Sponsor:

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BELGIUM

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PASS INFORMATION

Title	Cohort study on the safety of bimekizumab in patients with plaque psoriasis, psoriatic arthritis, or axial spondyloarthritis: A non-interventional post-authorization study
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Procedure number	EMEA/H/C/005316/MEA/002 (PS0038)
Marketing authorization holder	UCB Pharma SA
Joint PASS	No
Research question and objectives	The objective is to assess the comparative risk of safety outcomes of interest in bimekizumab users in the indicated psoriasis, psoriatic arthritis, or axial spondyloarthritis populations to users of other biologics indicated for moderate to severe plaque psoriasis, psoriatic arthritis, or axial spondyloarthritis, except for other anti-interleukin-17 biologics, with similar patient characteristics before treatment start
Country(-ies) of study	US, France
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MARKETING AUTHORIZATION HOLDER

Marketing Authorization Holder (MAH)	UCB Pharma SA Allée de la Recherche 60 B-1070 Brussels Belgium
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CONTACT DETAILS FOR THE TRANSMISSION OF (SERIOUS) ADVERSE EVENT/(SERIOUS) ADVERSE DRUG REACTION AND OTHER RELEVANT SAFETY INFORMATION TO UCB

This is a non-interventional study based on secondary use of data collected for other purposes, which consists of fully de-identified data. Therefore, individual case safety reports will not be required.

DECLARATION AND SIGNATURE OF STUDY INVESTIGATOR

I confirm that I have carefully developed this non-interventional PASS protocol and agree to conduct this non-interventional PASS as outlined in this protocol, as well as local laws and requirements.

I will ensure that all co-investigators, physicians, and other staff members read and understand all aspects of this non-interventional PASS protocol.

I have received and have read all study-related information provided to me.

The objectives and content of this non-interventional PASS protocol as well as the results deriving from it will be treated confidentially and will be published as agreed by a separate contract with UCB.

Study Investigator

Sebastian Schneeweiss, MD, ScD

Printed name	Date/signature

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute coronary syndrome
AEP	Aetion Evidence Platform
AS	As-Started
AT	As-Treated
axSpA	axial spondyloarthritis
CABG	coronary artery bypass graft
[redacted]	[redacted]
CD	Crohn's Disease
CHD	coronary heart disease
CI	confidence interval
CIP	Code Identifiant de Présentation
CNAM	Caisse National d'Assurance Maladie
CNIL	Commission Nationale de l'Informatique et des Libertés
COVID-19	Coronavirus Disease 2019
CT	computed tomography
[redacted]	[redacted]
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERW	exposure risk window
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
IL	interleukin
IMD	immune-modulating drug
IPTW	inverse probability of treatment weighting
IR	incidence rate
IRB	Institutional Review Board
LTD	long-term disease
MACE	major adverse cardiovascular event

Abbreviation	Definition
MAH	Marketing Authorization Holder
MI	myocardial infarction
MRI	magnetic resonance imaging
NDC	National Drug Code
nr-axSpA	nonradiographic axial spondyloarthritis
NSAID	nonsteroidal anti-inflammatory drug
PAS	post-authorization study
PASS	post-authorization safety study
[redacted]	[redacted]
PPV	positive predicted value
PS	propensity score
PsA	psoriatic arthritis
PSO	psoriasis
PSUR	periodic safety update report
Q	Quarter
r-axSpA	radiographic axial spondyloarthritis
RCT	randomized controlled trial
[redacted]	[redacted]
[redacted]	[redacted]
UC	ulcerative colitis

3 RESPONSIBLE PARTIES

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4 ABSTRACT

Title

Cohort study on the safety of bimekizumab in patients with plaque psoriasis, psoriatic arthritis, or axial spondyloarthritis: A non-interventional post-authorization study

Rationale and background

Randomized trials comparing bimekizumab against placebo and active comparators have shown a favorable benefit/risk profile for bimekizumab in 3 indications: patients with psoriasis (PSO), psoriatic arthritis (PsA), or axial spondyloarthritis (axSpA [including radiographic axial spondyloarthritis (r-axSpA) and nonradiographic axial spondyloarthritis (nr-axSpA)]). However, continued monitoring and evaluation of the safety of bimekizumab in clinical practice is needed.

Research question and objectives

The objective is to assess the comparative risk of safety outcomes of interest in bimekizumab users in 3 indications (PSO, PsA, and axSpA) to users of other biologics indicated for these 3 indications, except for other anti-interleukin (IL)-17 biologics, with similar patient characteristics before treatment start. Safety outcomes of interest will include, but are not limited to, the following: major adverse cardiovascular events (MACE), malignancy, inflammatory bowel disease (IBD), serious infection, and serious hypersensitivity.

Study design

The study is a sequential new-user active comparator cohort design using healthcare databases in EU and US. Separate analyses will be conducted for each indication: PSO, PsA, and axSpA.

Population

Adult patients with moderate to severe plaque PSO, PsA, or axSpA who are new users of biologic treatments (ie, use of a drug of the same class of the specific treatment of interest in the 180 days before treatment start) among commercially insured patients in the US, and patients included in the national [redacted].

Variables

Exposures: Three pair-wise treatment comparisons will be made across the 3 indications (PSO, PsA, and axSpA) with minor variations per indication that are specified in the protocol:

1. New use of bimekizumab (drug of interest) vs new use of any other biologic treatment indicated for the treatment of the given indication, except for other anti-IL-17 biologics, with previous use of a different biologic treatment or apremilast.
2. New use of bimekizumab (drug of interest) vs new use of any other biologic treatment indicated for the treatment of the given indication, except for other anti-IL-17 biologics, with no prior use of any biologic treatment or apremilast but with prior use of conventional systemic medications.
3. New use of bimekizumab (drug of interest) vs new use of any other biologic treatment indicated for the treatment of the given indication, except for other anti-IL-17 biologics, and no prior use of any systemic medications (to the extent that such treatment patterns are observable in clinical practice).

Main outcomes: Incidence of MACE, malignancy, IBD, serious infection, and serious hypersensitivity reaction.

Patient characteristics: A range of pretreatment risk factors for the outcomes, socio-demographics, indication-specific variables, and healthcare utilization intensity.

Data sources

This study will be based on large, well-documented US and EU healthcare databases which are well-established for post authorization safety studies (two in the US and one in the EU). The final data source(s) to be used in this study will be defined based on the uptake of bimekizumab reflected in respective databases.

US data sources

The [redacted] includes medical and pharmacy closed claims (sourced from insurance providers and payers) and administrative hospital billing data for inpatient and outpatient encounters from a variety of health data sources covering all of the US states. Closed claims data are available in the database with approximately 3 months of delay.

The [redacted] includes closed claims data covering >180 million commercially insured US residents nationally. The [redacted] database has been demonstrated to produce similar findings to studies in European data sources and refreshes every 9 months.

French data sources

The [redacted]: the national healthcare insurance database links out-of-hospital reimbursed claims to the national hospital discharge summaries database system and the national death registry using pseudonymization of the unique national identifier. The data cover 99% of the French population, including over 67 million persons. Outpatient data are updated monthly with a 12-month lag and inpatient data are updated yearly with a 9- to 10-month lag.

Study size

The planned sequential cohort study is designed to conduct comparative analyses once a study size is achieved that would allow identification of at least a 3-fold increased risk (6-fold for the rare IBD and serious hypersensitivity reactions outcomes). Calculations assume 70% power, 2-sided alpha=0.05, assuming 1.5 years of exposed follow up per patient, and 1 comparator patient for every bimekizumab-exposed patient. The study enrollment period is expected to last for 8 years (2023 to 2031).

Data analysis

For each indication (PSO, PsA, and axSpA) a separate analysis will be conducted. The study will use outcome-specific 1:1 propensity score matching to achieve balance of all measured pretreatment patient characteristics for each pair-wise comparison. After inspecting the achieved balance (standardized differences), effects comparing bimekizumab to other biologics will be estimated by computing hazard ratios (HRs) with 95% confidence intervals (CIs). Prespecified subgroups by age, gender, and other characteristics of interest will be analyzed, and a range of sensitivity analyses will be conducted.

Milestones

For each of the considered databases, the progress of bimekizumab uptake will be monitored. Indeed, a particular database will be dropped (all analyses related to a particular database stopped) if 4 years after the date of market access of bimekizumab in the respective countries, the database has not accrued sufficient numbers of bimekizumab users (ie, sufficient numbers to assess at least two study outcomes). If the minimum required study size is not reached in any of the databases, all three databases will be retained and an additional EU database may be included. For databases achieving the minimum required study size, the sequential cohort study continues until the end of the study. Should at least one database reach the minimum required study size, no additional databases will be included. At least one database will be retained for the duration of the study. Progress updates and/or interim reports (once comparative analyses are available) will be produced annually. The final report is due in [redacted].

5 AMENDMENTS AND UPDATES

The protocol was amended as required by the European Medicines Agency during review of the psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) marketing applications for bimekizumab.

Section # and name	Description of change	Brief rationale
Title page	• Study title revised	Updated in response to EMA for the PsA and axSpA submissions
Section 2 List of abbreviations	• List updated	
Section 4 Abstract	• Text updated	
Section 5 Amendments and updates	• Section updated	
Section 6 Milestones	• Planned milestone dates updated	
Section 7 Rationale and background	• Text updated to include PsA and axSpA indications	
Section 8 Research questions and objectives	• Text updated to include PsA and axSpA indications	
Section 9 Research methods	• Text updated in relevant subsections to include PsA and axSpA indications; Tables 9-1 and 9-2 updated to include PsA and axSpA indications; Figures 9-2 and 9-3 added for PsA and axSpA indications	
Section 12 Plans for disseminating and communication study results	• Text updated	
Section 13 References	• PsA and axSpA references added	
Appendix 2	• Study title revised	
Appendix 3	• Updated to include PsA and axSpA indications	

axSpA=axial spondyloarthritis; EMA=European Medicines Agency; PsA=psoriatic arthritis; PSO=psoriasis

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

The protocol and any significant changes that will be made as an amendment to the protocol must be approved by UCB, the respective IRBs of individual databases and/or institutions, regulatory authorities, and local institutions (if required), prior to being implemented.

6 MILESTONES

Milestones [a]	**Planned dates**
Protocol submission to EMA	29 Nov 2021
Protocol approval by EMA	30 Mar 2023
Registration in the EU PAS register	TBD
Start of data collection (first claims/admin data available to investigators)	[redacted]
Interim report 1	[redacted]
Interim report 2	[redacted]
End of data collection [b]	[redacted]
Final study report	[redacted]

EMA=European Medicines Agency; PAS=post-authorization study; Q=Quarter; TBD=to be determined

[a] Progress updates provided in the PSUR will include number of patients enrolled and exposed and latest available results. Interim reports will include descriptive analyses and comparative analysis for outcomes where sufficient patient counts have been accrued (see Section 12).

[b] Data collection will last for 10 years, including 8 years of patient enrollment.

7 RATIONALE AND BACKGROUND

The safety of bimekizumab has been evaluated in Phase 2 (PSO: PS0010, PS0011, PS0016, and PS0018; PsA: PA0008, PA0009; axSpA: AS0008, AS009) and Phase 3 (PSO: PS0008, PS0009, PS0013, and PS0014; PsA: PA0010, PA0011, and PA0012; axSpA: AS0010, AS0011, and AS0014) clinical studies for 3 indications for patients with moderate to severe plaque PSO, PsA, or axSpA. The results suggest a favorable benefit/risk profile for bimekizumab in all 3 indications (PSO, PsA, and axSpA); however, continued monitoring and evaluation of the safety of bimekizumab in clinical practice is needed. Healthcare data generated by the operation of a healthcare system (real-world data) are a critical tool in supporting regulatory decision-making, especially in post-authorization assessments of medicinal products (Eichler et al, 2020; Sherman et al, 2016). Therefore, prospectively analyzing secondary data within an active surveillance system (Schneeweiss, 2010) to sequentially monitor the number of patients and patient-years of bimekizumab exposure and number of outcomes (overall, not stratified by treatment), allowing for timely conduct of comparative analysis as soon as sufficient data have accrued in the growing database, will be performed. As part of this active surveillance system, the safety of bimekizumab in treating patients with PSO, PsA, or axSpA in clinical practice will be assessed. This study is required to satisfy a post-approval commitment from the European Medicines Agency (EMA).

The main objective of the proposed analysis is to evaluate potential differences in terms of specified outcomes of interest (including safety outcomes) in PSO, PsA, or axSpA patients who are new users of bimekizumab (ie, no use of a drug of the same class of the specific treatment of interest in the 180 days before treatment start) compared to other biologics indicated for moderate to severe plaque PSO, PsA, or axSpA, except for other anti-IL-17 biologics, in comparable patients in clinical practice. Other biologics targeting IL-17 will not be part of the goal in the current study to prevent dilution of effect estimates due to a potential class effect of outcomes of interest among anti-IL-17 biologics. The outcomes of interest include, but are not limited to, the occurrence of MACE, malignancy, IBD, serious infection, and serious hypersensitivity reaction. The study objectives will be achieved using US and EU healthcare databases.

The bimekizumab PSO, PsA, and axSpA patient populations in the US and EU are not anticipated to have meaningful demographic or clinical differences that would impact analysis of outcomes of interest. This is based on similar disease prevalence (Michalek et al, 2017), treatment guidelines (Ghani et al, 2019), comorbidity profiles (Radtke et al, 2017; Shah et al, 2017; Takeshita et al, 2017), and treatment options in the 2 regions. As the approved indications for bimekizumab may vary slightly between the US and EU, the aim will be to limit the analysis in US databases to patients who meet the definition of the EU indication.

The proposed approach will allow for timely accrual of bimekizumab-exposed patients, as well as accrual of comparable patients exposed to other biologics indicated for moderate to severe plaque PSO, PsA, or axSpA, except for other anti-IL-17 biologics, and will then be used for estimating risks and relative risks comparing those agents. Careful consideration was given to the data source selection to avoid delays in assessment of the proposed analysis and to capture a broadly representative patient population.

8 RESEARCH QUESTION AND OBJECTIVES

The primary purpose of this post-authorization safety study (PASS) within an active surveillance system will be to provide timely information on any potential increase in the risk of outcomes of interest in PSO, PsA, and axSpA patients using bimekizumab compared to other biologics indicated for moderate to severe plaque PSO, PsA, or axSpA, except for other anti-IL-17 biologics.

Outcomes of interest will include, but are not limited to, the following: MACE, malignancy, IBD, serious infection, and serious hypersensitivity. If additional outcomes of interest are identified, they will be considered for inclusion in the analysis to the extent that the data sources used in this study will contain sufficiently detailed information.

The objective is to assess the comparative risk of the outcomes of interest in bimekizumab users in the indicated PSO, PsA, or axSpA populations compared to users of other biologics indicated for PSO, PsA, or axSpA, except for other anti-IL-17 biologics, with similar pretreatment characteristics.

Specifically, the PSO cohort analysis objectives are:

1. To assess the risk-adjusted incidence rate (IR) of defined outcomes of interest and assess the comparative safety of bimekizumab users in the indicated population and in similar patients using other biologics indicated for moderate to severe PSO;
2. To assess in those analyses of PSO bimekizumab users vs their comparator patients the risk of outcomes of interest in patient subgroups of age categories, gender, and of prespecified risk factors for the respective outcome.

Specifically, the PsA cohort analysis objectives are:

1. To assess the risk-adjusted IR of defined outcomes of interest and assess the comparative safety of bimekizumab users in the indicated population and in similar patients using other biologics indicated for PsA;
2. To assess in those analyses of PsA bimekizumab users vs their comparator patients the risk of outcomes of interest in patient subgroups of age categories, gender, and of prespecified risk factors for the respective outcome.

Specifically, the axSpA cohort analysis objectives are:

1. To assess the risk-adjusted IR of defined outcomes of interest and assess the comparative safety of bimekizumab users in the indicated population and in similar patients using other biologics indicated for axSpA;
2. To assess in those analyses of axSpA bimekizumab users vs their comparator patients the risk of outcomes of interest in patient subgroups of age categories, gender, and of prespecified risk factors for the respective outcome.

9 RESEARCH METHODS

9.1 Study design

The study is a sequential new-user active-comparator cohort design using secondary healthcare data. In this cohort design, the incidence of defined outcomes of interest among moderate to

severe plaque PSO, PsA, and axSpA patients treated with bimekizumab or comparator drugs will be assessed.

For each indication (PSO, PsA, and axSpA) a separate cohort analysis will be conducted. The following study design approaches, i-iv, apply equally to all 3 indications, while v-vii are specific to each indication.

- (i) A sequential study design in each database was selected as analyses will be repeated annually as additional data have accrued (Schneeweiss et al, 2011).
- (ii) If after 4 years of marketing bimekizumab in the respective countries the database has not accrued sufficient numbers of bimekizumab users (ie, sufficient numbers to assess at least two study outcomes), then this database will be dropped. If the minimum required sample size is not reached in any of the databases, all three databases will be retained and an additional EU database may be included. For databases achieving the minimum required study size, the sequential cohort study continues until the end of the study. Should at least one database reach the minimum required study size, no additional databases will be included. At least one database will be retained for the duration of the study.
- (iii) New users (ie, no use of a drug of the same class of the specific treatment of interest in the 180 days before treatment start) of the study drug (bimekizumab) and comparator drugs were selected as this will emulate a clinical trial setting (Ray, 2003). It has been shown many times that the analysis of new users is a study design that lends itself to causal interpretations (Johnson et al, 2013). The alternative would be to allow ongoing (prevalent) users into the study population, but this has been demonstrated to introduce survivorship bias by depletion of susceptibles (Moride and Abenhaim, 1994). Studying new users has the added advantage to study the influence of duration of treatment on the outcomes of interest (Schneeweiss et al, 2021). Further, in the absence of baseline randomization, the fact that both the exposed and the comparator patients are initiating new treatment after having been evaluated by the prescribing physician makes these patients more similar regarding their disease state (Johnson et al, 2013).
- (iv) An active comparator was selected as using alternative medication to treat the same condition of approximately the same severity as a comparator will make patients more similar in the absence of baseline randomization (Schneeweiss and Avorn, 2005). Placebo comparators can be operationally emulated using nonusers of any indicated treatment; however, nonusers are usually substantially different for a variety of reasons and thus often lead to such strong confounding bias that is difficult to adjust with statistical analysis methods (Glynn et al, 2001).

The above study design approaches (i-v) apply equally to each of the 3 cohorts (PSO, PsA, axSpA).

- (v) For the PSO cohort analysis, moderate to severe plaque PSO patients will be identified through the initiation of treatment with bimekizumab or other biologics indicated for moderate to severe plaque PSO (eg, anti-tumor necrosis factor, anti-IL-12/23, anti-IL-23; except for other anti-IL-17 biologics) in addition to appropriate diagnostic codes for PSO.
- (vi) For the PsA cohort analysis, PsA patients will be identified through the initiation of treatment with bimekizumab or other biologics indicated for PsA (eg, anti-tumor necrosis

factor, CTLA-4-Ig, anti-IL-12/23, anti-IL-23; except for other anti-IL-17 biologics) in addition to appropriate diagnostic codes for PsA.

- (vii) For the axSpA cohort analysis, axSpA patients will be identified through the initiation of treatment with bimekizumab or other biologics indicated for axSpA (eg, anti-tumor necrosis factor, except for other anti-IL-17 biologics) in addition to appropriate diagnostic codes for axSpA.

This PASS design has been recommended by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (EMA/95098/2010, Rev 8), has been used in pharmacoepidemiology claims data studies in dermatology previously (Schneeweiss et al, 2021b; Dommasch et al, 2019; Schneeweiss et al, 2018), and has reproduced randomized controlled trial (RCT) findings in dermatology (Schneeweiss et al, 2021a).

The treatment will be prescribed by treating physicians in the usual manner according to the terms of the marketing authorization. The choice of medical treatment is made independently by the treating physicians in the regular course of practice and is not influenced by the non-interventional PASS protocol.

9.2 Setting

This non-interventional study will analyze secondary data from the US and EU healthcare system (Huybrechts and Schneeweiss, 2021). It is anticipated that all study patients in the EU and US databases will be identified in the respective databases starting Q1 2023 for the [redacted] and potentially Q3 2023 for the commercial US claims databases.

Briefly, these de-identified individual-level longitudinal healthcare databases contain dated information of all healthcare encounters, including medical information. This includes an enrollment file (for US databases), demographic information, physician services with diagnosis and procedure codes, all hospitalizations with diagnosis and procedure codes, pharmacy dispensing information with details on type, strength, and number of dispensed drugs, durable medical equipment, and, for US databases, admissions to nursing and other institutions (see Section 9.4).

9.2.1 Inclusion criteria and cohort entry

9.2.1.1 Inclusion criteria

The following selection criteria must be followed for patients entering each of the 3 cohort analyses for PSO, PsA, and axSpA:

***PSO*:**

- Patients with moderate to severe PSO who are new users of bimekizumab or 1 of the comparator drugs (see Table 9-1).
- For US [redacted]:
  - Patients with at least 180 days of continuous enrollment in the database before cohort entry. In pharmacoepidemiologic studies of systemic agents in dermatology, 180-day lookback is typically used in order to distinguish initiators of a medication from ongoing users (Schneeweiss et al, 2022; Schneeweiss et al, 2021; Jin et al, 2022; Dommasch et al, 2019). Extending the lookback period does not lead to better confounding adjustment in

typical situations (Nakasian et al, 2017). An extended lookback period (365 days) as a sensitivity analysis, also considering that requiring a longer enrollment period before cohort entry will exclude more subjects from the analyses and may delay findings, is preferred. There is no consensus on the value of unrestricted lookback periods using US claims data (Connolly et al, 2019; Brunelli et al, 2013).

  - Patients with at least 1 dermatologist PSO (L40.x, except L40.5) International Classification of Diseases (ICD) claim within all time of continuous enrollment before cohort entry.
  - Patient is 18 years or older at the time of cohort entry (bimekizumab or other biologics indicated for moderate to severe plaque PSO).

- For the [redacted]
  - Patients with at least 180 days of medical records before cohort entry.
  - Patients with at least 1 PSO ICD or at least 2 prescriptions of topical vitamin D (the recommended first-line treatment for psoriasis in France) within all time before cohort entry, the second prescription occurring within 2 years of the first prescription (Sbidian et al, 2021; Penso et al, 2021), or assigned with long-term disease status (see definition Section 9.4.2) for psoriasis.
  - Patient is 18 years or older at the time of cohort entry (initiation of bimekizumab or other biologics indicated for moderate to severe plaque PSO).

***PsA*:**

- Patients with PsA who are new users of bimekizumab or 1 of the comparator drugs (see Table 9-1).
- For US [redacted]:
  - Patients with at least 180 days of continuous enrollment in the database before cohort entry.
  - Patients with at least 1 rheumatologist/dermatologist PsA (L40.5) ICD claim within all time of continuous enrollment before cohort entry (Lee et al, 2020, Wallman et al, 2023).
  - Patient is 18 years or older at the time of cohort entry (bimekizumab or other biologics indicated for moderate to severe plaque PsA).
- For the [redacted]
  - Patients with at least 180 days of medical records before cohort entry.
  - Patients with at least 1 PsA ICD as inpatient diagnosis or assigned with long-term disease status (L40.5, M07) for PsA (Penso et al, 2021).
  - Patient is 18 years or older at the time of cohort entry (initiation of bimekizumab or other biologics indicated for PsA).

