# Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Databases

Protocol V4.0

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## Post-Authorization Safety Study (PASS) Information

| | |
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| **Title** | Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Databases |
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| **Research question and objectives** | The research questions are as follows:<br>• What is the frequency of key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe atopic dermatitis (AD) or prurigo nodularis (PN) who use commercially available nemolizumab during the 95 days (approximately 14 weeks) before their estimated conception date (ECD) or at any time during pregnancy and among a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?<br>• What is the effect of nemolizumab on key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe AD or PN who use commercially available nemolizumab during pregnancy compared to a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?<br>This study has the following objectives:<br>• To estimate the frequency of select adverse pregnancy and birth outcomes (i.e., ectopic pregnancy, elective termination, live birth, preterm birth, spontaneous abortion, and foetal death/stillbirth) among pregnant patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.<br>• To estimate the frequency of select adverse foetal, neonatal, and infant outcomes (i.e., major congenital malformations [MCMs] and small for gestational age [SGA] birth) among infants from pregnancies in patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.<br>• To estimate the adjusted relative risks (RRs) and hazard ratios (HRs) for the study outcomes in pregnant patients in the nemolizumab cohort versus the two comparator cohorts. |
| **Country of study** | United States |

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# 1. ABBREVIATIONS

| | |
|---|---|
| AD | Atopic dermatitis |
| ATT | Average treatment effect in the treated |
| CI | Confidence interval |
| CPT® | Current Procedural Terminology |
| DAPI | Dynamic Assessment of Pregnancies and Infants |
| ECD | Estimated conception date |
| EHR | Electronic Health Record |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| GPP | Good Pharmacoepidemiology Practices |
| HCPCS | Healthcare Common Procedure Coding System |
| HICL | Hierarchical Ingredient Code List |
| HIV | Human Immunodeficiency Virus |
| HR | Hazard ratio |
| ICD-10 | International Classification of Diseases, 10th Revision |
| ICD-10-CM | International Classification of Diseases, 10th Revision, Clinical Modification |
| IPTW | Inverse probability of treatment weighting |
| IRB | Institutional Review Board |
| ISPE | International Society for Pharmacoepidemiology |
| JAK | Janus kinase |
| LMP | Last menstrual period |
| MAH | Marketing authorization holder |
| MCM | Major congenital malformation |
| NDC | National Drug Code |
| NLP | Natural language processing |
| ORD | Optum Research Database |
| PASS | Post-authorization safety study |
| PN | Prurigo nodularis |
| PPV | Positive predictive value |
| PSUR | Periodic Safety Update Report |
| QBA | Quantitative bias analysis |
| RR | Relative risk |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis System |
| SGA | Small for gestational age |
| SOP | Standard operating procedure |
| TORCH | Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19, HIV [human immunodeficiency virus]), rubella, cytomegalovirus, and herpes simplex |
| UB | Uniform billing |
| US | United States |

## 2. ABSTRACT

**Rationale and background:** Nemolizumab is a monoclonal antibody that targets the interleukin-31 receptor alpha. In February 2025, the European Medicines Agency (EMA) authorized the use of nemolizumab for the treatment of adults with moderate to severe prurigo nodularis (PN) and patients aged 12 years and older with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy. In August 2024, the US Food and Drug Administration (FDA) approved nemolizumab for the treatment of adults with PN, and in December 2024 FDA further approved nemolizumab for the treatment of adults and pediatric patients 12 years of age and older with moderate to severe AD in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies. Animal studies have not indicated direct or indirect harmful effects, but there are limited human data on the safety of nemolizumab during pregnancy. This noninterventional observational post-authorization safety study (PASS) will fulfill an EMA requirement to assess pregnancy and infant outcomes in pregnant women exposed to nemolizumab.

**Research question and objectives:**

The research questions are as follows:

- What is the frequency of key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe AD or PN who use commercially available nemolizumab during the 95 days (approximately 14 weeks) before their estimated conception date (ECD) or at any time during pregnancy and among a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?
- What is the effect of nemolizumab on key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe AD or PN who use commercially available nemolizumab during pregnancy compared to a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?

This study has the following objectives:

- To estimate the frequency of select adverse pregnancy and birth outcomes (i.e., ectopic pregnancy, elective termination, live birth, preterm birth, spontaneous abortion, and foetal death/stillbirth) among pregnant patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.
- To estimate the frequency of select adverse foetal, neonatal, and infant outcomes (i.e., major congenital malformations [MCMs] and small for gestational age [SGA] birth) among infants from pregnancies in patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.
- To estimate the adjusted relative risks (RRs) and hazard ratios (HRs) for the study outcomes in pregnant patients in the nemolizumab cohort versus the two comparator cohorts.