***axSpA*:**

- Patients with r- and nr-axSpA who are new users of bimekizumab or 1 of the comparator drugs (see Table 9-1).
- For US [redacted]:
  - Patients with at least 180 days of continuous enrollment in the database before cohort entry.
  - Patients with at least 1 rheumatologist axSpA ICD claim (M45.x, M46.0, M46.1, M46.8, M46.9) within all time of continuous enrollment before cohort entry (Curtis et al, 2016; Curtis et al 2021).
  - Patient is 18 years or older at the time of cohort entry (bimekizumab or other biologics indicated for axSpA).
- For the [redacted]
  - Patients with at least 180 days of medical records before cohort entry.
  - Patients with at least 1 axSpA ICD as inpatient diagnosis, or assigned with long-term disease status (M45.x, M46.0, M46.1, M46.8, M46.9) for axSpA.
  - Patient is 18 years or older at the time of cohort entry (initiation of bimekizumab or other biologics indicated for axSpA).

9.2.1.2 Cohort entry date

The cohort entry date is the day of first dispensing of bimekizumab or comparator drug for the treatment of the 3 indications (PSO, PsA, axSpA). First dispensing in all databases is defined as not having had a dispensing of the drug in the past 180 days.

For US claims databases where patients can enroll and disenroll from the database, a 180-day continuous insurance enrollment period before cohort entry will also be required.

In a sensitivity analysis, the look-back window to assess prior treatment use (all databases) will be extended to 365 days.

PSO:

Using US claims databases, a single diagnosis of PSO by a dermatologist followed by a targeted treatment for PSO, after exclusion of patients with other chronic inflammatory conditions that may be treated similarly, results in a positive predicted value (PPV) higher than those from published validation studies requiring a single diagnosis of PSO from any physician, not necessarily a dermatologist, which show PPVs of 81% (Löfvendahl et al, 2014), 78% (Asgari et al, 2013), and 82% (Lee et al, 2021).

Using the [redacted] as outpatient diagnosis codes for PSO are only available in [redacted] for patients who have been assigned long-term disease status (see definition Section 9.4.2), PSO patients will be identified by the dispensation of topical vitamin D treatment, which is the first line of care for PSO in France (Grodner 2020; Sbidian et al, 2021; Penso et al, 2021; Penso et al, 2022), or long-term disease status for psoriasis. These criteria, when used in combination with hospital outpatient and inpatient diagnosis codes for PSO, has shown a

sensitivity of 98% in Danish administrative data (Egeberg 2016). This definition has been used in several studies assessing the therapeutic management of psoriasis and the benefit-risk balance of psoriasis related treatment in the [redacted] In order to not exclude patients diagnosed with psoriasis but without two prescriptions of topical vitamin D within two years during the look back period (notably patients with severe psoriasis and starting systemic treatment or biologics early after disease onset), the diagnosis of psoriasis will be also based on inpatient diagnosis code or long-term disease status.

The PSO cohort will include 3 sub-cohort analyses with different comparator drugs that will each be 1:1 matched by propensity scores:

PSO comparative sub-cohort 1 ("*Advanced-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of moderate to severe PSO (adalimumab, etanercept, certolizumab pegol, infliximab, ustekinumab, guselkumab, risankizumab, tildrakizumab), except for other anti-IL-17s. Patients are required to have had substantial prior treatment but to have not used the drug that qualified them for cohort entry or a drug of the same class.

Substantial prior treatment means to have used at least one other biologic immune-modulating drugs (IMDs; adalimumab, etanercept, certolizumab pegol, infliximab, ustekinumab, guselkumab, risankizumab, or tildrakizumab) or targeted synthetic oral small molecule IMDs (apremilast, deucravacitinib) during the 180 days before they initiated the study drugs. In other words, each study participant switched to the study medications from their previous treatment with systemic agents.

PSO comparative sub-cohort 2 ("*First-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of moderate to severe PSO, except for other anti-IL-17s. Patients are required to have used high-potency topical or systemic corticosteroids, or nonbiologic systemic IMDs, or phototherapy, topical calcineurin inhibitors, topical roflumilast, or topical tapinarof, or topical vitamin D analogs and not have used any biologics or targeted synthetic IMDs in the 180 days before cohort entry.

Biologic IMDs or targeted synthetic oral small molecule in this context include adalimumab, etanercept, certolizumab pegol, infliximab, ustekinumab, guselkumab, risankizumab, tildrakizumab, or apremilast.

PSO comparative sub-cohort 3 ("*Systemic Naïve*"): New use of bimekizumab vs new use of any other biologic treatment for moderate to severe PSO, except for other anti-IL-17s, and no use of any systemic medications, including systemic corticosteroids, in the 180 days before cohort entry. While a first systemic treatment is infrequently started using biologics, or interruptions in systemic treatment of more than 180 days are not standard of care for PSO, such treatment patterns are observed in clinical practice and should not be excluded from a comprehensive safety assessment of bimekizumab.

Any systemic medications in this context include biologic IMDs (adalimumab, etanercept, certolizumab pegol, infliximab, ustekinumab, guselkumab, risankizumab, or tildrakizumab), nonbiologic systemic IMDs (methotrexate, cyclosporine, acitretin), and targeted synthetic oral small molecules (apremilast, deucravacitinib).

PsA:

Using US claims databases, a single diagnosis of PsA by a rheumatologist/dermatologist followed by a targeted treatment for PsA, after exclusion of patients with other chronic inflammatory conditions (except PSO) that may be treated similarly, results in a PPV higher than those from published validation studies requiring a single diagnosis of PsA from a rheumatologist, which show PPVs 86% (Wallman et al, 2023), and 80% (Lee et al, 2020).

Using the [redacted] claims database (ie, [redacted]) as outpatient diagnosis codes for PsA are only available in [redacted] for patients who have been assigned long-term disease status (see definition Section 9.4.2), patients will be identified as having PsA if one of the following conditions are met: inpatient PsA diagnosis or long-term disease status for PsA (Penso et al, 2022; Vegas et al, 2022; Vegas et al, 2021). This definition has been used in several studies assessing the therapeutic management of PsA and the benefit-risk balance of PsA related treatment in the [redacted]. Given our study design, these criteria will be used in combination with dispensing of a PsA medication. While the [redacted] does not specify medication indication for outpatient pharmacy dispensings, patients being fully reimbursed for treatment related to severe, costly or chronic diseases have their health status recorded and coded according to ICD-10 (Vegas et al. 2022).

The PsA cohort will include 3 sub-cohorts with different comparator drugs that will each be 1:1 matched by propensity scores:

PsA comparative sub-cohort 1 ("*Advanced-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of PsA (adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, abatacept, ustekinumab, guselkumab, or risankizumab), except for other anti-IL-17s. Patients are required to have had substantial prior treatment but to have not used the drug that qualified them for cohort entry or a drug of the same class. As TNFi are the most effective treatment for PsA, patients usually have failed a TNFi before starting another biologic. The clinical trial (BE COMPLETE) for bimekizumab in patients with PsA reflects this in their trial design of assessing bimekizumab in the PsA patients with inadequate response or intolerance to a TNFi.

Substantial prior treatment means to have used at least one other biologic IMD (adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, abatacept, ustekinumab, guselkumab, or risankizumab) or targeted synthetic oral small molecule IMDs (apremilast, upadacitinib, or tofacitinib) during the 180 days before they initiated the study drugs. In other words, each study participant switched to the study medications from their previous treatment with systemic agents.

PsA comparative sub-cohort 2 ("*First-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of PsA, except for other anti-IL-17s. Patients are required to have used systemic corticosteroids (at least 2 consecutive dispensings), or nonsteroidal anti-inflammatory drugs (NSAIDs) (at least 2 consecutive dispensings), or intraarticular corticosteroid injection or nonbiologic systemic IMDs, and not have used any biologics or targeted synthetic IMDs in the 180 days before cohort entry.

Biologic IMDs or targeted synthetic oral small molecule in this context include adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, abatacept, ustekinumab, guselkumab, risankizumab, apremilast, upadacitinib or tofacitinib.

Nonbiologic systemic IMDs in this context include, methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine.

PsA comparative sub-cohort 3 ("*Systemic Naïve*"): New use of bimekizumab vs new use of any PsA other biologic treatment for PsA, except for other anti-IL-17s, and no use of any systemic medications, including systemic corticosteroids, in the 180 days before cohort entry. While a first systemic treatment is infrequently started using biologics, or interruptions in systemic treatment of more than 180 days are not standard of care for PsA, such treatment patterns are observed in clinical practice and should not be excluded from a comprehensive safety assessment of bimekizumab.

Any systemic medications in this context include biologic IMDs (adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, abatacept, ustekinumab, guselkumab, or risankizumab), nonbiologic systemic IMDs (methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine), and targeted synthetic oral small molecules (apremilast, upadacitinib, or tofacitinib).

axSpA:

Using US claims databases, a single diagnosis of axSpA by a rheumatologist followed by a targeted treatment for axSpA, after exclusion of patients with other chronic inflammatory conditions that may be treated similarly, results in a PPV higher than those from published validation studies requiring a single diagnosis of axSpA from a rheumatologist, which show PPVs of 79% to 82% (Lindström et al, 2015), 73% (Curtis et al, 2016), and 98% (Haglund et al, 2011).

Using the [redacted] claims database (ie, [redacted] as outpatient diagnosis codes for axSpA are only available in [redacted] for patients who have been assigned long-term disease status (see definition Section 9.4.2), patients will be identified as having axSpA if one of the following conditions are met: inpatient axSpA diagnosis or long-term disease status for axSpA (Penso et al, 2022). This definition has been used in several studies assessing the therapeutic management of axSpA and the benefit-risk balance of axSpA related treatment in the [redacted].

The axSpA cohort will include 3 sub-cohorts with different comparator drugs that will each be 1:1 matched by propensity scores:

axSpA comparative sub-cohort 1 ("*Advanced-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of nr-axSpA and r-axSpA (adalimumab, etanercept, certolizumab pegol, infliximab, or golimumab), except for other anti-IL-17s. Patients are required to have had substantial prior treatment but to have not used the drug that qualified them for cohort entry or a drug of the same class.

Substantial prior treatment means to have used at least one other biologic IMD (adalimumab, etanercept, certolizumab pegol, infliximab, or golimumab) or targeted synthetic oral small molecule IMDs (upadacitinib or tofacitinib) during the 180 days before they initiated the study drugs. In other words, each study participant switched to the study medications from their previous treatment with systemic agents.

axSpA comparative sub-cohort 2 ("*First-line Biologics*"): New use of bimekizumab vs new use of any other biologic treatment indicated for the treatment of r- and nr-axSpA, except for other anti-IL-17s. Patients are required to have used systemic corticosteroids (at least 2 consecutive

dispensings), or NSAIDs (at least 2 consecutive dispensings), or intraarticular corticosteroid injection and not have used any biologics or targeted synthetic IMDs in the 180 days before cohort entry.

Biologic IMDs or targeted synthetic oral small molecule in this context include adalimumab, etanercept, certolizumab pegol, infliximab, golimumab, upadacitinib, or tofacitinib.

axSpA comparative sub-cohort 3 ("*Systemic Naïve*"): New use of bimekizumab vs new use of any other biologic treatment for r- and nr-axSpA, except for other anti-IL-17s, and no use of any systemic medications, including systemic corticosteroids, in the 180 days before cohort entry.

Any systemic medications in this context include biologic IMDs (adalimumab, etanercept, certolizumab pegol, infliximab, or golimumab), and targeted synthetic oral small molecules (upadacitinib or tofacitinib).

9.2.2 Exclusion criteria

All exclusion criteria will be applied to the 180 days before cohort entry unless specifically stated otherwise. As each indication (PSO, PsA, axSpA) will have its own cohort analysis, exclusion criteria will be tailored to each indication.

PSO:

- Treatment ambiguity: Patients who started more than 1 comparator drug on the same day will be excluded.
- Enrollment: Patients who have less than 180 days of enrollment in the insurance plan (medical as well as pharmacy coverage) for US claims, or less than 180 days of medical history (based on any healthcare use) for [redacted], before the cohort entry date will be excluded. For US claims, coverage gaps of up to 30 days are allowed. In a sensitivity analysis, the enrollment window (US claims) and medical history [redacted] will be expanded to 365 days.
- Conditions that are equally treated with IMDs: Patients who may have received IMDs for other indications will be excluded. Those exclusions will be a recorded diagnosis of other systemic inflammatory disease, including rheumatoid arthritis, axial arthritis, PsA, IBD, autoimmune blistering diseases, malignancies, organ transplantation, or other autoimmune conditions (including uveitis).
- Non-PSO systemic IMDs: Patients using IMDs indicated for other inflammatory diseases, including dupilumab, leflunomide, mycophenolate, rituximab, tocilizumab, sarilumab, anakinra, cyclophosphamide, efalizumab, abatacept, tacrolimus (oral), sirolimus, sulfasalazine, olsalazine, balsalazide, mesalamine (oral and rectal), azathioprine, mercaptopurine, and vedolizumab, will be excluded.
- Pre-existing outcomes of interest: To study the new occurrence of the outcomes of interest, patients who already have the outcome will be excluded. This varies by outcome of interest and will be done separately for each outcome analysis. Specifically:
  - For the outcome of MACE: Patients with recorded diagnosis codes for myocardial infarction (MI), stroke, acute coronary syndrome (ACS), or procedure codes for coronary artery bypass graft (CABG) surgery or coronary stent implantation, or related long-term

disease status [redacted] only). The look-back window is at least 180 days before cohort entry plus all additionally available look-back time.

- For the outcome of malignancies: Patients with 2 or more diagnosis codes for a solid or hematologic cancer or related long-term disease status ([redacted] only). The look-back window is at least 180 days before cohort entry plus all additionally available look-back time.
- For the outcome of IBD (US): Patients with 2 or more diagnosis codes for either ulcerative colitis (UC) or Crohn's Disease (CD) or 1 code in combination with a colonoscopy or hospitalization. For the [redacted]: At least one hospital discharge diagnosis code (any position) or long-term status related to IBD. The look-back window is at least 180 days before cohort entry plus all additionally available look-back time.
- For the outcome of serious infection: Patients with chronic infections, including chronic osteomyelitis, chronic opportunistic infections, chronic mastoiditis, viral hepatitis, and chronic pyelonephritis. Patients with hospitalization for opportunistic infections (bacterial, viral, fungal, helminthic). The look-back window is at least 180 days before cohort entry.
- For the outcome of serious hypersensitivity: Patients with the use of single-dose epinephrine autoinjector (eg, EpiPen™) or recorded diagnosis codes of hypersensitivity followed by systemic corticosteroid treatment or hospitalizations for hypersensitivity. The look-back window is at least 180 days before cohort entry plus all additionally available look-back time.

***PsA*:**

- Treatment ambiguity: Patients who started more than 1 comparator drug on the same day will be excluded.
- Enrollment: Patients who have less than 180 days of enrollment in the insurance plan (medical as well as pharmacy coverage) for US claims, or less than 180 days of medical history (based on any healthcare use) for [redacted] before the cohort entry date will be excluded. For US claims, coverage gaps of up to 30 days are allowed. In a sensitivity analysis, the enrollment window (US claims) and medical history ([redacted]) will be expanded to 365 days.
- Conditions that are equally treated with IMDs: Patients who may have received IMDs for other indications will be excluded. Those exclusions will be a recorded diagnosis of other systemic inflammatory disease (except PSO), including rheumatoid arthritis, axial arthritis, IBD, autoimmune blistering diseases, malignancies, organ transplantation, or other autoimmune conditions.
- Non-PsA systemic IMDs: Patients using IMDs indicated for other inflammatory diseases, including dupilumab, mycophenolate, rituximab, tocilizumab, sarilumab, anakinra, cyclophosphamide, efalizumab, tacrolimus (oral), sirolimus, olsalazine, balsalazide, mesalamine (oral and rectal), azathioprine, mercaptopurine, and vedolizumab, will be excluded.
- Pre-existing outcomes of interest: same as above for PSO

***axSpA*:**

- Treatment ambiguity: Patients who started more than 1 comparator drug on the same day will be excluded.
- Enrollment: Patients who have less than 180 days of enrollment in the insurance plan (medical as well as pharmacy coverage) for US claims, or less than 180 days of medical history (based on any healthcare use) for [redacted] before the cohort entry date will be excluded. For US claims, coverage gaps of up to 30 days are allowed. In a sensitivity analysis, the enrollment window (US claims) and medical history ([redacted]) will be expanded to 365 days.
- Conditions that are equally treated with IMDs: Patients who may have received IMDs for other indications will be excluded. Those exclusions will be a recorded diagnosis of other systemic inflammatory disease, including rheumatoid arthritis, PSO, PsA, IBD, autoimmune blistering diseases, malignancies, organ transplantation, or other autoimmune conditions.
- Non-axSpA systemic IMDs: Patients using IMDs indicated for other inflammatory diseases, including dupilumab, leflunomide, mycophenolate, rituximab, tocilizumab, sarilumab, anakinra, cyclophosphamide, efalizumab, abatacept, tacrolimus (oral), sirolimus, sulfasalazine, olsalazine, balsalazide, mesalamine (oral and rectal), azathioprine, mercaptopurine, and vedolizumab, will be excluded.

Pre-existing outcomes of interest: same as above for PSO.

9.3 Variables

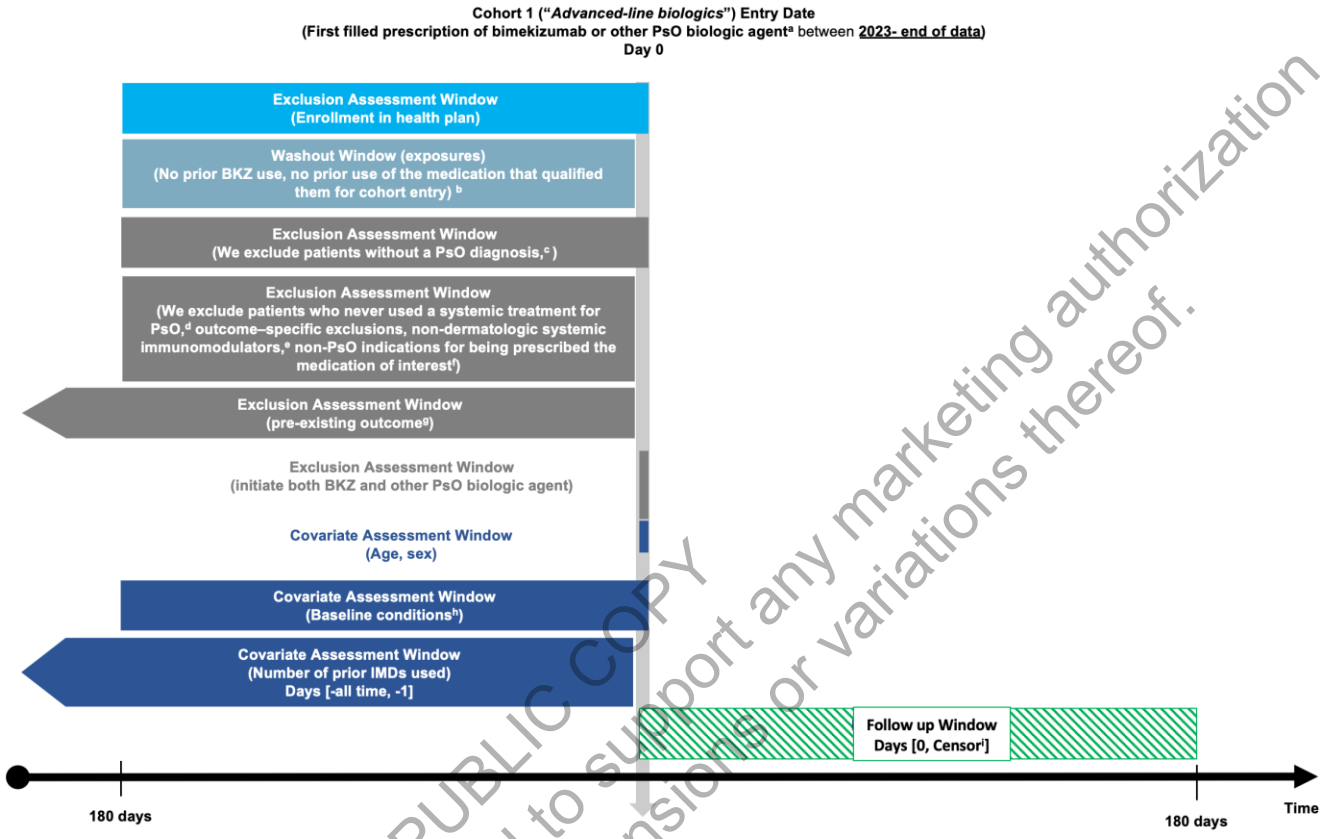
A range of variables will be measured in the longitudinal data stream (see preliminary code lists in Appendix 4), many of them over a defined time window.

Figure 9-1 illustrates the study time windows for PSO sub-cohort 1, and the same framework is applicable for sub-cohorts 2 and 3.

Figure 9-2 illustrates the study time windows for PsA sub-cohort 1, and the same framework is applicable for sub-cohorts 2 and 3.

Figure 9-3 illustrates the study time windows for axSpA sub-cohort 1, and the same framework is applicable for sub-cohorts 2 and 3.

Figure 9-1: Study design for PSO sub-cohort 1



BKZ=bimekizumab; i=inhibitor; ICD=International Classification of Diseases; IL=interleukin; IMD=immune-modulating drug; PSO=psoriasis; TNF=tumor necrosis factor

[a] Other PSO biologic agents, except for other anti-IL-17 biologics, including anti-TNF (adalimumab, etanercept, certolizumab pegol, infliximab), IL-12/23i (ustekinumab), IL-23i (risankizumab, guselkumab, and tildrakizumab).

[b] For *the Advanced-Line Biologics* cohort, patients are required to have used prior systemic treatment(s) for PSO, but to not have used the medication that qualified them for cohort entry.

[c] All patients must have at least 1 visit or hospitalization with a PSO ICD (ICD-10, not including L40.5 – psoriasis with arthropathy), defined as: 1 diagnosis by a dermatologist.

[d] Prior systemic treatment for PSO includes biologic IMDs (anti-TNF, IL-12/23i, IL-23i, IL-17i), systemic non-biologic IMDs, including conventional synthetic (methotrexate, cyclosporine, acitretin) and targeted synthetic (apremilast, deucravacitinib).

[e] Non-PSO systemic IMDs include dupilumab, leflunomide, mycophenolate, rituximab, tocilizumab, sarilumab, anakinra, cyclophosphamide, efalizumab, abatacept, tacrolimus (oral only), sirolimus, sulfasalazine, olsalazine, balsalazide, mesalamine (oral or rectal), azathioprine, mercaptopurine, or vedolizumab.

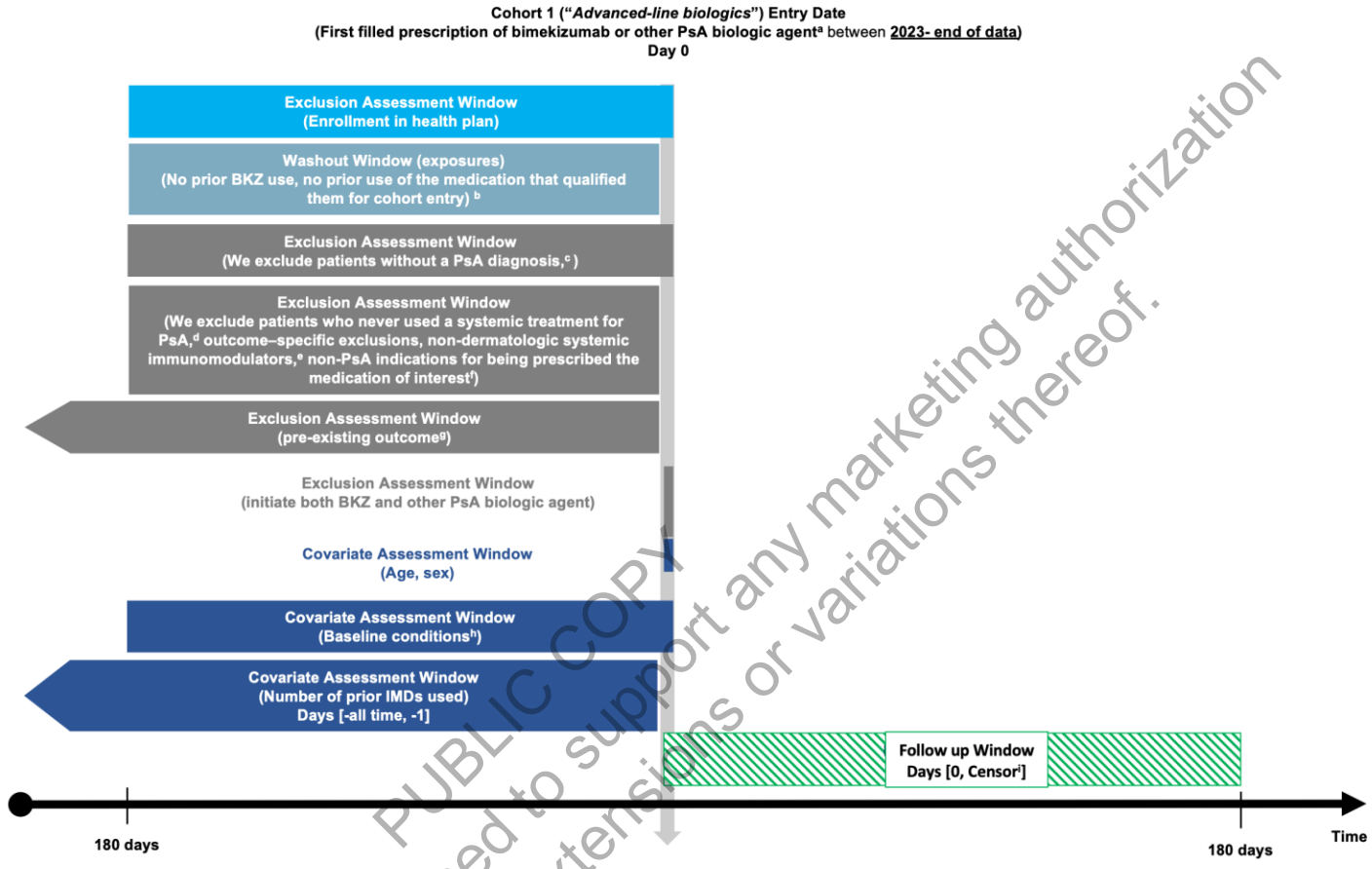
[f] Non-PSO indications for starting drug of interest includes: rheumatoid arthritis, inflammatory bowel disease, axial arthritis, PsA, autoimmune blistering diseases, organ transplant, and other autoimmune conditions eg, Behcet's disease, uveitis, sarcoidosis).

[g] Patients who had the outcome of interest prior to treatment initiation will be excluded. The exclusion window is 180 days for prior infections and 180 days plus all additional time for other outcomes.

[h] See Section 9.3.3 for baseline conditions/pretreatment patient characteristics.

[i] Earliest of outcome of interest, switching or discontinuation of study drugs, death, disenrollment, 180 days of follow up, end of the study period (follow-up length may vary for specific outcomes).

Figure 9-2: Study design for PsA sub-cohort 1



BKZ=bimekizumab; i=inhibitor; ICD=International Classification of Diseases; IL=interleukin; IMD=immune-modulating drug; PsA=psoriatic arthritis; TNF=tumor necrosis factor

[a] Other PsA biologic agents, except for other anti-IL-17 biologics, including anti-TNF (adalimumab, etanercept, certolizumab pegol, infliximab, golimumab), IL-12/23i (ustekinumab), IL-23i (risankizumab, guselkumab), CTLA4-Ig (abatacept).

[b] For *the Advanced-Line Biologics* cohort, patients are required to have used prior systemic treatment(s) for PsA, but to not have used the medication that qualified them for cohort entry.

[c] All patients must have at least 1 visit or hospitalization with a PsA ICD (ICD-10 L40.5), defined as: 1 diagnosis by a rheumatologist or dermatologist. This is not required for the [redacted]-based analyses.

[d] Prior systemic treatment for PsA includes biologic IMDs (anti-TNF, IL-12/23i, IL-23i, IL17i, CTLA4-Ig), systemic non-biologic IMDs, including conventional synthetic (methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) and targeted synthetic (eg, apremilast, upadacitinib, or tofacitinib).

[e] Non-PsA systemic IMDs include dupilumab, mycophenolate, rituximab, tocilizumab, sarilumab, anakinra, cyclophosphamide, efalizumab, tacrolimus (oral only), sirolimus, olsalazine, balsalazide, mesalamine (oral or rectal), azathioprine, mercaptopurine, or vedolizumab.

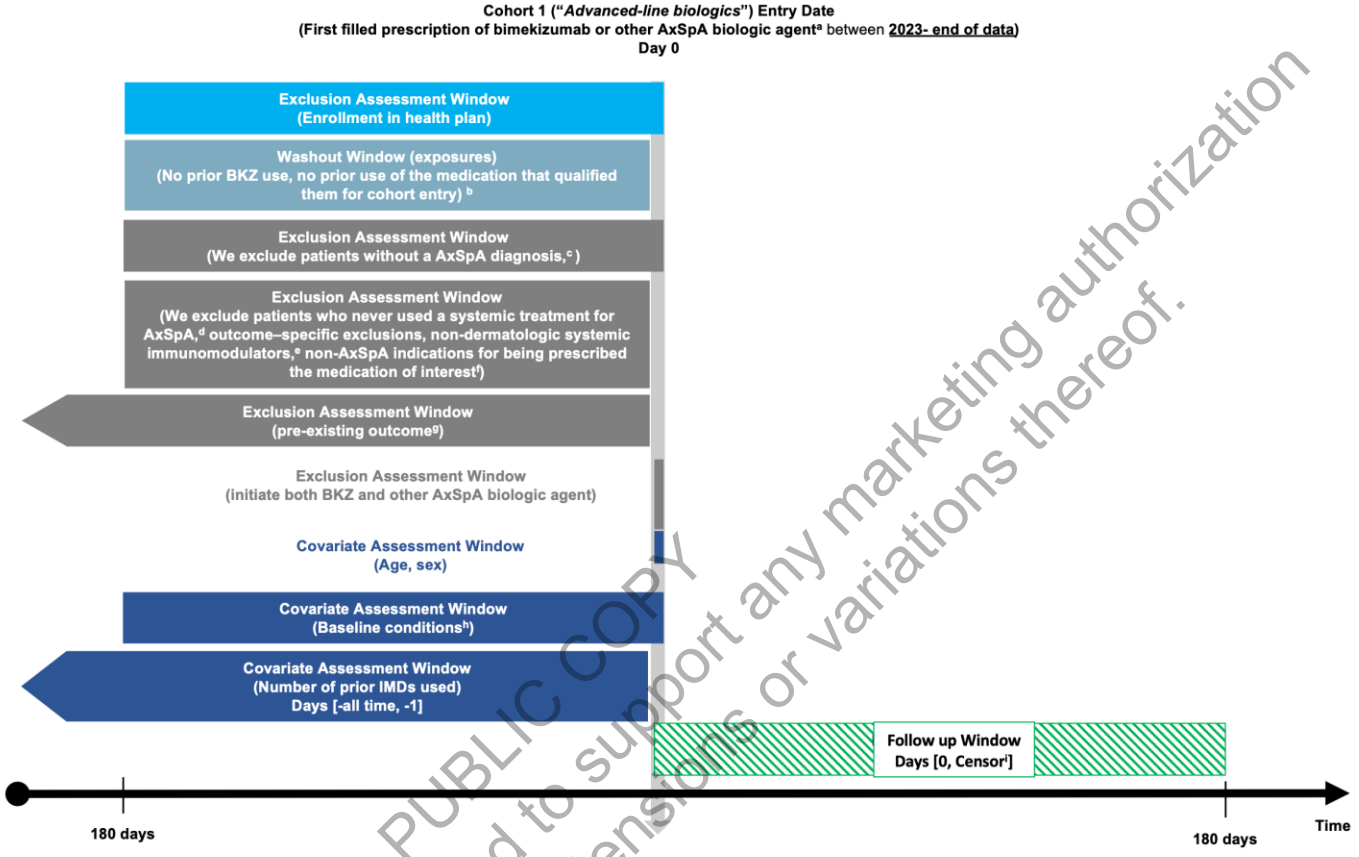
[f] Non-PsA indications for starting drug of interest includes: rheumatoid arthritis, inflammatory bowel disease, axial arthritis, autoimmune blistering diseases, organ transplant, and other autoimmune conditions (eg, Behcet's disease, uveitis, sarcoidosis).

[g] Patients who had the outcome of interest prior to treatment initiation will be excluded. The exclusion window is 180 days for prior infections and 180 days plus all additional time for other outcomes.

[h] See Section 9.3.3 for baseline conditions/pretreatment patient characteristics.

[i] Earliest of outcome of interest, switching or discontinuation of study drugs, death, disenrollment, 180 days of follow up, end of the study period (follow-up length may vary for specific outcomes).

Figure 9-3: Study design for axSpA sub-cohort 1



axSpA=axial spondyloarthritis; BKZ=bimekizumab; i=inhibitor; ICD=International Classification of Diseases; IL=interleukin; IMD=immune-modulating drug; PsA=psoriatic arthritis; PSO=psoriasis; TNF=tumor necrosis factor

[a] Other axSpA biologic agents, except for other anti-IL-17 biologics, including anti-TNF (adalimumab, etanercept, certolizumab pegol, infliximab, and golimumab).

[b] For *the Advanced-Line Biologics* cohort, patients are required to have used prior systemic treatment(s) for axSpA, but to not have used the medication that qualified them for cohort entry.

[c] All patients must have at least 1 visit or hospitalization with a axSpA ICD (ICD-10 M45.x, M46.0, M46.1, M46.8, M46.9) for axSpA), defined as: 1 diagnosis by a rheumatologist.

[d] Prior systemic treatment for axSpA includes biologic IMDs (anti-TNF-and targeted synthetic (eg, upadacitinib, tofacitinib).

[e] Non-axSpA systemic IMDs include dupilumab, leflunomide, mycophenolate, rituximab, sarilumab, tocilizumab, anakinra, cyclophosphamide, efalizumab, abatacept, tacrolimus (oral only), sirolimus, sulfasalazine, olsalazine, balsalazide, mesalamine (oral or rectal), azathioprine, mercaptopurine, or vedolizumab.

[f] Non-axSpA indications for starting drug of interest includes: rheumatoid arthritis, inflammatory bowel disease, PsA, PSO, autoimmune blistering diseases, organ transplant, and other autoimmune conditions (eg, Behcet's disease, uveitis, sarcoidosis).

[g] Patients who had the outcome of interest prior to treatment initiation will be excluded. The exclusion window is 180 days for prior infections and 180 days plus all additional time for other outcomes.

[h] See Section 9.3.3 for baseline conditions/pretreatment patient characteristics.

[i] Earliest of outcome of interest, switching or discontinuation of study drugs, death, disenrollment, 180 days of follow up, end of the study period (follow-up length may vary for specific outcomes).

9.3.1 Exposure of interest

The first occurrence of the exposure to bimekizumab or the comparator drug defines the cohort entry date (see Section 9.2.1.2). The use of a specific drug is defined by the dispensing of the drug in a pharmacy.

In the US, claims drugs are coded using the National Drug Code (NDC) maintained by the US FDA. The agents are defined by their brand name as well as their generic or biosimilar name. The infusible infliximab will be identified through a Healthcare Common Procedure Coding System procedure code from the provider. It has been demonstrated multiple times in US claims data that pharmacy dispensing of medications is more accurate than electronic health records and patient recall (West et al, 1997; West et al, 1995, West et al, 1994). For the [redacted], drugs are coded using a French national registration code (Code Identifiant de Présentation [CIP]) and Anatomical Therapeutic Chemical codes maintained by the WHO (WHO, 1993).

Details about the exposure definitions are summarized in Table 9-1.

Table 9-1: Exposure group definitions[a]

Exposure Status	Generic name	Brand name	Mechanism of action	Route of administration	Typical dosing	Days' supply[b]	Grace period	ERW
Exposure, PSO	Bimekizumab	Bimzelx	IL-17A/F	sc injection	Q8W	56 days	30	7-180 days[c]
Exposure, PsA	Bimekizumab	Bimzelx	IL-17A/F	sc injection	Q4W	28 days	30	7-180 days[c]
Exposure, axSpA	Bimekizumab	Bimzelx	IL-17A/F	sc injection	Q4W	28 days	30	7-180 days[c]
Comparator, PSO	Risankizumab-rzaa	Skyrizi	IL-23 p19 subunit	sc injection	Q12W	84 days	30	7-180 days[c]
Comparator, PSO	Guselkumab	Tremfya	IL-23 p19 subunit	sc injection	Q8W	56 days	30	7-180 days[c]
Comparator, PSO	Tildrakizumab	Ilumya	IL-23 p19 subunit	sc injection	Q12W	84 days	30	7-180 days[c]
Comparator, PSO	Ustekinumab	Stelara	IL-12/23	sc injection	Q12W	84 days	30	7-180 days[c]
Comparator, PSO	Infliximab	Remicade	TNF inhibitor	iv infusion	Q8W	56 days	30	7-180 days[c]
Comparator, PSO	Etanercept	Enbrel	TNF inhibitor	sc injection	Q1W	7 days*4	30	7-180 days[c]
Comparator, PSO	Adalimumab	Humira	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, PSO	Certolizumab pegol	Cimzia	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, PsA	Risankizumab-rzaa	Skyrizi	IL-23 p19 subunit	sc injection	Q12W	84 days	30	7-180 days[c]
Comparator, PsA	Guselkumab	Tremfya	IL-23 p19 subunit	sc injection	Q8W	56 days	30	7-180 days[c]

Comparator, PsA	Ustekinumab	Stelara	IL-12/23	sc injection	Q12W	84 days	30	7-180 days[c]
Comparator, PsA	Infliximab	Remicade	TNF inhibitor	iv infusion	Q8W	56 days	30	7-180 days[c]
Comparator, PsA	Etanercept	Enbrel	TNF inhibitor	sc injection	Q1W	7 days*4	30	7-180 days[c]
Comparator, PsA	Adalimumab	Humira	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, PsA	Certolizumab pegol	Cimzia	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, PsA	Golimumab	Simponia	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, PsA	Abatacept	Orencia	CTLA4-Ig analog	Sc injection	Q1W	7 days	30	7-180 days[c]
Comparator, axSpA	Infliximab	Remicade	TNF inhibitor	iv infusion	Q8W	56 days	30	7-180 days[c]
Comparator, axSpA	Etanercept	Enbrel	TNF inhibitor	sc injection	Q1W	7 days*4	30	7-180 days[c]
Comparator, axSpA	Adalimumab	Humira	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, axSpA	Certolizumab pegol	Cimzia	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]
Comparator, axSpA	Golimumab	Simponia	TNF inhibitor	sc injection	Q2W	14 days*2	30	7-180 days[c]

axSpa= axial spondyloarthritis; ERW=exposure risk window; IL=interleukin; iv=intravenous; PsA=psoriatic arthritis; Q1W=once every week; Q2W=once every 2 weeks; Q8W=once every 8 weeks; Q12W=once every 12 weeks; sc=subcutaneous; TNF=tumor necrosis factor.
Note: other IL-17 biologics (ixekizumab, secukinumab, brodalumab) will not be included as comparators in the analysis.
[a] New biologics which are approved for moderate to severe PSO during the study period will be added to the list of comparator drugs.
[b] The listed days' supply are informed by the empirical assessment by Hendrix et al (2020) and drug label information. To be specific, we will not use a "days' supply" field that is sometimes recorded in pharmacy dispensing files but we compute the days' supply from the number of syringes dispensed and the bioavailability.
[c.] The ERW is outcome specific (see Section 9.3.2) and the longer of the grace period and the ERW will be added.

9.3.2 Follow up and outcomes of interest

The follow-up and outcomes of interest are the same across the 3 cohort analyses, (PSO, PsA, axSpA).

Follow-up starts the day after cohort entry (see Section 9.2.1.2), with the exception of hypersensitivity outcome analysis for which the follow-up time starts on the day of cohort entry. Two follow-up models that have different endpoints will be defined:

1. In an As-Treated (AT) analysis, patients will be followed for the duration of treatment, or until the occurrence of the outcome, the end of enrollment, or the end of data availability, whichever comes first. An AT analysis focuses on the treatment effects on the specified study outcomes while under treatment with the drugs of interest and not after treatment was stopped; it is sometimes also referred to as "on-treatment," and is similar to "per-protocol" analyses in RCTs. The end of treatment is defined by not having refilled a prescription within the end of the days' supply of the last prescription. We define a grace period of 30 days to bridge individual prescription refills. Censoring due to the lack of a refill may be due to multiple reasons, including discontinuation of treatment or switching to another treatment. The days' supply algorithm is product specific and listed in Table 9-1. We further define an outcome-specific exposure risk windows within which an effect can still be causally attributed to the exposure. The longer of the two, grace period or ERW, will be added to the end of the day's supply to define end of exposure to the drug of interest. The default exposure risk window (ERW) of 14 days, the number of days added after the end of days' supply during which the patients will still be categorized as exposed to the index drug, will be adapted to each study outcome in light of the likely biology and pathophysiology as listed below.
2. In an As-Started (AS) analysis, patients will be followed up to a fixed duration (adapted to each outcome), the occurrence of the outcome, the end of the data stream, or death, whichever comes first; it is sometimes also referred to as "once-exposed, always at risk," or "first exposure carried forward." It is conceptually similar to an intention-to-treat analysis of RCT data. As in RCTs, this analysis is not subject to informative censoring.

In each of the three pairwise comparisons (comparative Cohort 1 through 3), patients contribute only once. Patients are not allowed to reenter the same cohort once their follow-up for the primary analysis has ended (ie, a patient who switches from bimekizumab to a comparator biologic will not be included in the comparator cohort after switch, follow-up will be censored). However, subjects are allowed to contribute once to each of the pairwise comparisons. Subjects will be followed up for each outcome and may contribute to risk analysis for more than one outcome.

In the new-user cohort designs cumulative dose effects can be inferred directly from Kaplan-Meier plots. Further explicit quantification of cumulative dose effects are not planned.

Some follow-up details will vary by outcome, and details are described next to each outcome definition. Outcome definitions have been adapted to each database according to the data available in respective databases.

At least the occurrence of the following outcomes will be studied. The event date is the date when all event criteria are fulfilled (see Appendix 4 for coding details):

1. Major adverse cardiovascular event:
   - US claims: Patients hospitalized with a diagnosis code for MI, ACS, stroke, or CABG surgery as the primary discharge code, or an emergency room visit with the diagnosis of MI, ACS, or coronary heart disease (CHD) that is combined with a coronary stent implantation.
   - [redacted]: Patients hospitalized with a diagnosis code for MI, ACS, stroke, or CABG surgery as the primary discharge code, or CHD that is combined with a coronary stent implantation.
   - The ERW is defined as 14 days and the fixed follow-up time as 365 days. Given the biology of coronary heart disease and the potential factors intervening in this biology, it seems reasonable to assume that MACE outcomes within a year of starting treatment could be causally connected if at all.
2. Malignancies:
   - US claims: Patients with 2 diagnosis codes for a solid or hematologic cancer within 1 month (Setoguchi et al, 2006) and an imaging procedure, including computed tomography (CT) scan, magnetic resonance imaging (MRI), or bone scan.
   - [redacted] patients with 1) a discharge diagnosis code related to cancer as primary or related diagnosis, or 2) appointment of a long-term cancer disease status after index date, or 3) dispensation of chemotherapy, or 4) or radiotherapy procedure.
   - The ERW for malignancies is defined as 180 days and the fixed follow-up time as up to 5 years. Given the biology of cancer induction and cancer promotion and the potential factors intervening in this biology it seems reasonable to assume that newly occurring cancers may become clinically apparent with several years of delay (Lebwohl et al, 2021). Even if cancers newly occur several years after treatment initiation there may still be a causal link.
3. New IBD:
   - US claims: Patients hospitalized with a diagnosis code for either UC or CD as the primary discharge code or 1 outpatient diagnosis code in combination with a colonoscopy or flexible sigmoidoscopy.
   - [redacted] two hospital discharge diagnoses of CD or UC (ICD-10 codes K50 and K51, respectively), or one hospital discharge diagnosis and a prescription filled for one of the following drugs: aminosalicylic acid, mesalazine, olsalazine, enteral budesonide, azathioprine, mercaptopurine, vedolizumab, or an appointment of a long-term IBD disease status after the index date.
   - The ERW for new IBD is defined as 14 days and the fixed follow-up time as 365 days. Given the biology of UC and CD and the potential factors intervening in this biology, it seems reasonable to assume that IBD may occur within a year of starting treatment could be causally connected if at all (Schneeweiss et al, 2022a).

4. Serious infection:
   - US claims and [redacted]: Patients hospitalized with a diagnosis code for bacterial, viral, or opportunistic infections (bacterial, fungal, viral, helminthic) as the primary discharge code.
   - The ERW for serious infections is defined as 90 days and the fixed follow-up time as 180 days. The new occurrence of infections due to changes in the immune response are hypothesized to happen fairly soon after treatment initiation if at all. Previous studies on the risk of infections in IMDs in dermatologic conditions have focused on 180 days of follow-up (Schneeweiss et al, 2022; Schneeweiss et al, 2021; Schneeweiss et al, 2020; Jin et al, 2022; Dommasch et al, 2019).
5. Serious hypersensitivity reaction:
   - US claims: Patients with recorded diagnosis codes of hypersensitivity followed by corticosteroid treatment or hospitalizations for hypersensitivity as the primary discharge code.
   - [redacted] patients hospitalized for hypersensitivity as the primary discharge code.
   - The ERW is defined as 7 days and the fixed follow-up time as 90 days. The new occurrence of hypersensitivity is hypothesized to happen shortly after treatment start, possibly with the second injection. Therefore, a follow-up window of 90 days seems appropriate.
6. Other outcomes of interest (eg, oral candidiasis).

9.3.3 Pretreatment patient characteristics for confounding control

A range of pretreatment patient characteristics will be measured during the 180 days before and including the cohort entry date (or during all available time prior to cohort entry as specified below):

9.3.3.1 Characteristics specific to cohort analyses (PSO, PsA, axSpA, respectively)

PSO:

- Demographics: Age, gender, and calendar year of cohort entry.
- Severity markers of PSO: Any use of systemic glucocorticoids, recent use of systemic glucocorticoids (<30 days before cohort entry), cumulative dose of systemic glucocorticoids. Use of non-corticosteroid IMDs, including targeted nonbiologic agents (methotrexate, acitretin, or cyclosporine), targeted synthetic IMDs (eg, apremilast, deucravacitinib), biologics (eg, TNFi, IL12/23i, IL23i), number of prior IMDs (1, 2+), and number of dermatologist visits (2, 3+). Note: although the listed markers for PSO severity will be balanced in the analysis, these are not, or are at worst weak, independent predictors for the outcome of interest and hence are unlikely to cause major confounding.