**Study design:** This will be a multi-database observational cohort study.

**Study population:** The source population for this study will include pregnancies that began (based on ECD) between 12 August 2024 and 31 March 2032 (or most recent data available at the time of the last data extract). Three study cohorts will be identified among individuals with moderate to severe AD or PN: (1) pregnancies exposed to nemolizumab; (2) pregnancies not exposed to nemolizumab but exposed to select other moderate to severe AD or PN treatments; and (3) pregnancies unexposed to nemolizumab and select other moderate to severe AD and PN treatments.

**Variables:**

*Exposures:*

Nemolizumab and exposure to other moderate to severe AD and PN treatments will be identified by drug codes on pharmacy claims and procedure codes for drug administrations.

*Outcomes:*

The pregnancy outcomes will include ectopic pregnancy, elective termination, live birth, preterm birth, spontaneous abortion, and foetal death/stillbirth, while infant outcomes will include MCM (primary outcome) and SGA birth. Outcomes will be identified using published, validated claims-based algorithms when available.

*Covariates:*

Baseline covariates will include patient demographics, healthcare utilization, comorbidities, pregnancy history and risk factors for the study outcomes, and AD and PN history and treatments.

**Data sources:** The patients included in this study will be drawn from the Optum Research Database [ORD], a proprietary research database containing eligibility and pharmacy and medical claims data from a large United States (US) health plan affiliated with Optum. Within the ORD, we will identify pregnancies and employ mother-child linkages using Optum's Dynamic Assessment of Pregnancies and Infants (DAPI), a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner, within the ORD. As additional data sources will be needed to achieve an adequate sample size for the study of rare pregnancy and infant outcomes, Optum's Market Clarity Data (linked claims-electronic health record [EHR] database) and a feasibility assessment of additional potential data sources will be included in the 2029 Periodic Safety Update Report (PSUR; see Section 4).

**Study size:** The target size is 352 nemolizumab-exposed pregnancies and 1,408 pregnancies in each comparator group, which will provide 80% power to detect a relative risk of 2.5 for MCMs, while 219 nemolizumab-exposed pregnancies and 876 pregnancies in each comparator group will provide 80% power to detect a relative risk of 3 for MCMs.

**Data analysis:** The accrual of nemolizumab-exposed pregnancies and live births in the data sources will be reported in the PSURs. For the final report, this study will be conducted using a

sequential cohort design that aligns cohort entry at gestational week of drug dispensing or administration. Exposed pregnancies will be matched in a 1:4 ratio to active comparator and unexposed pregnancies based on maternal age at cohort entry, gestational week of dispensing, indication, and calendar week. We will estimate RRs using robust Poisson regression models and HRs using Cox proportional hazards models.

## 3. AMENDMENTS AND UPDATES

Not applicable

## 4. MILESTONES

| Milestone | Planned Date |
|---|---|
| Protocol submission | 29 April 2025 |
| Registration in the HMA-EMA Catalogues of RWD studies | 31 October 2025 |
| Feasibility assessment | 01 June 2029 |
| Start of data collection[1] | 08 December 2032 |
| End of data collection[2] | 24 October 2033 |
| Final study report | 03 May 2034 |

Abbreviations: HMA-EMA, Heads of Medicines Agencies-European Medicines Agency; RWD, real world data
[1] The start of the data collection refers to the date from which data extraction for the final study report will begin.
[2] The end of data collection refers to the date from which the analytical dataset is completely available per the guideline on good pharmacovigilance practices (GVP, Module VIII). The analytic dataset is the minimum set of data required to perform the statistical analysis for the final report.

## 5. RATIONALE AND BACKGROUND

Atopic dermatitis (AD) is a common and chronic inflammatory skin condition characterized by pruritic patches and plaques (Alexander et al., 2017). The estimated overall prevalence of AD among adults in the United States (US) is 10%, of which approximately 20% (or 2% of the US adult population) can be classified as moderate to severe AD (DaVeiga, 2012). Treatments for moderate to severe AD in adults include corticosteroids, oral Janus kinase (JAK) inhibitors, biologics, and phototherapy.

Prurigo nodularis (PN) is a rare chronic inflammatory skin condition characterized by multiple pruritic nodules. The estimated prevalence is approximately 72 per 100,000 and is more common among older adults and African Americans (Huang et al., 2020a). Treatments for PN are similar to AD, and include topical therapies, systemic therapies, phototherapy, gabapentinoids, antidepressants, and immunosuppressants (e.g., methotrexate, cyclosporine).

Nemolizumab (NEMLUVIO®) is a monoclonal antibody that targets the interleukin-31 receptor alpha and reduces itch in AD and PN (Nemoto et al., 2016; Kwatra et al., 2023; Silverberg et al., 2024; Ständer et al., 2020). As of April 2025, nemolizumab has been approved for the treatment of moderate to severe AD and PN in Japan, the US, Europe, United Kingdom, Switzerland, Australia, and Singapore (Keam, 2022; Mitchga PI, 2024; Nemluvio SmPC, 2025). In Phase 3

trials, a greater percentage of patients receiving a subcutaneous injection of nemolizumab had a reduction in itch response compared to placebo (Kwatra et al., 2023; Silverberg et al., 2024).