PsA:

- Demographics: Age, gender, and calendar year of cohort entry.
- Severity markers of PsA: Any use of systemic glucocorticoids, recent use of systemic glucocorticoids (<30 days before cohort entry), cumulative dose of systemic glucocorticoids. Use of non-corticosteroid IMDs, including targeted nonbiologic agents (methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine), biologics (TNFi including golimumab, IL12/23i, IL23i, CTLA4-Ig), targeted synthetic IMDs (eg, apremilast, upadacitinib, tofacitinib), number of prior IMDs (1, 2+), intra-auricular corticosteroid injection, NSAID use (2 consecutive dispensings), comorbid PSO, and number of rheumatologist visits (2, 3+). Note: although the listed markers for PsA severity will be balanced in the analysis, these are not, or are at worst weak, independent predictors for the outcome of interest and hence are unlikely to cause major confounding.

axSpA:

- Demographics: Age, gender, and calendar year of cohort entry.
- Severity markers of axSpA: Any use of systemic glucocorticoids, recent use of systemic glucocorticoids (<30 days before cohort entry), cumulative dose of systemic glucocorticoids. Use of non-corticosteroid IMDs, biologics (TNFi, including golimumab), targeted synthetic IMDs (eg, upadacitinib, tofacitinib), number of prior IMDs (1, 2+), intra-auricular corticosteroid injection, NSAID use (2 consecutive dispensings), comorbid PSO and number of rheumatologist visits (2, 3+).

9.3.3.2 Characteristics common to all cohort analyses (PSO, PsA, axSpA, respectively)

- Specific risk factors for the outcomes of interest (in addition to the exclusions that have already been applied at this stage):
  - MACE: Diagnoses of diabetes, hypertension, hyperlipidemia, peripheral vascular disease, drugs to treat diabetes, hypertension, hyperlipidemia, CHD, arrhythmias, antiplatelet agents, smoking, obesity, renal disease or renal failure, cardiologist visit (yes/no).
  - Malignancies: Smoking, alcohol use at any time before cohort entry.
  - IBD: Diarrhea, constipation, irritable bowel syndrome, gastroesophageal reflux disease, prior *Clostridium difficile* infection, abdominal/pelvic CT scan or MRI, fecal pathogen tests ordered (including *Clostridium difficile*), hospitalization related to abdominal issues, any abdominal surgery, smoking and proxy measures for smoking (eg, chronic obstructive pulmonary disease), gastroenterologist visit (yes/no).
  - Serious infection outcome: Intravenous drug use, inhaled corticosteroid use, end stage renal disease, diabetes, oral antibiotic use, intravenous antibiotic use, vaccinations for influenza, pneumonia, herpes, hepatitis.
  - Serious hypersensitivity outcome: Angiotensin converting enzyme inhibitor use, anaphylactic reaction to food, other or unspecified allergies, patch testing, desensitization to allergens procedure, contact dermatitis (allergic, irritant, unspecified), allergic rhinitis, drug allergy, food allergy, allergist visit.

- General comorbidities: The Combined Comorbidity Index that summarizes the prevalence of codes for a set of 36 conditions will be constructed (Gagne et al, 2011).
- Health service utilization intensity: Number of physician visits, hospitalization (yes/no), emergency room visit (yes/no), number of different medications used (Schneeweiss et al, 2001). These variables or their proxy will be derived where possible.

9.3.4 Patient subgroups

A range of pretreatment patient characteristics (see Section 9.3.3) will be measured during the 180 days before cohort entry to identify subgroups and study effect measure modification:

- Age: Separate analyses will be conducted for age groups, eg, 18 to 30, 31 to 64, 65 and older, and by gender.
- Gender: Separate analyses will be conducted for male and female patients.
- Coronavirus Disease 2019 (COVID-19) vaccination status: Separate analyses will be conducted for patients with recorded COVID-19 vaccination. COVID-19 vaccines stimulate immune responses that may interact with bimekizumab and other systemic IMDs. While this is the case for all vaccines, given the high prevalence of COVID-19 vaccinations due to the severe acute respiratory syndrome coronavirus 2 pandemic, COVID-19 vaccination should be part of a comprehensive safety assessment.

Other prespecified stratification criteria for the respective outcome may be defined.

9.4 Data sources

The bimekizumab patient populations (PSO, PsA, and axSpA) in the US and EU are not anticipated to have meaningful demographic or clinical differences that would impact analysis of outcomes of interest (Ighani et al, 2019; Michalek et al, 2017; Radtke et al, 2017; Shah et al, 2017; Takeshita et al, 2017). This study will use well documented and well-established healthcare databases for post authorization safety studies in the EU and US.

The US databases will be used through a licensing agreement with the Brigham and Women's Hospital. Due to substantial differences in healthcare systems between the US and France and differences in the types of data (administrative versus claims), this may lead to significant heterogeneity in country level estimates, precluding pooling of data across countries.

9.4.1 US data sources

The [redacted] database

The [redacted] databases consist of de-identified patient-level claims data submitted to insurance companies by US providers of inpatient, outpatient, pharmacy, and laboratory services, as well as lab test results in a subset of patients, which are aggregated by [redacted]. The largest database held by [redacted] covers over 150 million patients across the US.

Several validation methods found a linkage sensitivity of 98.2% and multiple independent estimates using the method of mutual exclusivity consistently provide an estimated specificity of 99.6% to 99.7% (Polinski et al, 2022). The [redacted] database has been used for drug safety and vaccine effectiveness studies in the past (Harvey et al, 2021; Gordon et al, 2020; Murk et al, 2020; Schneeweiss et al, 2020).

The medical service claims in [redacted] databases have detailed information for inpatient and outpatient healthcare encounters, including date and place of service, provider type, and plan- and patient-paid amounts. International Classification of Diseases coding is used for diagnoses and facility procedures. Common Procedural Terminology© codes are used for physician claims. Healthcare Common Procedure Coding System codes are used for procedures, durable medical equipment provided to patients, and drugs administered by physicians. Death data are recorded through linkage with the social security master file.

Pharmacy claims include detailed information on medications dispensed to patients, including the NDC, strength, quantity, route of administration (injectable, oral), dispensing date, and plan- and patient-paid amounts. The insurance enrollment file contains information on age, gender, US census region, health insurance payer type, and enrollment status.

Closed claims are available with a lag-time of about 3 months.

The [redacted] database [redacted]

The [redacted] database covers >180 million commercially insured US residents nationally. The [redacted] database is a large convenience sample of individuals with employer-sponsored private insurance (for employees and/or their spouses or dependents). The [redacted] are a sample of retirees (primarily 65 years of age and older). It contains similar data to [redacted], representing both the employer-paid and Medicare-paid components of care, predominantly fee-for-service plan data, projectable to the US population with Medicare insurance.

The medical service claims in [redacted] databases have detailed information for inpatient and outpatient healthcare encounters, including date and place of service, provider type, and plan- and patient-paid amounts. International Classification of Diseases coding is used for diagnoses and facility procedures. Common Procedural Terminology© codes are used for physician claims. Healthcare Common Procedure Coding System codes are used for procedures, durable medical equipment provided to patients, and drugs administered by physicians. Death data are not available in the [redacted] database.

Pharmacy claims include detailed information on medications dispensed to patients, including the NDC, strength, quantity, route of administration (injectable, oral), dispensing date, and plan- and patient-paid amounts. The insurance enrollment file contains information on age, gender, US census region, health insurance payer type, and enrollment status. An individual's claims of all types are linkable by an encrypted patient identification number and a unique family identification number that links family members on the same insurance plan.

The [redacted] database refreshes every 9 months.

9.4.2 EU data sources

[redacted]

The [redacted] includes the [redacted] database, which is the [redacted] and the [redacted] linked by a unique patient identifier.

The [redacted] contains individualized, anonymous data about reimbursement claims of individuals insured to the main insurance schemes in France. Since 2005, these data are prospectively and exhaustively recorded covering 99% of the entire French population (~67 million inhabitants) (Tuppin et al, 2017; Scailteux et al, 2019). The [redacted] provides for each insured inhabitant the following information: birthdate, sex, the long-term disease (LTD) status (Affections Longue Durée; 100% health insurance coverage for serious and costly long-term diseases [including psoriasis] coded according to ICD-10), out-patient visits and procedures, and biological tests (but not the results).

According to the National Health Insurance scheme, 30 long-term diseases are associated in France with full reimbursement of care, such as cancer, diabetes, chronic cardiovascular disease, and IBD (Articles Annexe à l'article A931-10-10 à Annexe 5) - Légifrance (legifrance.gouv.fr). Psoriatic arthritis and axSpA (but not PSO) is listed in the 30 LTDs. However, any severe disease not listed in the 30 LTD but requiring frequent and expensive healthcare use, such as moderate-to-severe PSO requiring biologics is eligible to LTD (LTD number 31) and is usually included in the LTD status.

Introduction of reimbursement for LTD healthcare is recommended after diagnosis to ensure that patients will be fully covered for healthcare related to the chronic disease of interest. Full coverage is subject to prior national health insurance approval, after examination of an official form signed by a physician (general practitioner and/or dermatologist) certifying that the patient has psoriasis.

All drug reimbursements and the date of dispensation are collected among other prescriptions which result in a reimbursement but not the medical indication for the prescription. Medications are classified according to a unique national registration code (CIP) and the Anatomical Therapeutic Chemical (ATC) Classification System. The number of packs is included; the number of tablets and strength are therefore reported.

The medical summary of hospital discharge from all hospital stays of public and private hospitals is available for subjects in the [redacted] via a linkage to the [redacted]. These discharge summaries contain the primary, related, and associated (secondary events and associated comorbidities) diagnosis coded according to ICD-10, some costly drugs, biological tests, and procedures using the common classification system for medical procedures (Classification Commune des Actes Médicaux) that were performed during the hospitalization. Diagnosis codes for hospital visits without an overnight stay (including Emergency Room visits) are not available.

Date of death is available in the [redacted] and cause of death is progressively being integrated to [redacted] but remains unavailable for most patients (Scailteux et al, 2019).

To obtain access to [redacted] data, the regulations require the authorization of the national commission on data privacy (Commission Nationale de l'Informatique et des Libertés [CNIL]).

This project will require the approval of the Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé and the authorization of the CNIL via the Health Data Hub.

After approval, technical aspects of [redacted] data extraction will be discussed with the database holder Caisse National d'Assurance Maladie (CNAM) and a data sharing agreement will be elaborated.

Recently, the Institut National de la Santé et de la Recherche Médicale and Assistance Publique-Hôpitaux de Paris are authorized to have permanent access to the [redacted]. However, these accesses are not yet effective; if they are when the authorizations are obtained, the access could be done by this method.

9.5 Study size

In order to assess at what point of ongoing patient accrual the monitoring program should conduct the first comparative analysis for a given database and a given outcome of interest, a series of study size calculations are presented. Given the nature of a monitoring program with repeated analysis with each data refresh and given the nature of a safety-focused analysis, 70% statistical power was selected in contrast to the frequently used 80% so that the first comparative analyses will be done sooner and can then be confirmed in subsequent analyses with increased study size.

Once the point of a first comparative analysis for a given outcome is reached, the analysis will be repeated after each annual data refresh, and the statistical power will be reflected in the estimated 95% CIs. Post-hoc power calculations are discouraged (Goodman and Berlin, 1994).

The study size necessary to conduct the proposed comparative analyses was assessed, based on estimated background rates of the potential outcomes of interest available in peer-reviewed literature for the PSO, PsA, and axSpA patient populations (Table 9-2). Calculations assume 70% power, 2-sided alpha=0.05, assuming 1.5 years of exposed follow up per patient, and 1 comparator patient for every bimekizumab exposed- patient.

Databases which do not meet the minimum necessary study size (ie, sufficient to perform comparative analyses for at least two outcomes) after 4 years will be dropped from the study. At least one database will be maintained for the full duration of the study. For the database(s) where the minimum necessary study size has been reached, enrollment of study subjects will continue until the last data delivery. This will allow an increase in the precision of estimates and possibly the detection of weaker associations. The statistical power of the analysis for the final report may well be meaningfully higher than 70% depending on the frequency of bimekizumab use.

Despite the fact that no meaningfully increased risk was observed in RCTs for the outcomes of interest, the planned sequential cohort study is designed to conduct comparative analyses once a study size is achieved that would allow identification of at least a 3-fold increased risk (6-fold for the rare IBD and serious hypersensitivity reactions outcomes). As more patients will use bimekizumab in clinical practice, the cohort size of this monitoring system will thus increase, and all subsequent analyses will make it possible to detect weaker signals (smaller rate ratios).

The necessary study sizes for each outcome of interest are listed in Table 9-2. For example, for the serious infection outcome, comparative analyses will be conducted once 215 or more patients who had received bimekizumab have accrued in the cohort and at least 10 events have occurred in the total population. All subsequent analyses of the serious infection outcome will include comparative analyses.

Table 9-2: Study size estimates for proposed analysis of outcomes of interest for PSO, PsA, and axSpA

Outcomes of interest that are the subject of this PASS	Estimated background rate[a] in	Minimal observable rate ratio	Target study size	
			Other biologics	Bimekizumab
PSO				
Serious infection	20/1000 PY	3.0	215	215
MACE	5/1000 PY	3.0	875	875
Malignancy	3/1000 PY	3.0	1460	1460
IBD	1/1000 PY	6.0	1020	1020
Serious hypersensitivity reactions	1/1000 PY	6.0	1020	1020
PsA				
Serious infection	20/1000 PY	3.0	215	215
MACE	5/1000 PY	3.0	875	875
Malignancy	3/1000 PY	3.0	1460	1460
IBD	1/1000 PY	6.0	1020	1020
Serious hypersensitivity reactions	1/1000 PY	6.0	1020	1020
axSpA				
Serious infection	20/1000 PY	3.0	215	215
MACE	5/1000 PY	3.0	875	875
Malignancy	3/1000 PY	3.0	1460	1460
IBD	3/1000 PY	3.0	1460	1460
Serious hypersensitivity reactions	1/1000 PY	6.0	1020	1020

axSpA= axial spondyloarthritis; IBD=inflammatory bowel disease; MACE=major adverse cardiovascular event; PASS=post-authorization safety study; PsA=psoriatic arthritis; PSO=psoriasis, PY=patient years

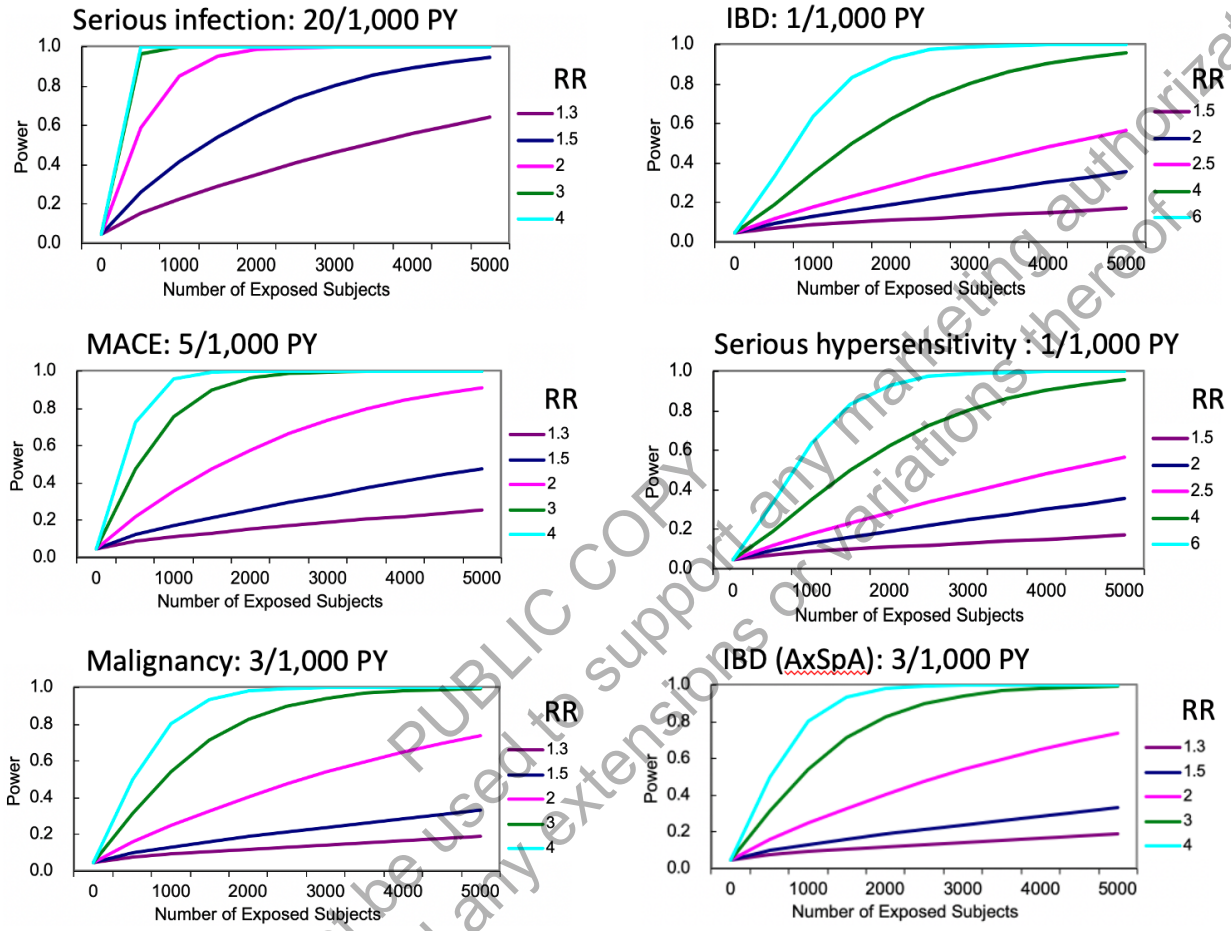
[a] Estimated rates for PSO based on the observational literature: serious infection (Li et al, 2020; Kalb et al, 2015), IBD (Aletaha et al, 2019; Shah et al, 2017; Li et al, 2013), MACE (Ogdie et al, 2015; Papp et al, 2015), malignancy (Vaengebjerg et al, 2020; Kimball et al, 2015), and serious hypersensitivity reactions (Gulsen et al, 2020).

Estimated rates for PsA based on the observational literature: serious infection (Ritchlin et al, 2019; Jin et al, 2022), IBD (Bengtsson et al, 2021, Charlton et al, 2018), MACE (Egeberg et al, 2018; Ritchlin et al, 2019), malignancy (Vaengebjerg et al, 2020; Kimball et al, 2015), and serious hypersensitivity reactions (Gulsen et al, 2020).

Estimated rates for axSpA based on the observational literature: serious infection (Vinson et al, 2020), IBD (Bengtsson et al, 2021), MACE (Walsh et al, 2018; Fakih et al, 2023), malignancy (Vaengebjerg et al, 2020; Kimball et al, 2015), and serious hypersensitivity reactions (Gulsen et al, 2020).

The computed statistical power under the same assumptions as described above for a range of relative risk estimates and resulting study sizes is shown in Figure 9-4.

Figure 9-4: Study size estimates for a range of hypothetical RR estimates and the corresponding study size requirements



IBD=inflammatory bowel disease; MACE=major adverse cardiovascular event; PY=patient years; RR=rate ratio
Note: Number of exposed subjects=patients starting bimekizumab

9.6 Data management

Data management for each of the databases is organized separately, to comply with both the General Data Protection Regulation and local regulations:

a. US [redacted] claims databases:

The raw longitudinal patient-level data will be connected with the Aetion Evidence Platform (AEP). The platform records all investigator-defined transformations of the raw data into measures in a transparent and reproducible way. The AEP provides audit trails recording who implemented what study element at what date and time. Any post hoc changes to the implementation of the predefined protocol are thus recorded.

Access to the AEP can be shared with regulators without sharing any patient-level data, thus complying with European and North American data privacy regulations. The communication between regulator and the analytic data environment strictly only includes query commands and aggregate-level study results. This allows regulators to conduct sensitivity analyses by varying study definitions and analytic parameters to assess the robustness of findings.

If desired, the AEP can produce a final anonymized analytic dataset for deposition with the regulator.

b. [redacted]

The pseudonymized raw longitudinal patient-level data will be accessible through the secure server of the French National Health Insurance (CNAM). The data management and analysis will be performed on SAS statistical software (SAS Institute).

All study reports will contain only aggregated data and will not identify individual patients or physicians.

9.7 Data analysis

For each of the databases, after identifying the patient cohort, applying the exclusion criteria, and measuring the pretreatment patient characteristics and outcomes as described above, the data will be analyzed in a causal inference framework (Schneeweiss and Huybrechts, 2021).

Analyses will be performed at the country level. Combining country level data and estimates is not planned due to significant differences in data sources and healthcare systems between the US and France. Data from the US [redacted] databases will be combined to provide country-level estimates. Further details are provided in Section 9.7.4.

All analyses will be conducted separately at the indication level PSO, PsA, and axSpA.

A patient attrition table will be prepared to fully understand the analytic cohort's representativeness.

9.7.1 Descriptive analyses

A Sankey plot of treatment patterns that lead up to the exposure or comparator treatment, including topical and systemic treatments of the underlying indication (PSO, PsA, axSpA), will be presented.

At least all pretreatment patient characteristics listed in Section 9.3.3 will be tabulated by treatment status. Proportions with 95% CIs, as well as means with standard deviations, will be presented. The mean and median follow-up time with reasons for censoring will be computed. The overall number of events and overall IRs for each outcome of interest will be calculated. Treatment-specific incidence rates will not be computed until a sufficient number of bimekizumab-exposed patients have accumulated (see Section 9.5). After the predefined number of patients has been reached (see Table 9-2), the comparative analyses described in Section 9.7.2 and Section 9.7.3 will be conducted.

9.7.2 Comparative analyses

In the absence of baseline randomization of treatment, balance will be achieved in baseline risk factors for the respective outcome by applying propensity score techniques. For each outcome, an outcome-specific propensity score model will be fit, including all predefined covariates

without further variable selection. As indicated in Section 9.3.3, some patient characteristics are specific to each outcome. A logistic regression model will be fit to the data using the binary exposure status (new use of exposure/comparator) as the dependent variable and all covariates as independent without further variable selection.

A 1:1 propensity score (PS) matching of all eligible cohort members using a 5% caliper to achieve balance will be used. A 1:1 PS matching over 1:2 or 1:3 PS matching is favored because it is anticipated that bimekizumab will be the smaller group in each of the pair-wise comparisons and the 1:1 matching will preserve the majority of bimekizumab users, and also because it is known that the second match is not as good as the first match, which will possibly increase residual confounding with no or minimal gain in precision. Weighted analyses (inverse probability or matcib weights) were decided against as it is known to cause biased findings if the PS is mis-specified in the extreme of the PS distribution which cannot be ruled out. Post-matching balance will be demonstrated by computing absolute and standardized differences for each patient characteristic. If the standardized difference for binary markers is smaller than 0.1, it will be assumed that a sufficient balance was achieved (Austin et al, 2005). If such standardized differences are meaningfully larger than 0.1 for important risk factors of the outcomes, an indication of meaningful treatment preferences by that marker with limited positivity, restricting the population by excluding patients with that characteristic and refitting the propensity score model in the new population will be considered. Patient characteristics will be tabulated before and after 1:1 propensity score matching. Inverse probability of treatment weighting (IPTW) using the estimated propensity score from above has been considered; however, it has been shown many times that IPTW is particularly susceptible to residual confounding in those patients with extreme propensity score values (Zhou et al, 2020; Seeger et al, 2017; Stürmer et al, 2010). The often-suggested fix to this issue would be truncating the resulting extreme weights, which will not allow the otherwise useful causal interpretation of the IPTW-based effect estimate.

A Consolidated Standards of Reporting Trials diagram illustrating the population selection will be produced. In a table, the mean and median follow-up times and reasons for censoring will be described.

For each treatment category and for each outcome of interest, the number of patients, the person-time, the number of outcomes, and outcome rates, including 95% CIs, will be tabulated.

The AT treatment effect will be computed by fitting a proportional hazards outcome regression to the 1:1 matched cohort data to estimate HRs with 95% CIs.

The AS treatment effect will be computed by fitting an unconditional logistic regression model to the 1:1 matched cohort data to estimate odds ratios with 95% CIs.

In sum, at least the following 36 separate analytic models will be implemented for each of the 3 indications per database:

- 3 causal contrasts (see Section 9.2.1)
- At least 6 outcomes, including outcome-specific propensity score models (see Section 9.3.2)
- 2 follow-up models (see Section 9.3.2)

The prespecified analyses will be conducted in each of those 36 analyses per database.

In this causal estimation framework, 95% CIs will be presented and p-values will not be presented. The multiple comparisons will not require any Bonferroni's adjustment and will not apply Bayesian shrinkage, as the best and unaltered empirical estimate will be presented (Martin et al, 2018).

All analyses with [redacted] will be performed using the AEP v4.35 (including R v3.4.2), which has been scientifically validated by accurately repeating a range of previously published studies, and by replicating or predicting clinical trial findings (Patorno et al, 2019; Fralick et al, 2018; Wang et al, 2016). As the AEP is not currently connected with the French administrative data, programmers will use SAS or R to conduct all analyses of the French administrative data.

9.7.3 Sensitivity analyses

Several sensitivity analyses are preplanned:

1. Extend the required enrollment window/medical history and covariate assessment window from 180 days to 365 days before cohort entry in the primary analysis. While the 180-day window is generally most appropriate in the [redacted] data sources, this analysis explores whether an extended look-back window will meaningfully change results. Minimal to no impact is anticipated for the [redacted] database as a longer lookback time than in US claims is available for the majority of patients in this database.
2. Extend the respective ERWs by 50%.
3. Exclude those patients from the main analysis where there is reason to believe that the previous biologic is not yet washed out at the cohort entry date at which the bimekizumab exposure or its comparator exposure starts. This exclusion will consider the last dispensing date of the previous biologic and the likely duration of its biologic activity.

Other sensitivity analyses may arise and will be added in the statistical analysis plan with a specific hypothesis of what question it can answer.

9.7.4 Combining of findings (US only)

In order to maximize study size, particularly in the first 2 years after marketing, findings of the two US claims database analyses will be combined using fixed effects meta-analytic methods. In case of zero events in one group, aggregate person-time and event numbers will be pooled. Findings will not be combined if substantial effect measure modification is observed. Confidence intervals will be corrected for any overlap in the two US databases.

9.8 Quality control

Source data

For analysis of US claims data, the raw longitudinal patient-level data will be connected with the AEP. The platform records all investigator-defined transformations of the raw data into measures in a transparent and reproducible way. The AEP provides audit trails recording who implemented what study element at what date and time. Any posthoc changes to the implementation of the predefined protocol are thus recorded.

For the [redacted], the statistical analyses will be programmed by a statistician and checked by another statistician. All variables used in the analyses will be described in order to evaluate

the validity of derived variables. All SAS programs are archived by Institut Pierre Louis d'Epidémiologie et de Santé Publique.

Archiving and data retention

The analytic data set and all analysis codes in the AEP and outside will be retained by the investigator team for at least 5 years after the final study report or until first publication of the non-interventional PASS results become available, whichever comes later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s).

Reporting

This study has been designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (ISPE, 2015), the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al, 2008), and with the ethical principles set forth in the Declaration of Helsinki.

This study is fulfilling the criteria of an ENCePP study and follows the ENCePP Code of Conduct (EMA/929209/2011, Rev 4). The study protocol will be deposited in the PASS database at ENCePP.eu within 3 months of finalization.

9.9 Limitations

Despite their substantial acceptance, any nonrandomized research with secondary healthcare data is subject to limitations.

1. Randomized controlled trials assign treatment randomly and therefore reduce confounding at baseline. As follow-up time progresses, confounding may increase due to selective drop out and treatment changes, not unlike in nonrandomized studies. While the new-user active-comparator design has been shown to reduce confounding, including confounding by unobservable factors (Johnson et al, 2013; Patorno et al, 2018) and even with the adjustment for many pretreatment patient characteristics that predict the outcomes using propensity score matching and confirming the achieved balance (Franklin et al, 2014), this is no guarantee for complete balance between treatment groups.
2. Working with secondary real-world data limits the investigator in measuring baseline factors exactly the way it was intended and leaves surveillance of the outcomes of interest to the routine operation of the healthcare system. Adjustment for many proxy measures for pretreatment characteristics will be applied to reduce the adverse consequences for confounding adjustment (Schneeweiss et al, 2009) and balance patients on healthcare access and utilization patterns to equalize surveillance across treatment groups (Schneeweiss et al, 2001). There will be a focus on highly specific measurement of outcomes (see Section 9.7), which leads to unbiased relative effect measures (HR, relative risk) even if the sensitivity of outcome assessment is less than optimal (Schneeweiss and Avorn, 2005).
3. Specifically, several pretreatment characteristics are measured incompletely and may have limited effects on our ability to control confounding, including smoking (proxied by codes for smoking which are under-recorded, as well as consequences of smoking, including chronic obstructive pulmonary disease (COPD), chronic bronchitis, asthma, coronary heart

disease, peripheral vascular disease, etc.) and obesity (proxied by codes for overweight and obesity which are under-recorded, as well as consequences of being overweight, including type-2 diabetes, coronary heart disease, weight reduction medication use, bariatric surgery, etc.). Other variables may equally be under-recorded (eg, alcohol use), but are less likely to cause meaningful confounding as they are weak risk factors if any, of the outcomes of interest.

4. Due to significant differences in healthcare systems between the US and France and differences in data collection (eg, limited outpatient diagnosis data in [redacted]), this may lead to meaningful heterogeneity in results between the US and France. Indeed, outpatient diagnosis codes are only available in [redacted] for a limited number of chronic conditions (LTDs) and diagnostic codes for Emergency Room visits are not available. Identification of relevant diseases not covered in this list will be accomplished through the use of specification medication algorithms, inpatient diagnosis, procedure codes, and/or LTD status as used in previous [redacted] studies.
5. The statistical power of the analysis, and thus the completion date of the study, depends on the uptake of the newly marketed bimekizumab and/or its insurance coverage.
6. In order to increase the chance of spotting and reporting, as early as possible, important signals, it was decided to monitor, and this in parallel, more than one large database, with different coding systems and at time not necessarily with comparable depth and/or breath of information and data quality. Because of this, should two or more databases reach the required sample size, for a particular outcome, there is a small risk of having findings that are not necessarily completely aligned. All possible steps will be taken to minimize these or at least to ensure that, should that happen, each of the results will be put into appropriate context to facilitate a fully informed overall conclusion. This also justifies why a pooled analysis (meta-analysis) has not been suggested as primary analysis.
7. While the limitations are recognized, there is ample prior work on the safety of targeted immunomodulating drugs in dermatology using US claims data, including those from our group, that aligned with findings from RCTs (Schneeweiss et al, 2022; Schneeweiss et al, 2021; Jin et al, 2021; Dommasch et al, 2019).

9.10 Other aspects

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

The investigator team will seek IRB approval of this noninterventional database study via the Brigham and Women's Hospital IRB.

Since patients are neither contacted nor intervened upon, this research is deemed minimal risk. All data are de-identified and re-identification of individual patents is not possible. All these aspects will be evaluated by the IRB, and no research will start before the IRB provides its full approval.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

For non-interventional PASS based on secondary use of data, the submission of suspected adverse reactions in the form of individual case safety reports is not required. For those non-interventional PASS, all adverse events/reactions collected should be recorded and summarized in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification. All reports and information received from the study will be evaluated per UCB's standard safety signal detection practices.

The objective of this pharmacoepidemiologic study is to identify population-level causal relationships between drug use and predefined safety outcomes by using large de-identified healthcare databases. It will not rely on single case causality assessment, it will not identify, and it will therefore not report individual patients who may have suffered from an adverse event of any type.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Progress updates provided in the periodic safety update reports (PSURs) will include number of patients enrolled and exposed and event counts for each outcome. In addition, 2. interim reports with descriptive statistics and preliminary comparative analyses will be submitted to EMA at the predefined scheduled dates (see Section 6 Milestones) as standalone documents. Interim reports will include descriptive analyses and comparative analysis for outcomes where sufficient patient counts have been accrued.

Each report will have separate results sections for PSO, PsA, and axSpA, respectively.

The final study report will include updated descriptive and comparative analyses for all outcomes and will be submitted as a stand-alone document.

Dissemination activities will be undertaken, including articles in scientific journals and presentations at conferences. Authorship will be determined in accordance with the International Committee of Medical Journal Editors guidelines. UCB scientists will have an opportunity to comment during 45 business days.

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Cohort study on the safety of bimekizumab in patients with plaque psoriasis, psoriatic arthritis, or axial spondyloarthritis: A non-interventional post authorization study

EU PAS Register® number:
Study reference number (if applicable):

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
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

The final timelines will depend on the date of the protocol approval

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? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1, 9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	9.1
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

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:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and gender	☒	☐	☐	9.2.4
	4.2.3 Country of origin	☒	☐	☐	9.2.4
	4.2.4 Disease/indication	☒	☐	☐	9.2.4
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.5
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.4

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? (e.g. 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? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

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?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.4

Comments:

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? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, gender, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.3.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. 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?	☒	☐	☐	9.6

Comments:

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Sebastian Schneeweiss, MD, ScD

Date: dd/Month/year

Signature: _____

APPENDIX 3. STUDY VARIABLE DEFINITIONS

Psoriasis, Psoriatic arthritis, Axial Spondyloarthritis **definition**

Variable	US claims ICD-10-CM codes	[redacted] ATC codes
Psoriasis	L40.x, excluding L40.5x (arthropathic Psoriasis)	[redacted]
Psoriatic arthritis	L40.5x (arthropathic Psoriasis)	L40.5, M07
Axial spondyloarthritis	M45.x, M46.0, M46.1, M46.8, M46.9	M45.x, M46.0, M46.1, M46.8, M46.9

ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification

Outcome definitions:

At least the occurrence of the following outcomes will be studied. The event date is the date when all event criteria are fulfilled (see Appendix 4 for coding details):

1. Major adverse cardiovascular event:
   - US claims: Patients hospitalized with a diagnosis code for MI, ACS, stroke, or CABG surgery as the primary discharge code, or an emergency room visit with the diagnosis of MI, ACS, or CHD that is combined with a coronary stent implantation.
   - [redacted] Patients hospitalized with a diagnosis code for MI, ACS, stroke, or CABG surgery as the primary discharge code, or CHD that is combined with a coronary stent implantation.
   - The ERW is defined as 14 days and the fixed follow-up time as 365 days. Given the biology of coronary heart disease and the potential factors intervening in this biology, it seems reasonable to assume that MACE outcomes within a year of starting treatment could be causally connected if at all.
2. Malignancies:
   - US claims: Patients with 2 diagnosis codes for a solid or hematologic cancer within 1 month (Setoguchi et al, 2006) and an imaging procedure, including CT scan, MRI, or bone scan.
   - [redacted]: Patients with 1) a discharge diagnosis code related to cancer as primary or related diagnosis, or 2) appointment of a long-term cancer disease status after index date, or 3) dispensation of chemotherapy, or 4) or radiotherapy procedure.
   - The ERW for malignancies is defined as 180 days and the fixed follow-up time as up to 5 years. Given the biology of cancer induction and cancer promotion, and the potential factors intervening in this biology, it seems reasonable to assume that newly occurring cancers may become clinically apparent with several years of delay (Lebwohl et al, 2021). Even if cancers newly occur several years after treatment initiation, there may still be a causal link.
3. New IBD:

- US claims: Patients hospitalized with a diagnosis code for either UC or CD as the primary discharge code or 1 outpatient diagnosis code in combination with a colonoscopy or flexible sigmoidoscopy.
- [redacted] two hospital discharge diagnoses of CD or UC (ICD-10 codes K50 and K51, respectively), or one hospital discharge diagnosis and a prescription filled for one of the following drugs: aminosalicylic acid, mesalazine, olsalazine, enteral budesonide, azathioprine, mercaptopurine, vedolizumab, or an appointment of a long-term IBD disease status after the index date.
- The ERW for new IBD is defined as 14 days and the fixed follow-up time as 365 days. Given the biology of UC and CD, and the potential factors intervening in this biology, it seems reasonable to assume that IBD that occurs within a year of starting treatment could be causally connected if at all (Schneeweiss et al, 2022a).

4. Serious infection:
   - US claims and [redacted] Patients hospitalized with a diagnosis code for bacterial, viral, or opportunistic infections (bacterial, fungal, viral, helminthic) as the primary discharge code.
   - The ERW for serious infections is defined as 90 days and the fixed follow-up time as 180 days. The new occurrence of infections due to changes in the immune response are hypothesized to happen fairly soon after treatment initiation if at all. Previous studies on the risk of infections in IMDs in dermatologic conditions have focused on 180 days of follow-up (Schneeweiss et al, 2022; Schneeweiss et al, 2021; Schneeweiss et al, 2020; Jin et al, 2022; Dommasch et al, 2019).
5. Serious hypersensitivity reaction:
   - US claims: Patients with recorded diagnosis codes of hypersensitivity followed by corticosteroid treatment or hospitalizations for hypersensitivity as the primary discharge code.
   - [redacted] Patients hospitalized for hypersensitivity as the primary discharge code.
   - The ERW is defined as 7 days and the fixed follow-up time as 90 days. The new occurrence of hypersensitivity is hypothesized to happen shortly after treatment start, possibly with the second injection. Therefore, a follow-up window of 90 days seems appropriate.
6. Other outcomes of interest (eg, oral candidiasis).

APPENDIX 4. PRELIMINARY CODE LISTS TO IDENTIFY STUDY VARIABLES

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
MACE/IBD/ Malignancy/ infection	Alcohol abuse	F10.1, F10.10, F10.12, F10.120, F10.121, F10.129, F10.14, F10.15, F10.150, F10.151, F10.159, F10.18, F10.180, F10.181, F10.182, F10.188, F10.19, F10.2, F10.20, F10.21, F10.22, F10.220, F10.221, F10.229, F10.23, F10.230, F10.231, F10.232, F10.239, F10.24, F10.25, F10.250, F10.251, F10.259, F10.26, F10.27, F10.28, F10.280, F10.281, F10.282, F10.288, F10.29, F10.9, F10.92, F10.920, F10.921, F10.929, F10.94, F10.95, F10.950, F10.951, F10.959, F10.96, F10.97, F10.98, F10.980, F10.981, F10.982, F10.988, F10.99, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.0, T51.0X, T51.0X1, T51.0X1A, T51.0X1D, T51.0X1S, T51.0X2, T51.0X2A, T51.0X2D, T51.0X2S, T51.0X3, T51.0X3A, T51.0X3D, T51.0X3S, T51.0X4, T51.0X4A, T51.0X4D, T51.0X4S, T51.1, T51.1X, T51.1X1, T51.1X1A, T51.1X1D, T51.1X1S, T51.1X2, T51.1X2A, T51.1X2D, T51.1X2S, T51.1X3, T51.1X3A, T51.1X3D, T51.1X3S, T51.1X4, T51.1X4A, T51.1X4D, T51.1X4S, T51.2, T51.2X, T51.2X1, T51.2X1A, T51.2X1D, T51.2X1S, T51.2X2, T51.2X2A, T51.2X2D, T51.2X2S, T51.2X3, T51.2X3A, T51.2X3D, T51.2X3S, T51.2X4, T51.2X4A, T51.2X4D, T51.2X4S, T51.3, T51.3X, T51.3X1, T51.3X1A, T51.3X1D, T51.3X1S, T51.3X2, T51.3X2A, T51.3X2D, T51.3X2S, T51.3X3, T51.3X3A, T51.3X3D, T51.3X3S, T51.3X4, T51.3X4A, T51.3X4D, T51.3X4S, T51.8, T51.8X, T51.8X1, T51.8X1A, T51.8X1D, T51.8X1S, T51.8X2, T51.8X2A, T51.8X2D, T51.8X2S, T51.8X3, T51.8X3A, T51.8X3D, T51.8X3S, T51.8X4, T51.8X4A, T51.8X4D, T51.8X4S, T51.9, T51.91, T51.91XA, T51.91XD, T51.91XS, T51.92, T51.92XA, T51.92XD, T51.92XS, T51.93, T51.93XA, T51.93XD, T51.93XS, T51.94, T51.94XA, T51.94XD, T51.94XS, Z71.4	F10.1, F10.2, F10.9, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.0, T51.1, T51.2, T51.3, T51.8, T51.9, Z71.4

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
MACE/ IBD/ Malignancy	Obesity	E66.01, E66.2, R63.5, R93.9, Z68.30, Z68.33, Z68.35, Z68.37, Z68.42, Z68.43, Z68.44, Z68.45, E66.3, E66.9, Z68.31, Z68.32, Z68.34, Z68.36, Z68.38, Z68.39, Z68.41	E66.2, R63.5, R93.9, E66.3, E66.9
MACE/ IBD/ Malignancy/	Smoking	F17.2, F17.20, F17.200, F17.201, F17.209, F17.21, F17.210, F17.211, F17.221, F17.229, F17.291, F17.298, T65.21, T65.211, T65.212A, T65.212D, T65.212S, T65.213, T65.214, T65.214A, T65.214S, T65.22, T65.221, T65.221S, T65.222S, T65.223, T65.223A, T65.224, T65.224D, T65.291, T65.291A, T65.291S, T65.292A, T65.292D, T65.293, T65.293S, T65.294A, Z71.6, Z72.0, F17, F17.203, F17.208, F17.213, F17.218, F17.219, F17.22, F17.220, F17.223, F17.228, F17.29, F17.290, F17.293, F17.299, T65.2, T65.211A, T65.211D, T65.211S, T65.212, T65.213A, T65.213D, T65.213S, T65.214D, T65.221A, T65.221D, T65.222, T65.222A, T65.222D, T65.223D, T65.223S, T65.224A, T65.224S, T65.29, T65.291D, T65.292, T65.292S, T65.293A, T65.293D, T65.294, T65.294D, T65.294S	F17.2, Z71.6, Z72.0, F17, T65.2
MACE/ IBD/ Malignancy/	COPD	I27.8, I27.9, J68.4, J70.1, J70.3, J41.0, J41.1, J41.8, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J45.2, J45.20, J45.21, J45.22, J45.3, J45.30, J45.31, J45.32, J45.4, J45.40, J45.41, J45.42, J45.5, J45.50, J45.51, J45.52, J45.9, J45.90, J45.901, J45.902, J45.909, J45.99, J45.990, J45.991, J45.998, J47.0, J47.1, J47.9, J62.0, J62.8, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.6, J66.0, J66.1, J66.2, J66.8, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9	I27.8, I27.9, J68.4, J70.1, J70.3, J41.0, J41.1, J41.8, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J45.2, J47.0, J47.1, J47.9, J62.0, J62.8, J63.0, J63.1, J63.2, J63.3, J63.4, J63.5, J63.6, J66.0, J66.1, J66.2, J66.8, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9
MACE	Diabetes, severe or complicated	E10.8, E11.8, E13.8, E10.2, E10.21, E10.22, E10.29, E10.3, E10.31, E10.311, E10.319, E10.32, E10.321, E10.329, E10.33, E10.331, E10.339, E10.34, E10.341, E10.349, E10.35, E10.351, E10.359, E10.36, E10.39, E10.4, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.5, E10.51, E10.52, E10.59, E10.6, E10.61, E10.610, E10.618, E10.62, E10.620, E10.621, E10.622, E10.628, E10.63, E10.630,	E10.8, E11.8, E13.8, E10.2, E10.4, E10.5, E10.6, E11.2, E11.3, E11.4, E11.5, E11.6, E13.2, E13.5, E13.6

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		E10.638, E10.64, E10.641, E10.649, E10.65, E10.69, E11.2, E11.21, E11.22, E11.29, E11.3, E11.31, E11.311, E11.319, E11.32, E11.321, E11.329, E11.33, E11.331, E11.339, E11.34, E11.341, E11.349, E11.35, E11.351, E11.359, E11.36, E11.39, E11.4, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.5, E11.51, E11.52, E11.59, E11.6, E11.61, E11.610, E11.618, E11.62, E11.620, E11.621, E11.622, E11.628, E11.63, E11.630, E11.638, E11.64, E11.641, E11.649, E11.65, E11.69, E13.2, E13.21, E13.22, E13.29, E13.3, E13.31, E13.311, E13.319, E13.32, E13.321, E13.329, E13.33, E13.331, E13.339, E13.34, E13.341, E13.349, E13.35, E13.351, E13.359, E13.36, E13.39, E13.4, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.5, E13.51, E13.52, E13.59, E13.6, E13.61, E13.610, E13.618, E13.62, E13.620, E13.621, E13.622, E13.628, E13.63, E13.630, E13.638, E13.64, E13.641, E13.649, E13.65, E13.69	
MACE	Hypertension	I67.4, I11.0, I11.9, I12, I12.0, I12.9, I13.0, I13.1, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9	I67.4, I11.0, I11.9, I12, I12.0, I12.9, I13.0, I13.1, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9
MACE	Hyperlipidemia	E78.1, E78.2, E78.4, E78.5, CPT codes: 0556F, G8585	E78.1, E78.2, E78.4, E78.5
MACE	Peripheral vascular disease	A52.0, I73.0, I73.1, I73.8, I73.9, I77.1, I79.0, K55.1, K55.8, K55.9, Z95.8, Z95.9, I70.0, I70.1, I70.2, I70.20, I70.201, I70.202, I70.203, I70.208, I70.209, I70.21, I70.211, I70.212, I70.213, I70.218, I70.219, I70.22, I70.221, I70.222, I70.223, I70.228, I70.229, I70.23, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.24, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248, I70.249, I70.25, I70.26, I70.261, I70.262, I70.263, I70.268, I70.269, I70.29, I70.291, I70.292, I70.293, I70.298, I70.299, I70.3, I70.30, I70.301, I70.302, I70.303, I70.308, I70.309, I70.31, I70.311, I70.312, I70.313, I70.318, I70.319, I70.32, I70.321, I70.322, I70.323, I70.328,	A52.0, I73.0, I73.1, I73.8, I73.9, I77.1, I79.0, K55.1, K55.8, K55.9, Z95.8, Z95.9, I70.0, I70.1, I70.2, I70.3, I70.4, I70.5, I70.6, I70.7, I71.0, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		I70.329, I70.33, I70.331, I70.332, I70.333, I70.334, I70.335, I70.338, I70.339, I70.34, I70.341, I70.342, I70.343, I70.344, I70.345, I70.348, I70.349, I70.35, I70.36, I70.361, I70.362, I70.363, I70.368, I70.369, I70.39, I70.391, I70.392, I70.393, I70.398, I70.399, I70.4, I70.40, I70.401, I70.402, I70.403, I70.408, I70.409, I70.41, I70.411, I70.412, I70.413, I70.418, I70.419, I70.42, I70.421, I70.422, I70.423, I70.428, I70.429, I70.43, I70.431, I70.432, I70.433, I70.434, I70.435, I70.438, I70.439, I70.44, I70.441, I70.442, I70.443, I70.444, I70.445, I70.448, I70.449, I70.45, I70.46, I70.461, I70.462, I70.463, I70.468, I70.469, I70.49, I70.491, I70.492, I70.493, I70.498, I70.499, I70.5, I70.50, I70.501, I70.502, I70.503, I70.508, I70.509, I70.51, I70.511, I70.512, I70.513, I70.518, I70.519, I70.52, I70.521, I70.522, I70.523, I70.528, I70.529, I70.53, I70.531, I70.532, I70.533, I70.534, I70.535, I70.538, I70.539, I70.54, I70.541, I70.542, I70.543, I70.544, I70.545, I70.548, I70.549, I70.55, I70.56, I70.561, I70.562, I70.563, I70.568, I70.569, I70.59, I70.591, I70.592, I70.593, I70.598, I70.599, I70.6, I70.60, I70.601, I70.602, I70.603, I70.608, I70.609, I70.61, I70.611, I70.612, I70.613, I70.618, I70.619, I70.62, I70.621, I70.622, I70.623, I70.628, I70.629, I70.63, I70.631, I70.632, I70.633, I70.634, I70.635, I70.638, I70.639, I70.64, I70.641, I70.642, I70.643, I70.644, I70.645, I70.648, I70.649, I70.65, I70.66, I70.661, I70.662, I70.663, I70.668, I70.669, I70.69, I70.691, I70.692, I70.693, I70.698, I70.699, I70.7, I70.70, I70.701, I70.702, I70.703, I70.708, I70.709, I70.71, I70.711, I70.712, I70.713, I70.718, I70.719, I70.72, I70.721, I70.722, I70.723, I70.728, I70.729, I70.73, I70.731, I70.732, I70.733, I70.734, I70.735, I70.738, I70.739, I70.74, I70.741, I70.742, I70.743, I70.744, I70.745, I70.748, I70.749, I70.75, I70.76, I70.761, I70.762, I70.763, I70.768, I70.769, I70.79, I70.791, I70.792, I70.793, I70.798, I70.799, I70.8, I70.9, I70.90, I70.91, I70.92, I71.0, I71.00, I71.01, I71.02, I71.03, I71.1, I71.2, I71.3, I71.4, I71.5, I71.6, I71.8, I71.9, I72.0, I72.1, I72.2, I72.3, I72.4, I72.8, I72.9	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
MACE	Heart failure	I09.9, I09.81, I11.0, I13.0, I13.2, I25.5, I42.0, I42.9, I42.5, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.40, I50.41, I50.42, I50.43, I50.9	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.9, I42.5, I50.1, I50.2, I50.3, I50.4, I50.9
MACE	Cardiac arrhythmia	I44.3, I45.6, I45.9, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0, I44.1, I47.0, I47.1, I47.2, I47.9, I49.0, I49.01, I49.02, I49.1, I49.2, I49.3, I49.4, I49.40, I49.49, I49.5, I49.8, I49.9	I44.3, I45.6, I45.9, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0, I44.1, I47.0, I47.1, I47.2, I47.9, I49.0, I49.1, I49.2, I49.3, I49.4, I49.40, I49.49, I49.5, I49.8, I49.9
MACE	Renal disease or renal failure	N25.0, Z94.0, Z99.2, I13.10, I13.11, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, Z49.0, Z49.01, Z49.02, Z49.3, Z49.31, Z49.32	N25.0, Z94.0, Z99.2, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, Z49.0, Z49.3
MACE	Antiplatelet use	aspirin, aspirin (calcium carb & magnesium buffers)/pravastatin, aspirin/acetaminophen, aspirin/acetaminophen/caffeine, aspirin/acetaminophen/caffeine/calcium, aspirin/acetaminophen/caffeine/potassium, aspirin/acetaminophen/calcium carbonate, aspirin/acetaminophen/magnesium/aluminum hydroxide/caffeine, aspirin/caffeine, aspirin/calcium carbonate, aspirin/calcium carbonate/magnesium, aspirin/calcium carbonate/magnesium/aluminum hydroxide, aspirin/codeine phosphate, aspirin/diphenhydramine citrate, aspirin/diphenhydramine hcl, aspirin/diphenhydramine/sodium bicarbonate/citric acid, aspirin/dipyridamole, aspirin/magnesium carbonate/dihydroxyaluminum aminoacetate, aspirin/magnesium hydroxide/aluminum hydroxide, aspirin/magnesium hydroxide/aluminum hydroxide/caffeine, aspirin/meprobamate, aspirin/salicylamide/acetaminophen/caffeine, aspirin/salicylamide/caffeine, aspirin/sodium bicarbonate/citric acid, cilostazol, clopidogrel bisulfate, dipyridamole, prasugrel hcl, ticagrelor, vorapaxar sulfate, abciximab, butalbital/aspirin/caffeine, carisoprodol/aspirin, chlorpheniramine mal/phenylephrine/d-methorphan hb/aspirin, chlorpheniramine maleate/phenylephrine bitartrate/aspirin, cinnamedrine hcl/aspirin/caffeine, codeine phosphate/butalbital/aspirin/caffeine, codeine phosphate/carisoprodol/aspirin, codeine/aspirin/salicylamide/acetaminophen/caffeine, dihydrocodeine bitartrate/aspirin/caffeine, dihydrocodeine/aspirin/caffeine, ephedrine/aspirin/acetanilide/caffeine, hydrocodone bitartrate/aspirin, methocarbamol/aspirin, orphenadrine citrate/aspirin/caffeine, oxycodone hcl/aspirin, oxycodone hcl/oxycodone terephthalate/aspirin, oxycodone/aspirin, pentazocine hcl/aspirin, phenylephrine hcl/aspirin, phenylpropanolamine bitartrate/aspirin, phenylpropanolamine bitartrate/aspirin/chlorpheniramine, phenylpropanolamine hcl/aspirin, phenylpropanolamine hcl/aspirin/chlorpheniramine, phenylpropanolamine hcl/aspirin/chlorpheniramine/caffeine,	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		phenylpropanolamine hcl/aspirin/diphenhydramine, propoxyphene hcl/aspirin/caffeine, pseudoephedrine hcl/aspirin/chlorpheniramine	
MACE	Statin use	amlodipine besylate/atorvastatin calcium, aspirin (calcium carb & magnesium buffers)/pravastatin, atorvastatin calcium, ezetimibe/atorvastatin calcium, ezetimibe/simvastatin, fluvastatin sodium, lovastatin, niacin/lovastatin, niacin/simvastatin, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, simvastatin, sitagliptin phosphate/simvastatin	
MACE	Antihypertensive use (alpha blockers, ACE/ARB, beta-adrenergic blockers, vasodilators, loop diuretic, potassium sparing diuretic, thiazide diuretic, calcium channel blockers,	doxazosin mesylate, prazosin hcl, prazosin hcl/polythiazide, terazosin hcl aliskiren/valsartan, amlodipine besylate/olmesartan medoxomil, amlodipine besylate/valsartan, amlodipine besylate/valsartan/hydrochlorothiazide, azilsartan medoxomil, azilsartan medoxomil/chlorthalidone, candesartan cilexetil, candesartan cilexetil/hydrochlorothiazide, eprosartan mesylate, eprosartan mesylate/hydrochlorothiazide, irbesartan, irbesartan/hydrochlorothiazide, losartan potassium, losartan potassium/hydrochlorothiazide, olmesartan medoxomil, olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide, olmesartan medoxomil/hydrochlorothiazide, telmisartan, telmisartan/amlodipine besylate, telmisartan/hydrochlorothiazide, valsartan, valsartan/hydrochlorothiazide, acebutolol hcl, atenolol, atenolol/chlorthalidone, betaxolol hcl, bisoprolol fumarate, bisoprolol fumarate/hydrochlorothiazide, brimonidine tartrate/timolol maleate, carteolol hcl, carvedilol, carvedilol phosphate, dorzolamide hcl/timolol maleate, dorzolamide hcl/timolol maleate/pf, esmolol hcl, esmolol hcl in sodium chloride, iso-osmotic, labetalol hcl, metoprolol succinate, metoprolol succinate/hydrochlorothiazide, metoprolol tartrate, metoprolol tartrate/dietary supplement,comb.10, metoprolol tartrate/hydrochlorothiazide, nadolol, nadolol/bendroflumethiazide, nebivolol hcl, penbutolol sulfate, pindolol, propranolol hcl, propranolol hcl/hydrochlorothiazide, sotalol hcl, timolol, timolol maleate, timolol maleate/hydrochlorothiazide, timolol maleate/pf, alprostadil, hydralazine hcl, hydralazine hcl/hydrochlorothiazide, hydralazine hcl/reserpine/hydrochlorothiazide, isosorbide dinitrate/hydralazine hcl, minoxidil, nesiritide, nitroglycerin, nitroglycerin/dextrose 5 % in water, nitroprusside sodium, riociguat, apraclonidine hcl, clonidine, clonidine hcl, clonidine hcl/chlorthalidone, clonidine hcl/pf, methyldopa, methyldopa/chlorothiazide, methyldopa/hydrochlorothiazide, methyldopate hcl, bumetanide, ethacrynate sodium, ethacrynic acid, furosemide, furosemide in 0.9 % sodium chloride, torsemide, amiloride hcl, amiloride hcl/hydrochlorothiazide, eplerenone, spironolactone, spironolactone, micronized, spironolactone/hydrochlorothiazide, triamterene, triamterene/hydrochlorothiazide, aliskiren hemifumarate/amlodipine/hydrochlorothiazide, aliskiren hemifumarate/hydrochlorothiazide, amiloride hcl/hydrochlorothiazide, amlodipine besylate/valsartan/hydrochlorothiazide, atenolol/chlorthalidone, azilsartan medoxomil/chlorthalidone, benazepril hcl/hydrochlorothiazide, bisoprolol fumarate/hydrochlorothiazide, candesartan cilexetil/hydrochlorothiazide, captopril/hydrochlorothiazide, chlorothiazide, chlorothiazide sodium,	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		chlorthalidone, clonidine hcl/chlorthalidone, deserpidine/hydrochlorothiazide, deserpidine/methyclothiazide, enalapril maleate/hydrochlorothiazide, eprosartan mesylate/hydrochlorothiazide, fosinopril sodium/hydrochlorothiazide, guanethidine sulfate/hydrochlorothiazide, hydralazine hcl/hydrochlorothiazide, hydralazine hcl/reserpine/hydrochlorothiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, irbesartan/hydrochlorothiazide, lisinopril/hydrochlorothiazide, losartan potassium/hydrochlorothiazide, methyclothiazide, methyldopa/chlorothiazide, methyldopa/hydrochlorothiazide, metolazone, metoprolol succinate/hydrochlorothiazide, metoprolol tartrate/hydrochlorothiazide, moexipril hcl/hydrochlorothiazide, olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide, olmesartan medoxomil/hydrochlorothiazide, polythiazide, prazosin hcl/polythiazide, propranolol hcl/hydrochlorothiazide, quinapril hcl/hydrochlorothiazide, reserpine/chlorothiazide, reserpine/hydrochlorothiazide, reserpine/hydroflumethiazide, reserpine/methyclothiazide, reserpine/polythiazide, spironolactone/hydrochlorothiazide, telmisartan/hydrochlorothiazide, timolol maleate/hydrochlorothiazide, triamterene/hydrochlorothiazide, trichlormethiazide, valsartan/hydrochlorothiazide, aliskiren hemifumarate/amlodipine besylate, aliskiren hemifumarate/amlodipine/hydrochlorothiazide, amlodipine besylate, amlodipine besylate/atorvastatin calcium, amlodipine besylate/benazepril hcl, amlodipine besylate/olmesartan medoxomil, amlodipine besylate/valsartan, amlodipine besylate/valsartan/hydrochlorothiazide, bepridil hcl, clevidipine butyrate, diltiazem hcl, diltiazem hcl in 0.9 % sodium chloride, diltiazem hcl/dextrose 5 % in water, diltiazem malate, enalapril maleate/felodipine, felodipine, isradipine, mibefradil di-hcl, nicardipine hcl, nicardipine in dextrose 5 %-water, nicardipine in dextrose, iso-osmotic, nicardipine in sodium chloride, iso-osmotic, nifedipine, nimodipine, olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide, telmisartan/amlodipine besylate, trandolapril/verapamil hcl, verapamil hcl, amlodipine besylate/benazepril hcl, benazepril hcl, benazepril hcl/hydrochlorothiazide, captopril, captopril/hydrochlorothiazide, enalapril maleate, enalapril maleate/felodipine, enalapril maleate/hydrochlorothiazide, enalaprilat dihydrate, fosinopril sodium, fosinopril sodium/hydrochlorothiazide, lisinopril, lisinopril/dietary supplement,comb.10, lisinopril/hydrochlorothiazide, moexipril hcl, moexipril hcl/hydrochlorothiazide, perindopril erbumine, quinapril hcl, quinapril hcl/hydrochlorothiazide, ramipril, trandolapril, trandolapril/verapamil hcl	
MACE	Injectable non-insulin antidiabetic drugs	exenatide, exenatide microspheres, liraglutide, pramlintide acetate	
MACE	Non-insulin anti-diabetic drug	acarbose, alogliptin benzoate, alogliptin benzoate/metformin hcl, alogliptin benzoate/pioglitazone hcl, canagliflozin, canagliflozin/metformin hcl, chlorpropamide, dapagliflozin propanediol, exenatide,	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		exenatide microspheres, glimepiride, glipizide, glipizide/metformin hcl, glyburide, glyburide,micronized, glyburide/metformin hcl, linagliptin, linagliptin/metformin hcl, liraglutide, metformin hcl, miglitol, nateglinide, pioglitazone hcl, pioglitazone hcl/glimepiride, pioglitazone hcl/metformin hcl, pramlintide acetate, repaglinide, repaglinide/metformin hcl, rosiglitazone maleate, rosiglitazone maleate/glimepiride, rosiglitazone maleate/metformin hcl, saxagliptin hcl, saxagliptin hcl/metformin hcl, sitagliptin phosphate, sitagliptin phosphate/metformin hcl, sitagliptin phosphate/simvastatin, tolazamide, tolbutamide, empagliflozin	
IBD	Abdominal/pelvic CT scan or MRI	ICD-10 procedure code: BR2CYZZ, BW2000Z, BW21Y0Z, BW21YZZ, BW21ZZZ, BW25YZZ, BR2C0ZZ, BW2010Z, BW210ZZ, BW2510Z, BR2C1ZZ, BW2500Z, BW25Y0Z, BW20Y0Z, BW20YZZ, BW20ZZZ, BW2100Z, BW211ZZ, BW250ZZ, BR2CZZZ, BW200ZZ, BW201ZZ, BW2110Z, BW251ZZ, BW25ZZZ CPT/HCPCS procedure code: 72193, 72195, 74181, 74185, 72198, 74150, 74160, 74176, 74178, 74183, 72196, 74177, 72192, 72194, 72197, 74170, 74182	Will be included in the SAP.
IBD	Number of CRP tests ordered	CPT/HCPCS procedure code: 86140, 86141	Will be included in the SAP.
IBD	Fecal pathogen tests (including clostridiodes difficile)	CPT/HCPCS procedure code: 3520F, 87045, 87046, 87493, 87506, 87507, 87803, 87230, 87324, 87505	Will be included in the SAP.

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
IBD	Hospitalization related to abdominal issues	K50.00, K50.013, K50.11, K50.113, K50.118, K50.8, K50.81, K50.811, K50.813, K50.818, K50.819, K50.90, K50.911, K50.913, K50.914, K50.918, K51.0, K51.00, K51.01, K51.011, K51.012, K51.20, K51.21, K51.214, K51.3, K51.311, K51.312, K51.313, K51.314, K51.319, K51.4, K51.40, K51.418, K51.419, K51.50, K51.511, K51.512, K51.519, K51.812, K51.813, K51.91, K51.914, K51.918, K50, K50.0, K50.01, K50.011, K50.012, K50.014, K50.018, K50.019, K50.1, K50.10, K50.111, K50.112, K50.114, K50.119, K50.80, K50.812, K50.814, K50.9, K50.91, K50.912, K50.919, K51, K51.013, K51.014, K51.018, K51.019, K51.2, K51.211, K51.212, K51.213, K51.218, K51.219, K51.30, K51.31, K51.318, K51.41, K51.411, K51.412, K51.413, K51.414, K51.5, K51.51, K51.513, K51.514, K51.518, K51.8, K51.80, K51.81, K51.811, K51.814, K51.818, K51.819, K51.9, K51.90, K51.911, K51.912, K51.913, K51.919	K50.8, K51.0, K51.3, K51.4, K50, K50.0, K50.1, K50.9, K51, K51.2, K51.5, K51.8, K51.9
IBD	History of clostridium difficile infection	A04.7, A04.71, A04.72	A04.7
Infection	Physician administered IV antifungal, antibiotic, or antiviral medication	CPT/HCPCS procedure code: J0120, J0133, J0285, J0286, J0287, J0288, J0289, J0290, J0295, J0278, J0348, J0456, J0558, J0559, J0561, J0560, J0690, J0692, J0694, J0695, J0696, J0697, J0698, J0710, J0712, J0713, J0715, J0718, J0744, J1335, J1364, J1362, J1450, J1580, J1570, J1835, J1840, J1850, J1890, J1956, J2010, J2020, J2185, J2180, J2248, J2265, J2280, J2460, J2510, J2540, J2543, J2700, J3000, J3095, J3230, J3243, J3260, J3370, J3465, J7685, J7682, Q4075, S0071	Will be included in the SAP.
Infection	Prior antibiotic use	adapalene/benzoyl peroxide/clindamycin phosphate, azithromycin hydrogen citrate, azithromycin/chondroitin sulfate a sodium/pf, bismuth subsalicylate/metronidazole/tetracycline hcl, cefepime hcl in dextrose 5 % in water, cefepime hcl in iso-osmotic dextrose, ceftazidime sodium, ceftazidime sodium in 0.9 % sodium chloride, ceftazidime/avibactam sodium, ceftriaxone	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		sodium/lidocaine hcl, cefuroxime sodium in 0.9 % sodium chloride/pf, cefuroxime sodium/dextrose, iso-osmotic, cefuroxime sodium/water for injection,sterile, clindamycin phosphate/benzoyl peroxide/emollient comb no.94, dexamethasone sod ph/moxifloxacin hcl in nacl,iso-osmotic/pf, doxycycline calcium, doxycycline hyclate/eyelid cleanser no2/eyelid cleanser no3, doxycycline monohydrate/salicylic acid/octinoxate/zinc oxide, doxycycline monohydrate/skin cleanser combination no.9, gentamicin sulfate/sodium citrate, meropenem in 0.9 % sodium chloride, minocycline hcl/emol comb no.16/skin clnsr l4/top agent no.3, minocycline hcl/eyelid cleanser combination no. 1, nafcillin sodium/dextrose 5 % in water, omeprazole/clarithromycin/amoxicillin trihydrate, oxytetracycline hcl/hydrocortisone acetate, oxytetracycline hcl/polymyxin b sulfate, oxytetracycline hcl/sulfamethizole/phenazopyridine, oxytetracycline/lidocaine, piperacillin sodium/dextrose 5 % in water, prednisolone acetate/moxifloxacin hcl/bromfenac sodium, prednisolone sodium phosphate/moxifloxacin hcl/bromfenac sod, rifampin/isoniazid/pyrazinamide, tretinoin/benzoyl peroxide/clindamycin phosphate/niacinamide, tretinoin/clindamycin phosphate/spironolactone/niacinamide, vancomycin hcl in sterile water, vancomycin hcl/balanced salt solution no.2/pf, amikacin, amikacin sulfate in 0.9 % sodium chloride, amikacin sulfate liposomal with nebulizer accessories, ceftaroline fosamil acetate, ceftolozane sulfate/tazobactam sodium, cefuroxime sodium/dextrose 5 % in water, ciprofloxacin hcl/dexamethasone, clindamycin phosphate/benzoyl peroxide/skin cleanser no.5, clindamycin/benzoyl/octinox/octyl/octocryl/oxyben/titanium, clindamycin/octinoxate/octyl salicyl/octocryl/oxybenz/titan, colloidal bismuth subcitrate/metronidazole/tetracycline hcl, dexamethasone sod ph/moxifloxacin hcl/ketorolac/sod chlor/pf, doxycycline monohydrate/omega-3 combination no.1/eye mask, eravacycline di-hydrochloride, erythromycin gluceptate, fidaxomicin, fluconazole/ibuprofen/itraconazole/terbinafine hcl, linezolid in 0.9 % sodium chloride, meropenem/vaborbactam, moxifloxacin hcl in sodium acetate and sulfate,water,iso-osm, moxifloxacin hcl in sodium chloride, iso-osmotic, moxifloxacin hcl in sodium chloride,iso-osmotic/pf, prednisolone acetate/moxifloxacin hcl, prednisolone sodium phosphate/moxifloxacin hcl, rifampin/isoniazid, tobramycin sulfate/dextrose 5 % in water, tobramycin/loteprednol etabonate, tobramycin/nebulizer, tretinoin/clindamycin phosphate/niacinamide, triamcinolone acetonide/moxifloxacin hcl/water/pf, bacampicillin hcl, bedaquiline fumarate, benzoyl peroxide/clindamycin phosphate/niacinamide, cefotaxime sodium/dextrose 5 % in water, cefotaxime sodium/dextrose, iso-osmotic, cefotetan disodium in iso-osmotic dextrose, ceftazidime in dextrose 5% and water, ceftazidime sodium in iso-osmotic dextrose, chlortetracycline hcl, clindamycin phosphate/benzoyl peroxide/hyaluronate sodium, clindamycin phosphate/skin cleanser comb no.19, clindamycin/niacinamide, doxycycline monohydrate/benzoyl peroxide, imipenem/cilastatin sodium/relebactam, minocycline hcl/wipes with skin cleanser no.4, omadacycline tosylate, oxacillin sodium in iso-osmotic dextrose, rifapentine, tobramycin sulfate/sodium chloride, vancomycin hcl in	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		water for injection (peg-400, nada), amikacin sulfate/pf, cefoxitin sodium/dextrose, iso-osmotic, ceftazidime in dextrose, iso-osmotic, ceftazidime/arginine, doxycycline hyclate/eyelid cleanser 3/eyelid emollient no.1, minocycline hcl microspheres, omeprazole magnesium/amoxicillin trihydrate/rifabutin, oxytetracycline, prednisolone acetate/moxifloxacin hcl/nepafenac, tetracycline, ticarcillin disodium/potassium clavulanate, ceftriaxone sodium in iso-osmotic dextrose, ciprofloxacin hcl/fluocinolone acetonide, lansoprazole/amoxicillin trihydrate/clarithromycin, moxifloxacin hcl in balanced salt solution no.2/pf, nafcillin in dextrose, iso-osmotic, rifabutin, cefazolin sodium/dextrose 5 % in water, cefoxitin sodium/dextrose 5 % in water, clindamycin phosphate in 0.9 % sodium chloride, doxycycline hyclate/skin cleanser combination no.19, trimethoprim, micronized, cefazolin sodium/dextrose, iso-osmotic, gentamicin sulfate/pf, gentamicin sulfate/prednisolone acetate, cefazolin sodium/water for injection,sterile, cefotetan in dextrose, clindamycin palmitate hcl, cefditoren pivoxil, ciprofloxacin, ciprofloxacin hcl/hydrocortisone, clindamycin phosphate/tretinoin, piperacillin and tazobactam in dextrose, iso-osmotic, gentamicin sulfate/sodium chloride, ampicillin anhydrous, ertapenem sodium, fluconazole in dextrose, iso-osmotic, ciprofloxacin lactate, cefazolin sodium in 0.9 % sodium chloride, gentamicin sulfate in sodium chloride, iso-osmotic, piperacillin sodium, tobramycin in 0.225 % sodium chloride, cephalexin hcl, vancomycin in 5 % dextrose in water, cefotetan disodium, linezolid in dextrose 5 % in water, erythromycin base/benzoyl peroxide, sulfamethoxazole/phenazopyridine hcl, imipenem/cilastatin sodium, polymyxin b sulfate/trimethoprim, erythromycin lactobionate, pyrazinamide, lincomycin hcl, ciprofloxacin/ciprofloxacin hcl, ciprofloxacin lactate/dextrose 5 % in water, clindamycin phosphate/dextrose 5 % in water, linezolid, levofloxacin/dextrose 5 % in water, cefoxitin sodium, clindamycin phosphate/benzoyl peroxide, cefepime hcl, ethambutol hcl, cefpodoxime proxetil, meropenem, tobramycin/dexamethasone, fluconazole in sodium chloride, iso-osmotic, cefotaxime sodium, oxytetracycline hcl, cefixime, amikacin sulfate, moxifloxacin hcl, ceftazidime, sulfamethoxazole, ampicillin sodium/sulbactam sodium, vancomycin in 0.9 % sodium chloride, trimethoprim, cefuroxime sodium, tobramycin, erythromycin base in ethanol, rifampin, tobramycin sulfate, cefdinir, nafcillin sodium, erythromycin estolate, erythromycin ethylsuccinate/sulfisoxazole acetyl, cloxacillin sodium, piperacillin sodium/tazobactam sodium, doxycycline monohydrate, ofloxacin, oxacillin sodium, acetic acid, cefuroxime axetil, ceftriaxone sodium, cefazolin sodium, ampicillin sodium, vancomycin hcl, cephradine, clarithromycin, clindamycin phosphate, fluconazole, isoniazid, dicloxacillin sodium, minocycline hcl, levofloxacin, cefadroxil, clindamycin hcl, erythromycin ethylsuccinate, azithromycin, gentamicin sulfate, erythromycin stearate, amoxicillin/potassium clavulanate, ciprofloxacin hcl, erythromycin base, ampicillin trihydrate, tetracycline hcl, penicillin v potassium, sulfamethoxazole/trimethoprim, doxycycline hyclate, cephalexin, amoxicillin	

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
Infection	Antiviral use	famciclovir, acyclovir, valacyclovir hcl	
Infection	Antifungal use	Amphotericin B, imidazoles ketoconazole, miconazole, terbinafine, griseofulvin, flucytosine, itraconazole, fluconazole	
Infection	TB medication use	ethambutol hcl, isoniazid, pyrazinamide, rifampin, rifampin/isoniazid, rifampin/isoniazid/pyrazinamide	
Infection	Opioid abuse or dependence	"F11", "F11.1", "F11.10", "F11.11", "F11.12", "F11.120", "F11.121", "F11.122", "F11.129", "F11.13", "F11.14", "F11.15", "F11.150", "F11.151", "F11.159", "F11.18", "F11.181", "F11.182", "F11.188", "F11.19", "F11.2", "F11.20", "F11.21", "F11.22", "F11.220", "F11.221", "F11.222", "F11.229", "F11.23", "F11.24", "F11.25", "F11.250", "F11.251", "F11.259", "F11.28", "F11.281", "F11.282", "F11.288", "F11.29", "F11.9", "F11.90", "F11.92", "F11.920", "F11.921", "F11.922", "F11.929", "F11.93", "F11.94", "F11.95", "F11.950", "F11.951", "F11.959", "F11.98", "F11.981", "F11.982", "F11.988", "F11.99"	F11, F11.1, F11.2, F11.9
Hypersensitivity reaction	Anaphylactic reaction due to food	T78.0, T78.00, T78.00X, T78.00XA, T78.00XD, T78.00XS, T78.01, T78.01X, T78.01XA, T78.01XD, T78.01XS, T78.02, T78.02X, T78.02XA, T78.02XD, T78.02XS, T78.03, T78.03A, T78.03XA, T78.03XD, T78.03XS, T78.04, T78.04XA, T78.04XD, T78.04XS, T78.05, T78.050D, T78.05XA, T78.05XD, T78.05XS, T78.06, T78.06AA, T78.06XA, T78.06XD, T78.06XS, T78.07, T78.07X, T78.07XA, T78.07XD, T78.07XS, T78.08, T78.08XA, T78.08XD, T78.08XS, T78.09, T78.09XA, T78.09XD, T78.09XS	T78.0
Hypersensitivity reaction	Epi-Pen™	J0170, J0171 Generic name: epinephrine hcl, epinephrine, epinephrine hcl/pf, epinephrine, epinephrine hcl/pf Brand name: epipen, epipen 2-pak, epipen jr, epipen jr 2-pak, epi e-z pen, epi e-z pen jr., adrenaclick, adrenalin, adrenalin	epinephrine hcl, epinephrine, epinephrine hcl/pf, epinephrine, epinephrine hcl/pf

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
		chloride, auvi-q, twinject, episnap, epinephrinesnap-v, epinephrinesnap-ems, symjepi	
Hypersensitivity reaction	Other and unspecified allergy	T78.4, T78.40, T78.40XA, T78.40XD, T78.40XS, T78.49, T78.49XA, T78.49XD, T78.49XS	T78.4
Hypersensitivity reaction	Patch testing, Allergy testing or desensitization to allergens	Procedure code: Z01.82, Z51.6 CPT code: 95052	Will be included in the SAP.
Hypersensitivity reaction	Allergy to vaccine	Z28.04	NA
Hypersensitivity reaction	Allergic rhinitis	J30.1, J30.2, J30.5, J30.8, J30.81, J30.89, J30.9,	J30.1, J30.2, J30.5, J30.8, J30.9
Hypersensitivity reaction	Contact dermatitis (allergic, irritant, unspecified)	H01.11, H01.111, H01.112, H01.113, H01.114, H01.115, H01.116, H01.119, L23, L23.0, L23.1, L23.2, L23.3, L23.4, L23.5, L23.6, L23.7, L23.8, L23.81, L23.89, L23.9, L56.1, L23, L23.0, L23.1, L23.2, L23.3, L23.4, L23.5, L23.6, L23.7, L23.8, L23.81, L23.89, L23.9, L24, L24.0, L24.1, L24.2, L24.3, L24.4, L24.5, L24.6, L24.7, L24.8, L24.81, L24.89, L24.9, L25, L25.0, L25.1, L25.2, L25.3, L25.4, L25.5, L25.8, L25.9, L56.2	L23, L23.0, L23.1, L23.2, L23.3, L23.4, L23.5, L23.6, L23.7, L23.8, L23.9, L56.1, L23, L23.0, L23.1, L23.2, L23.3, L23.4, L23.5, L23.6, L23.7, L23.8, L23.9, L24, L24.0, L24.1, L24.2, L24.3, L24.4, L24.5, L24.6, L24.7, L24.8, L24.9, L25, L25.0, L25.1, L25.2, L25.3, L25.4, L25.5, L25.8, L25.9, L56.2
Hypersensitivity reaction	Allergy status to drugs, medicaments and biological substances	Z88, Z88.0, Z88.1, Z88.2, Z88.3, Z88.4, Z88.5, Z88.6, Z88.7, Z88.8, Z88.9, Z91.0	Z88, Z88.0, Z88.1, Z88.2, Z88.3, Z88.4, Z88.5, Z88.6, Z88.7, Z88.8, Z88.9, Z91.0
Hypersensitivity reaction	Food allergy status and food additive allergy status and latex allergy or	Z91.01, Z91.010, Z91.011, Z91.012, Z91.013, Z91.018, Z91.02, Z91.03, Z91.030, Z91.038, Z91.04, Z91.040, Z91.041, Z91.048, Z91.09	NA

Endpoint	Covariates	ICD-10-CM codes	ICD-10 codes
	radiographic dye allergy		
Hypersensitivity reaction	ACE inhibitor	amlodipine besylate/benazepril hcl, benazepril hcl, benazepril hcl/hydrochlorothiazide, captopril, captopril/hydrochlorothiazide, enalapril maleate, enalapril maleate/felodipine, enalapril maleate/hydrochlorothiazide, enalaprilat dihydrate, fosinopril sodium, fosinopril sodium/hydrochlorothiazide, lisinopril, lisinopril/dietary supplement,comb.10, lisinopril/hydrochlorothiazide, moexipril hcl, moexipril hcl/hydrochlorothiazide, perindopril erbumine, quinapril hcl, quinapril hcl/hydrochlorothiazide, ramipril, trandolapril, trandolapril/verapamil hcl	
PSO severity	Glucocorticoids (systemic)	Triamcinolone, prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone, cortisone, budesonide, betamethasone Route of administration is oral	

ACE=angiotensin converting enzyme; ARB=angiotensin-receptor blockers; COPD=Chronic obstructive pulmonary disease; CPT=Common Procedural Terminology; CRP=C-reactive protein; CT=computerized tomography; HCPCS=Healthcare Common Procedure Coding System; IBD=inflammatory bowel disease; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; IV=intravenous; MACE=major adverse cardiovascular event; MRI=magnetic resonance imaging; NA=not applicable; PSO=psoriasis; SAP=statistical analysis plan; TB=tuberculosis

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
Inflammatory bowel disease	Ulcerative colitis	K51.0, K51.00, K51.013, K51.018, K51.019, K51.2, K51.20, K51.211, K51.214, K51.3, K51.311, K51.312, K51.313, K51.319, K51.41, K51.412, K51.414, K51.418, K51.5, K51.51, K51.512, K51.519, K51.81, K51.811, K51.812, K51.813, K51.818, K51.819, K51.90, K51.911, K51.914, K51.919, K51, K51.01, K51.011, K51.012, K51.014, K51.21, K51.212, K51.213, K51.218, K51.219, K51.30, K51.31, K51.314, K51.318, K51.4, K51.40, K51.411, K51.413, K51.419, K51.50, K51.511, K51.513, K51.514, K51.518, K51.8, K51.80, K51.814, K51.9, K51.91, K51.912, K51.913, K51.918	K51.0, K51.2, K51.3, K51.5, K51, K51.4, K51.8, K51.9
	Crohn's disease	K50.00, K50.013, K50.11, K50.113, K50.118, K50.8, K50.81, K50.811, K50.813, K50.818, K50.819, K50.90, K50.911, K50.913, K50.914, K50.918, K50, K50.0, K50.01, K50.011, K50.012, K50.014, K50.018, K50.019, K50.1, K50.10, K50.111, K50.112, K50.114, K50.119, K50.80, K50.812, K50.814, K50.9, K50.91, K50.912, K50.919	K50, K50.0
	Lower GI endoscopy (colonoscopy or flexible sigmoidoscopy)	CPT procedure code, flexible sigmoidoscopy: 45341, 45342, 45335, 45338, 45340, 45334, 45339, 45345, G0104, 45330, 45331, 45333, 45332, 45337 CPT procedure code, colonoscopy: 45381, 45387, 45389, G0121, 45378, 45379, 45382, 45386, 45390, 45385, 45388, 45391, G0105, 45392, 45380, 45383, 45384	Will be included in the SAP.
	Clostridium difficile	A04.7	A04.7

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
Bacterial infection	Encephalitis/meningitis, bacterial	A39.81, G04.2, A17.0, A27.81, A32.11, A39.0, A51.41, A52.13, A54.81, B02.1, G00.0, G00.9, G01, G02, A01.01, A02.21, A17.82, B00.3, G00.1, G00.2, G00.3, G00.8	G04.2, A17.0, A39.0, B02.1, G00.0, G00.9, G01, G02, B00.3, G00.1, G00.2, G00.3, G00.8
	Endocarditis	A32.82, A52.03, I33.0, I33.9, A39.51, I39	I33.0, I33.9, I39
	Mastoiditis	H70.003, H70.009, H70.011, H70.012, H70.013, H70.019, H70.092, H70.093, H70.099, H70.91, H70.92, H70.001, H70.002, H70.091, H70.90, H70.93	NA
	Osteomyelitis	H05.021, H05.029, M46.24, M46.25, M46.26, M46.28, M86.012, M86.021, M86.031, M86.059, M86.062, M86.072, M86.079, M86.08, M86.111, M86.112, M86.121, M86.122, M86.129, M86.139, M86.141, M86.149, M86.159, M86.171, M86.179, M86.18, M86.8X0, M86.8X3, M86.8X5, M86.8X6, M86.8X7, M86.8X8, M86.8X9, M86.9, A01.05, A02.24, A54.43, H05.022, H05.023, M46.20, M46.21, M46.22, M46.23, M46.27, M86.00, M86.011, M86.019, M86.022, M86.029, M86.032, M86.039, M86.041, M86.042, M86.049, M86.051, M86.052, M86.061, M86.069, M86.071, M86.09, M86.10, M86.119, M86.131, M86.132, M86.142, M86.151, M86.152, M86.161, M86.162, M86.169, M86.172, M86.19, M86.8X1, M86.8X2, M86.8X4	M86.9
	Pneumonia, bacterial	A01.03, A37.01, A37.91, J13, J15.1, J15.212, J15.3, J15.5, J15.7, J16.0, J18.1, J18.9, J86.0, J86.9, A02.22, A37.11, A37.81, A48.1, A54.84, J14, J15.0, J15.20, J15.211, J15.29, J15.4, J15.6, J15.8, J15.9, J16.8, J17, J18.0, J18.8	J13, J15.1, J15.3, J15.5, J15.7, J16.0, J18.1, J18.9, J86.0, J86.9, A48.1, J14, J15.0, J15.4, J15.6, J15.8, J15.9, J16.8, J17, J18.0, J18.8

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Bacteremia or septicemia	A40.1, A40.3, A40.9, A41.01, A41.02, A41.1, A41.2, A41.3, A41.4, A41.51, A41.89, A48.3, R78.81, A32.7, A39.2, A39.4, A40.0, A40.8, A41.50, A41.52, A41.53, A41.59, A41.81, A41.9, A54.86, A02.1	A40.1, A40.3, A40.9, A41.1, A41.2, A41.3, A41.4, A48.3, A32.7, A39.2, A39.4, A40.0, A40.8, A41.9, A02.1
	Pyelonephritis or UTI	N10, N39.0, N13.6, A02.25	N10, N39.0, N13.6
	Pyomyositis	M60.009	NA
	Retropharyngeal and parapharyngeal abscess	J39.0, J36, J39.1	J39.0, J36, J39.1
	Septic arthritis	M00.011, M00.012, M00.029, M00.039, M00.042, M00.061, M00.079, M00.129, M00.132, M00.142, M00.149, M00.151, M00.152, M00.159, M00.161, M00.169, M00.171, M00.179, M00.19, M00.212, M00.219, M00.221, M00.222, M00.229, M00.232, M00.239, M00.241, M00.242, M00.251, M00.252, M00.262, M00.271, M00.28, M00.29, M00.811, M00.819, M00.821, M00.829, M00.831, M00.832, M00.839, M00.841, M00.842, M00.852, M00.869, M00.88, M00.00, M00.019, M00.021, M00.022, M00.031, M00.032, M00.041, M00.049, M00.051, M00.052, M00.059, M00.062, M00.069, M00.071, M00.072, M00.08, M00.09, M00.10, M00.111, M00.112, M00.119, M00.121, M00.122, M00.131, M00.139, M00.141, M00.162, M00.172, M00.18, M00.20, M00.211, M00.231, M00.249, M00.259, M00.261, M00.269, M00.272, M00.279, M00.80, M00.812, M00.822, M00.849, M00.851, M00.859, M00.861, M00.862, M00.871, M00.872, M00.879, M00.89, M00.9	NA

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Skin and soft tissue	A48.0, H05.012, H05.013, H05.019, K12.2, L01.02, L01.09, L01.1, L02.02, L02.03, L02.11, L02.13, L02.213, L02.214, L02.215, L02.219, L02.221, L02.222, L02.231, L02.232, L02.233, L02.412, L02.414, L02.415, L02.416, L02.419, L02.421, L02.423, L02.424, L02.426, L02.429, L02.431, L02.439, L02.511, L02.512, L02.521, L02.531, L02.612, L02.619, L02.622, L02.629, L02.639, L02.828, L02.838, L02.91, L02.92, L02.93, L03.011, L03.012, L03.031, L03.039, L03.111, L03.112, L03.113, L03.115, L03.116, L03.119, L03.121, L03.122, L03.124, L03.129, L03.211, L03.221, L03.311, L03.313, L03.315, L03.317, L03.319, L03.323, L03.324, L03.326, L03.898, L03.91, L08.89, M72.6, A46, H05.011, L01.00, L01.01, L01.03, L02.01, L02.12, L02.223, L02.224, L02.225, L02.226, L02.229, L02.234, L02.235, L02.236, L02.239, L02.31, L02.32, L02.33, L02.411, L02.413, L02.422, L02.425, L02.432, L02.433, L02.434, L02.435, L02.436, L02.519, L02.522, L02.529, L02.532, L02.539, L02.611, L02.621, L02.631, L02.632, L02.811, L02.818, L02.821, L02.831, L03.019, L03.021, L03.022, L03.029, L03.032, L03.041, L03.042, L03.049, L03.114, L03.123, L03.125, L03.126, L03.212, L03.222, L03.312, L03.314, L03.316, L03.321, L03.322, L03.325, L03.327, L03.329, L03.811, L03.818, L03.891, L03.90, L08.1, L08.9	A48.0, K12.2, L01.1, M72.6, A46, L08.1, L08.9
Viral infection	Influenza	J09.X2, J09.X9, J10.00, J10.01, J10.08, J10.1, J10.81, J11.00, J11.08, J11.1, J11.2, J11.82, J11.83, J09.X1, J09.X3, J10.2, J10.82, J10.83, J10.89, J11.81, J11.89, J12.2	J10.1, J11.1, J11.2, J12.2

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Pneumonia, viral	J12.0, J12.1, J12.89, J12.3, J12.81, J12.9	J12.0, J12.1, J12.3, J12.9
	Encephalitis/meningitis, viral	A32.12, A83.0, A83.1, A83.4, A83.5, A83.8, A84.0, A84.8, A85.2, A92.31, A83.2, A83.3, A83.6, A83.9, A84.1, A84.9, B00.4, B02.0, G04.90, G05.3, B27.12, B27.02, B01.11, B10.01, B01.1, B06.01, B10.09, B26.2	A83.0, A83.1, A83.4, A83.5, A83.8, A84.0, A84.8, A85.2, A83.2, A83.3, A83.6, A83.9, A84.1, A84.9, B00.4, B02.0, G05.3, B01.1, B26.2
	Herpes (simplex/zoster)	A60.00, A60.03, A60.09, B00.0, B00.1, B00.2, B00.51, B00.52, B00.7, B00.82, B02.1, B02.33, B02.34, B02.39, B02.7, B02.8, A60.01, A60.02, A60.04, A60.1, A60.9, B00.3, B00.4, B00.50, B00.53, B00.59, B00.81, B00.89, B00.9, B02.0, B02.30, B02.31, B02.32, B02.9	B00.0, B00.1, B00.2, B00.7, B02.1, B02.7, B02.8, A60.1, A60.9, B00.3, B00.4, B00.9, B02.0, B02.9
Opportunistic infection (bacterial)	Mycobacterium infection, TB and non-TB	A15.0, A15.4, A15.5, A15.9, A17.0, A17.81, A17.89, A18.2, A18.32, A18.39, A18.50, A18.52, A18.53, A18.54, A18.59, A18.7, A18.81, A18.82, A18.83, A18.85, A19.1, A19.2, A15.6, A15.7, A15.8, A17.1, A17.82, A17.83, A17.9, A18.01, A18.03, A18.31, A18.4, A18.51, A18.6, A18.84, A18.89, A19.0, A19.8, A19.9, A31.0, A31.1, A31.2, A31.8, A31.9	A15.0, A15.4, A15.5, A15.9, A17.0, A18.2, A18.7, A19.1, A19.2, A15.6, A15.7, A15.8, A17.1, A17.9, A18.4, A18.6, A19.0, A19.8, A19.9, A31.0, A31.1, A31.2, A31.8, A31.9
	Listeria	A32.11, A32.12, A32.81, A32.82, A32.9, A32.0, A32.7, A32.89,	A32.9, A32.0, A32.7
	Progressive multifocal leukoencephalopathy	A81.2	A81.2
	Histoplasmosis	B39.2, B39.3, B39.5, B39.9, B39.0, B39.4	B39.2, B39.3, B39.5, B39.9, B39.0, B39.4
	Actinomycosis	A42.0, A42.1, A42.2, A42.81, A42.89, A42.9, A42.7, A42.82, B47.1	A42.0, A42.1, A42.2, A42.9, A42.7, B47.1
	Lobomycosis	B48.0	B48.0
	Toxoplasma	B58.01, B58.09, B58.2, B58.3, B58.81, B58.82, B58.89,	B58.2, B58.3

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Nocardiosis	A43.0, A43.1, A43.8, A43.9,	A43.0, A43.1, A43.8, A43.9,
Opportunistic infection (fungal)	Blastomycosis	B40.0, B40.7, B40.81, B40.89, B40.9, B40.2, B40.3	B40.0, B40.7, B40.9, B40.2, B40.3
	Cryptococcosis	B45.0, B45.1, B45.2, B45.3, B45.7, B45.8, B45.9	B45.0, B45.1, B45.2, B45.3, B45.7, B45.8, B45.9
	Coccidioidomycosis	B38.0, B38.2, B38.3, B38.89, B38.9, B38.4, B38.7, B38.81,	B38.0, B38.2, B38.3, B38.9, B38.4, B38.7
	Paracoccidioidomycosis	B41.0, B41.7, B41.8, B41.9	B41.0, B41.7, B41.8, B41.9
	Pneumocystosis	B59	B59
	Disseminated candida infection	B37.2, B37.6, B37.81, B37.1, B37.41, B37.5, B37.7, B37.82, B37.84	B37.2, B37.6, B37.1, B37.5, B37.7
	Mucormycosis	B46.0, B46.5, B46.1, B46.2, B46.3, B46.4,	B46.0, B46.5, B46.1, B46.2, B46.3, B46.4
	Aspergillosis	B44.0, B44.89, B44.9, B44.1, B44.2, B44.7,	B44.0, B44.9, B44.1, B44.2, B44.7
Opportunistic infection (viral)	Cytomegaloviral mononucleosis	B25.1, B25, B25.0, B25.2, B25.8, B25.9, B27.10, B27.12, B27.1, B27.11, B27.19,	B25.1, B25, B25.0, B25.2, B25.8, B25.9, B27.1
Opportunistic infection (helminthic)	Strongyloidiasis	B78.1	B78.1
	Ascariasis	B77.81	
Candidiasis	Oral candidiasis	B37.81, B37.83, B37.0	B37.0
MACE	ACS	I20.0, I24.9, I25.710, I24.1, I25.760, I24.0, I24.8, I25.750, I25.730, I25.790, I25.110, I25.700, I25.720	I20.0, I24.9, I24.1, I24.0, I24.8
	MI	I21.0, I21.02, I21.09, I21.19, I21.2, I21.29, I21.11, I21.4, I21.1, I21.3, I21.01, I21.21	I21.0, I21.2, I21.4, I21.1, I21.3

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Stroke	I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.00, I63.011, I63.012, I63.019, I63.02, I63.031, I63.032, I63.039, I63.09, I63.10, I63.111, I63.112, I63.119, I63.12, I63.131, I63.132, I63.139, I63.19, I63.20, I63.211, I63.212, I63.219, I63.22, I63.231, I63.232, I63.239, I63.29, I63.30, I63.311, I63.312, I63.319, I63.321, I63.322, I63.329, I63.331, I63.332, I63.339, I63.341, I63.342, I63.349, I63.39, I63.40, I63.411, I63.412, I63.419, I63.421, I63.422, I63.429, I63.431, I63.432, I63.439, I63.441, I63.442, I63.449, I63.49, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, I63.59, I63.6, I63.8, I63.9, I63.013, I63.033, I63.113, I63.133, I63.213, I63.233, I63.313, I63.323, I63.333, I63.343, I63.413, I63.423, I63.433, I63.443, I63.513, I63.523, I63.533, I63.543, I63.81, I63.89	I60.2, I60.4, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.6, I63.8, I63.9

	Coronary revascularization (PTCA, stenting, CABG)	ICD-10 procedure code: 021L0Z5, 0270056, 0270066, 0270076, 027007Z, 02700DZ, 02700GZ, 02700T6, 02700Z6, 027034Z, 0270376, 02703FZ, 02703Z6, 027045Z, 0270466, 02704F6, 02704T6, 0271066, 0271076, 027137Z, 02713F6, 02713GZ, 02713T6, 02713TZ, 02713ZZ, 0271446, 027144Z, 027145Z, 02714G6, 02714TZ, 02714Z6, 027206Z, 02720GZ, 0272356, 027235Z, 027237Z, 02723FZ, 02723T6, 027244Z, 02724E6, 02724T6, 0273046, 0273056, 02730E6, 02730G6, 02730ZZ, 0273376, 02733DZ, 0273446, 02734D6, 02C03ZZ, 02C23Z6, 02C30Z6, 02C34Z6, 021K0Z5, 027006Z, 02700E6, 02700FZ, 02700ZZ, 0270366, 02703D6, 02703E6, 02703ZZ, 0270446, 0270476, 02704GZ, 02704Z6, 02710E6, 02710FZ, 02710T6, 02710Z6, 0271346, 02713E6, 0271456, 0271476, 027147Z, 02714DZ, 02714F6, 027204Z, 0272056, 0272066, 02720E6, 02720EZ, 02720FZ, 02720G6, 02720T6, 02720ZZ, 0272366, 02723ZZ, 0272446, 0272466, 0272476, 02724FZ, 027304Z, 0273076, 027307Z, 02730DZ, 02730T6, 02733TZ, 027344Z, 0273456, 0273466, 02734E6, 02734EZ, 02734G6, 02734TZ, 02C03Z6, 02QA3ZZ, 0270046, 0270356, 027035Z, 027036Z, 02703F6, 02703G6, 02703TZ, 027044Z, 0270456, 02704E6, 02704G6, 0271046, 027105Z, 02710G6, 02710GZ, 02710TZ, 0271356, 02713D6, 02713DZ, 02713EZ, 0271466, 02714D6, 02714E6, 02714FZ, 027207Z, 02720F6, 02720Z6, 027234Z, 0272376, 02723D6, 02723E6, 02723EZ, 02723F6, 02723G6,	Will be included in the SAP.

		02723GZ, 02723Z6, 027246Z, 027247Z, 02724G6, 02724TZ, 02724ZZ, 027305Z, 02730F6, 02730FZ, 027334Z, 027337Z, 02733EZ, 02733G6, 02733GZ, 02733ZZ, 027347Z, 02734DZ, 02C13Z6, 02C14Z6, 02C23ZZ, 02C33ZZ, 02QB3ZZ, 02QC3ZZ, 02700EZ, 02700F6, 02700G6, 02700TZ, 027037Z, 027047Z, 02704ZZ, 027106Z, 02710DZ, 02710EZ, 027135Z, 02713FZ, 02713G6, 02714EZ, 02714T6, 027205Z, 0272076, 02720D6, 027236Z, 02724D6, 02724F6, 02724GZ, 0273066, 02730Z6, 0273346, 0273356, 027335Z, 0273366, 02733E6, 02733F6, 02733FZ, 02733T6, 02733Z6, 02C00Z6, 02C10Z6, 021K4Z5, 021L4Z5, 027004Z, 027005Z, 02700D6, 0270346, 02703DZ, 02703EZ, 02703GZ, 02703T6, 027046Z, 02704D6, 02704DZ, 02704EZ, 02704FZ, 02704TZ, 027104Z, 0271056, 027107Z, 02710D6, 02710F6, 02710ZZ, 027134Z, 0271366, 027136Z, 0271376, 02713Z6, 027146Z, 02714GZ, 02714ZZ, 0272046, 02720DZ, 02720TZ, 0272346, 02723DZ, 02723TZ, 0272456, 027245Z, 02724DZ, 02724EZ, 02724Z6, 027306Z, 02730D6, 02730EZ, 02730GZ, 02730TZ, 027336Z, 02733D6, 027345Z, 027346Z, 0273476, 02734F6, 02734FZ, 02734GZ, 02734T6, 02734Z6, 02734ZZ, 02C04Z6, 02C13ZZ, 02C20Z6, 02C24Z6, 02C33Z6, 02QA4ZZ, 02QB4ZZ, 02QC4ZZ CPT-4 procedure code: 33510, 33511, 33517, 92921, 92924, 92938, 92941, 92973, 92995, 33516, 33518, 33519, 33521, 33534, 33572, 92944, 92984, 33513, 33535, 92982, 92996, 33140, 33141, 33512, 33514, 33523, 33545,	

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
		92920, 92937, 92943, 33522, 33530, 33533, 33536, 92925	

Malignancy	Any malignant cancer or in-situ cancer *(lip, oral cavity, pharynx, digestive organs, respiratory and intrathoracic organs, bone and articular cartilage, melanoma, mesothelial soft tissue, breast, female genital organs, male genital organs, urinary tract, eye, brain, other CNS, thyroid and other endocrine glands, neuroendocrine tumors)*	C00.0, C00.3, C00.4, C01, C02.0, C02.2, C02.3, C03.1, C03.9, C04.0, C04.1, C04.8, C06.89, C07, C08.0, C09.0, C09.1, C10.1, C10.3, C10.8, C10.9, C11.1, C11.3, C11.8, C11.9, C12, C13.1, C14.0, C14.2, C15.5, C16.2, C16.3, C16.5, C16.9, C17.3, C17.8, C17.9, C18.1, C18.4, C18.5, C18.7, C18.8, C20, C21.8, C22.0, C22.1, C22.2, C22.8, C22.9, C24.1, C24.9, C25.4, C25.9, C26.9, C30.0, C30.1, C31.0, C32.1, C32.2, C32.3, C32.8, C34.00, C34.10, C34.2, C34.90, C37, C38.1, C38.2, C38.3, C39.9, C40.20, C41.4, C43.0, C43.10, C43.20, C43.30, C43.39, C43.4, C43.60, C43.70, C46.2, C46.50, C46.9, C48.0, C48.1, C48.2, C49.0, C49.10, C49.20, C49.4, C49.5, C49.6, C49.9, C50.029, C50.519, C50.819, C51.0, C51.2, C51.9, C52, C53.8, C54.2, C54.8, C57.00, C57.10, C58, C60.0, C60.1, C60.2, C60.9, C61, C62.10, C62.90, C64.9, C67.1, C67.2, C67.3, C67.4, C67.6, C67.7, C67.9, C68.0, C68.1, C68.9, C69.20, C69.30, C69.40, C69.60, C69.80, C69.90, C70.1, C71.1, C71.3, C71.6, C71.7, C71.8, C71.9, C72.1, C73, C75.0, C75.8, C75.9, C76.0, C76.50, C76.8, C77.0, C77.1, C77.2, C77.3, C77.4, C77.8, C78.00, C78.39, C78.6, C78.89, C79.00, C79.11, C79.19, C79.2, C79.31, C79.32, C79.51, C79.52, C79.60, C79.81, C79.82, C80.2, C81.00, C81.01, C81.05, C81.06, C81.08, C81.10, C81.13, C81.14, C81.20, C81.21, C81.24, C81.26, C81.27, C81.29, C81.30, C81.32, C81.34, C81.35, C81.38, C81.39, C81.43, C81.45, C81.46, C81.49, C81.70, C81.78, C81.79, C81.90, C81.91, C81.94, C81.95, C82.90, C82.92, C82.93, C82.96, C82.97, C82.98, C83.11, C83.13, C83.14, C83.31, C83.32,	C00.0, C00.3, C00.4, C01, C02.0, C02.2, C02.3, C03.1, C03.9, C04.0, C04.1, C04.8, C07, C08.0, C09.0, C09.1, C10.1, C10.3, C10.8, C10.9, C11.1, C11.3, C11.8, C11.9, C12, C13.1, C14.0, C14.2, C15.5, C16.2, C16.3, C16.5, C16.9, C17.3, C17.8, C17.9, C18.1, C18.4, C18.5, C18.7, C18.8, C20, C21.8, C22.0, C22.1, C22.2, C22.8, C22.9, C24.1, C24.9, C25.4, C25.9, C26.9, C30.0, C30.1, C31.0, C32.1, C32.2, C32.3, C32.8, C34.2, C37, C38.1, C38.2, C38.3, C39.9, C41.4, C43.0, C43.4, C46.2, C46.9, C48.0, C48.1, C48.2, C49.0, C49.4, C49.5, C49.6, C49.9, C51.0, C51.2, C51.9, C52, C53.8, C54.2, C54.8, C58, C60.0, C60.1, C60.2, C60.9, C61, C64.9, C67.1, C67.2, C67.3, C67.4, C67.6, C67.7, C67.9, C68.0, C68.1, C68.9, C70.1, C71.1, C71.3, C71.6, C71.7, C71.8, C71.9, C72.1, C73, C75.0, C75.8, C75.9, C76.0, C76.50, C76.8, C77.0, C77.1, C77.2, C77.3, C77.4, C77.8, C78.6, C79.2, C80.2, C96.Z, D03.4, D03.59, D03.61, D03.72, D03.8, C00.1, C00.2, C00.5, C00.6, C00.8, C02.1, C02.4, C02.8, C02.9, C03.0, C04.9, C05.0, C05.1, C05.2, C05.9, C06.0, C06.1, C06.2, C06.9, C08.1, C08.9, C09.9, C10.0, C10.2, C10.4, C11.0, C11.2, C13.0, C13.2, C13.8, C13.9, C14.8, C15.3, C15.4, C15.8, C15.9, C16.0, C16.1, C16.4, C16.6, C16.8, C17.0, C17.1, C17.2, C18.0, C18.2, C18.3, C18.6, C18.9, C19, C21.0, C21.1, C22.7, C23, C24.0, C24.8, C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, C26.0, C26.1, C31.1, C31.2, C31.3, C31.8, C31.9, C32.0, C32.9, C33, C38.0, C38.4, C38.8, C39.0, C41.0, C41.1, C41.2, C41.3, C41.9, C43.8, C43.9, C46.0, C46.1, C46.3, C46.4, C46.7, C47.8, C48.8, C49.3, C49.8, C51.1, C53.0,

		C83.34, C83.36, C83.38, C83.39, C83.50, C83.51, C83.54, C83.57, C83.70, C83.72, C83.77, C83.78, C83.83, C83.84, C83.87, C83.88, C84.00, C84.01, C84.02, C84.04, C84.06, C84.07, C84.10, C84.11, C84.13, C84.14, C84.16, C84.18, C84.42, C84.43, C84.44, C84.46, C84.47, C84.61, C84.62, C84.65, C84.68, C84.69, C84.70, C84.72, C84.73, C84.74, C84.75, C84.76, C84.78, C84.79, C85.80, C85.86, C88.8, C90.01, C90.02, C90.11, C90.22, C90.32, C91.01, C91.02, C91.11, C91.12, C91.40, C91.92, C91.Z0, C91.Z1, C91.Z2, C92.11, C92.21, C92.22, C92.40, C92.41, C92.50, C92.52, C92.90, C92.91, C92.92, C92.Z1, C92.Z2, C93.02, C93.10, C93.92, C93.Z0, C93.Z2, C94.01, C94.20, C94.21, C94.22, C94.30, C94.31, C94.32, C94.80, C94.82, C95.01, C95.02, C95.12, C95.92, C96.Z, D03.12, D03.21, D03.39, D03.4, D03.59, D03.61, D03.72, D03.8, C00.1, C00.2, C00.5, C00.6, C00.8, C02.1, C02.4, C02.8, C02.9, C03.0, C04.9, C05.0, C05.1, C05.2, C05.9, C06.0, C06.1, C06.2, C06.9, C08.1, C08.9, C09.9, C10.0, C10.2, C10.4, C11.0, C11.2, C13.0, C13.2, C13.8, C13.9, C14.8, C15.3, C15.4, C15.8, C15.9, C16.0, C16.1, C16.4, C16.6, C16.8, C17.0, C17.1, C17.2, C18.0, C18.2, C18.3, C18.6, C18.9, C19, C21.0, C21.1, C22.7, C23, C24.0, C24.8, C25.0, C25.1, C25.2, C25.3, C25.7, C25.8, C26.0, C26.1, C31.1, C31.2, C31.3, C31.8, C31.9, C32.0, C32.9, C33, C34.30, C34.80, C38.0, C38.4, C38.8, C39.0, C40.00, C40.10, C40.30, C41.0, C41.1, C41.2, C41.3, C41.9, C43.31, C43.59, C43.8, C43.9, C46.0, C46.1, C46.3, C46.4, C46.7, C47.8,	C53.1, C53.9, C54.0, C54.1, C54.3, C54.9, C55, C56.9, C57.3, C57.4, C57.7, C57.8, C57.9, C60.8, C63.2, C63.7, C63.8, C63.9, C65.9, C66.9, C67.0, C67.5, C67.8, C68.8, C70.0, C70.9, C71.0, C71.2, C71.4, C71.5, C72.0, C72.9, C75.1, C75.2, C75.3, C75.4, C75.5, C76.1, C76.2, C76.3, C77.5, C77.9, C78.1, C78.2, C78.4, C78.5, C78.7, C80.0, C80.1, C96.0, C96.4, C96.9, C96.A, D03.0, D03.9, D45

		C48.8, C49.3, C49.8, C50.019, C50.119, C50.219, C50.319, C50.419, C50.619, C50.919, C50.929, C51.1, C53.0, C53.1, C53.9, C54.0, C54.1, C54.3, C54.9, C55, C56.9, C57.20, C57.3, C57.4, C57.7, C57.8, C57.9, C60.8, C62.00, C63.00, C63.10, C63.2, C63.7, C63.8, C63.9, C65.9, C66.9, C67.0, C67.5, C67.8, C68.8, C69.00, C69.10, C69.50, C70.0, C70.9, C71.0, C71.2, C71.4, C71.5, C72.0, C72.50, C72.9, C74.90, C75.1, C75.2, C75.3, C75.4, C75.5, C76.1, C76.2, C76.3, C76.40, C77.5, C77.9, C78.1, C78.2, C78.4, C78.5, C78.7, C79.49, C79.70, C79.89, C80.0, C80.1, C81.02, C81.03, C81.04, C81.07, C81.09, C81.11, C81.12, C81.15, C81.16, C81.17, C81.18, C81.19, C81.22, C81.23, C81.25, C81.28, C81.31, C81.33, C81.36, C81.37, C81.40, C81.41, C81.42, C81.44, C81.47, C81.48, C81.71, C81.72, C81.73, C81.74, C81.75, C81.76, C81.77, C81.92, C81.93, C81.96, C81.97, C81.98, C81.99, C82.91, C82.94, C82.95, C82.99, C83.10, C83.12, C83.15, C83.16, C83.17, C83.18, C83.19, C83.30, C83.33, C83.35, C83.37, C83.52, C83.53, C83.55, C83.56, C83.58, C83.59, C83.71, C83.73, C83.74, C83.75, C83.76, C83.79, C83.80, C83.81, C83.82, C83.85, C83.86, C83.89, C84.03, C84.05, C84.08, C84.09, C84.12, C84.15, C84.17, C84.19, C84.40, C84.41, C84.45, C84.48, C84.49, C84.60, C84.63, C84.64, C84.66, C84.67, C84.71, C84.77, C84.93, C85.81, C85.82, C85.83, C85.84, C85.85, C85.87, C85.88, C85.89, C90.00, C90.10, C90.12, C90.20, C90.21, C90.30, C90.31, C91.00, C91.10, C91.41, C91.90, C91.91, C92.00, C92.01, C92.02,	

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
		C92.10, C92.12, C92.20, C92.30, C92.31, C92.32, C92.42, C92.51, C92.Z0, C93.00, C93.01, C93.11, C93.12, C93.90, C93.91, C93.Z1, C94.00, C94.02, C94.81, C95.00, C95.10, C95.11, C95.90, C95.91, C96.0, C96.4, C96.9, C96.A, D03.0, D03.10, D03.11, D03.20, D03.22, D03.30, D03.51, D03.52, D03.60, D03.62, D03.70, D03.71, D03.9, D45,	
	Lung	C34.10, C34.2, C34.90, C34.30, C34.80	C34.2
	Colorectal	C18.0, C18.2, C18.3, C18.6, C18.9 C18.1, C18.4, C18.5, C18.7, C18.8, C19, C20	C18.0, C18.2, C18.3, C18.6, C18.9 C18.1, C18.4, C18.5, C18.7, C18.8, C19, C20
	Stomach	C16.0, C16.1, C16.4, C16.6, C16.8, C16.2, C16.3, C16.5, C16.9	C16.0, C16.1, C16.4, C16.6, C16.8, C16.2, C16.3, C16.5, C16.9
	Breast	C50.029, C50.519, C50.819, C50.019, C50.119, C50.219, C50.319, C50.419, C50.619, C50.919, C50.929	Will be included in the SAP.

	Lymphoma	C81.00, C81.01, C81.05, C81.06, C81.08, C81.10, C81.13, C81.14, C81.20, C81.21, C81.24, C81.26, C81.27, C81.29, C81.30, C81.32, C81.34, C81.35, C81.38, C81.39, C81.43, C81.45, C81.46, C81.49, C81.70, C81.78, C81.79, C81.90, C81.91, C81.94, C81.95, C82.90, C82.92, C82.93, C82.96, C82.97, C82.98, C83.11, C83.13, C83.14, C83.31, C83.32, C83.34, C83.36, C83.38, C83.39, C83.50, C83.51, C83.54, C83.57, C83.70, C83.72, C83.77, C83.78, C83.83, C83.84, C83.87, C83.88, C84.00, C84.01, C84.02, C84.04, C84.06, C84.07, C84.10, C84.11, C84.13, C84.14, C84.16, C84.18, C84.42, C84.43, C84.44, C84.46, C84.47, C84.61, C84.62, C84.65, C84.68, C84.69, C84.70, C84.72, C84.73, C84.74, C84.75, C84.76, C84.78, C84.79, C85.80, C85.86, C81.02, C81.03, C81.04, C81.07, C81.09, C81.11, C81.12, C81.15, C81.16, C81.17, C81.18, C81.19, C81.22, C81.23, C81.25, C81.28, C81.31, C81.33, C81.36, C81.37, C81.40, C81.41, C81.42, C81.44, C81.47, C81.48, C81.71, C81.72, C81.73, C81.74, C81.75, C81.76, C81.77, C81.92, C81.93, C81.96, C81.97, C81.98, C81.99, C82.91, C82.94, C82.95, C82.99, C83.10, C83.12, C83.15, C83.16, C83.17, C83.18, C83.19, C83.30, C83.33, C83.35, C83.37, C83.52, C83.53, C83.55, C83.56, C83.58, C83.59, C83.71, C83.73, C83.74, C83.75, C83.76, C83.79, C83.80, C83.81, C83.82, C83.85, C83.86, C83.89, C84.03, C84.05, C84.08, C84.09, C84.12, C84.15, C84.17, C84.19, C84.40, C84.41, C84.45, C84.48, C84.49, C84.60, C84.63, C84.64, C84.66,	C86, C86.0, C86.1, C86.2, C86.3, C86.4, C86.5, C86.6

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
		C84.67, C84.71, C84.77, C84.93, C85.81, C85.82, C85.83, C85.84, C85.85, C85.87, C85.88, C85.89, C86, C86.0, C86.1, C86.10, C86.2, C86.3, C86.4, C86.5, C86.6	
	Leukemia	C91.01, C91.02, C91.11, C91.12, C91.40, C91.92, C91.Z0, C91.Z1, C91.Z2, C92.11, C92.21, C92.22, C92.40, C92.41, C92.50, C92.52, C92.90, C92.91, C92.92, C92.Z1, C92.Z2, C93.02, C93.10, C93.92, C93.Z0, C93.Z2, C94.01, C94.20, C94.21, C94.22, C94.30, C94.31, C94.32, C94.80, C94.82, C95.01, C95.02, C95.12, C95.92, C96.Z, C91.00, C91.10, C91.41, C91.90, C91.91, C92.00, C92.01, C92.02, C92.10, C92.12, C92.20, C92.30, C92.31, C92.32, C92.42, C92.51, C92.Z0, C93.00, C93.01, C93.11, C93.12, C93.90, C93.91, C93.Z1, C94.00, C94.02, C94.81, C95.00, C95.10, C95.11, C95.90, C95.91, C96.0, C96.4, C96.9, C96.A	C96.0, C96.4, C96.9, C96.A
Hyper-sensitivity reaction	Anaphylaxis	T78.2, T78.2XXA, T78.2XXD, T78.2XXS, T88.6x, T80.59x	T78.2
	Allergy, unspecified	T78.40XA, T78.40XD, T78.40XS, T88.7, Y57.9	NA
	Arthus phenomenon	T78.41, T78.41XA, T78.41XD, T78.41XS	NA
	Angioneurotic edema	T78.3, T78.3XXA, T78.3XXD, T78.3XXS	T78.3
	Stevens-Johnson syndrome/ Toxic epidermal necrolysis	L51.1, L51.2, L51.3	L51.1, L51.2, L51.3
	Allergic urticaria	L50.5	L50.5

Outcome	Suboutcome	ICD-10-CM codes	ICD-10 codes
	Skin eruption due to drugs and medicaments taken internally	L27.0, L27.1	L27.0, L27.1
	Epinephrine intramuscular injection (eg, Epi-Pen autoinjector)	Procedure code: J0170, J0171 Generic name: epinephrine hcl, epinephrine, epinephrine hcl/pf, epinephrine, epinephrine hcl/pf Brand name: epipen, epipen 2-pak, epipen jr, epipen jr 2-pak, epi e-z pen, epi e-z pen jr., adrenaclick, adrenalin, adrenalin chloride, auvi-q, twinject, episnap, epinephrinesnap-v, epinephrinesnap-ems, symjepiTable	Will be included in the SAP.

ACS=acute coronary syndrome; CABG=coronary artery bypass craft; CPT=Common Procedural Terminology; GI=gastrointestinal; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; MACE=major adverse cardiovascular event; MI=myocardial infarction; NA=not applicable; PCTA=percutaneous transluminal coronary angioplasty; SAP=statistical analysis plan; TB=tuberculosis; UTI=urinary tract infection

SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: ps0038-pass-protocol-amend-1

Version: 1.0

Document Number: CLIN-000227679

Title: PS0038-PASS-Protocol-Amendment 1

Approved Date: 21 Aug 2023

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 09-Aug-2023 21:04:50 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: EEA QPPV Date of Signature: 10-Aug-2023 12:12:03 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 11-Aug-2023 13:32:09 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 21-Aug-2023 14:23:08 GMT+0000