There are limited non-animal data on the safety of nemolizumab during pregnancy. In cynomolgus monkeys, more offspring of pregnant mothers who received a nemolizumab injection experienced an early postnatal death compared to offspring of controls, but the dose administered was up to 36 times the maximum recommended human dose (Nemluvio PI, 2024). While pregnant women were excluded from enrollment in the nemolizumab clinical trials, women of childbearing age may take nemolizumab before they know they are pregnant. In addition, women of childbearing age are more frequently affected by AD than men, highlighting the importance of monitoring nemolizumab exposure in pregnancy (Valentini and Shahriari, 2024). To address this need, Galderma has made a commitment to the European Medicines Agency (EMA) to conduct an observational post-authorization safety study (PASS) of pregnancy and infant outcomes in patients exposed to nemolizumab in the 95 days (5 times the half-life of nemolizumab, approximately 14 weeks) before their estimated conception date (ECD) or at any time during pregnancy. This study will provide important information on the safety of nemolizumab during pregnancy.

## 6. RESEARCH QUESTION AND OBJECTIVES

The research questions are as follows:

- What is the frequency of key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe AD or PN who use commercially available nemolizumab during the 95 days (approximately 14 weeks) before their ECD or at any time during pregnancy and among a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?
- What is the effect of nemolizumab on key pregnancy, foetal, and infant outcomes among pregnant patients with moderate to severe AD or PN who use commercially available nemolizumab during pregnancy compared to a disease-matched cohort of pregnant patients who use another treatment for AD/PN and a disease-matched unexposed cohort?

This study has the following objectives:

- To estimate the frequency of select adverse pregnancy and birth outcomes (i.e., ectopic pregnancy, elective termination, live birth, preterm birth, spontaneous abortion, and foetal death/stillbirth) among pregnant patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.
- To estimate the frequency of select adverse foetal, neonatal, and infant outcomes (i.e., major congenital malformations [MCMs] and small for gestational age [SGA] birth) among infants from pregnancies in patients with moderate to severe AD or PN who are (1) exposed to nemolizumab, (2) exposed to other treatments for moderate to severe AD or PN, and (3) unexposed.
- To estimate the adjusted relative risks (RRs) and hazard ratios (HRs) for the study outcomes in pregnant patients in the nemolizumab cohort versus the 2 comparator cohorts.

There are no *a priori* hypotheses.

# 7. RESEARCH METHODS

## 7.1 Study Design

This will be an observational cohort study that will use multiple existing databases to assess pregnancy and infant outcomes among patients with moderate to severe AD or PN. Among patients with moderate to severe AD or PN, pregnancies that begin (based on the ECD) between 12 August 2024 and 31 March 2032 (or latest data available) will be identified. This study will assess pregnancy and infant outcomes among pregnancies from patients within 3 cohorts:

- Nemolizumab Cohort: pregnancies among patients with moderate to severe AD or PN exposed to nemolizumab during pregnancy;
- Other AD/PN Treatment Cohort: pregnancies among patients with moderate to severe AD or PN exposed to other AD or PN treatments, including monoclonal antibodies other than nemolizumab, during pregnancy; and
- Unexposed Cohort: pregnancies among patients with moderate to severe AD or PN who are not exposed to nemolizumab or any of the comparator AD or PN treatments during pregnancy.

The subset of women whose pregnancy outcomes are live births will be linked to their infants to extend infant follow-up for up to one year. Maternal exposure to nemolizumab, as well as diagnoses of moderate to severe AD and PN, will be identified. All qualifying pregnancies per woman will be included in the study. The cohorts of women will be followed through the end of pregnancy to assess pregnancy outcomes of ectopic pregnancy, elective terminations, live births, preterm birth, spontaneous abortion, and stillbirth, with infant follow-up for up to one year after birth to assess the occurrence of infant outcomes of MCMs (primary outcome) and SGA birth.

During the monitoring phase, the accrual of nemolizumab-exposed pregnancies and live births in the Optum Research Database (ORD) will be reported in the Periodic Safety Update Reports (PSURs). As additional data sources will be needed to achieve an adequate sample size for the study of rare pregnancy and infant outcomes, Optum's Market Clarity Data (linked claims-electronic health record [EHR] database) and a feasibility assessment of the potential data sources under consideration will be included in the 2029 PSUR. To allow time for uptake of nemolizumab, accrual of nemolizumab-exposed pregnancies and live births in all selected databases will be reported in the PSURs beginning at the midpoint of the study (2030).

For the final report, pregnancies exposed to nemolizumab and their matched comparators will be identified in the selected databases. The final report analyses will employ a target trial emulation approach using a sequential matched cohort design that aligns cohort entry by gestational week (Caniglia et al., 2023; Hernández-Diaz et al., 2023). Nemolizumab-exposed pregnancies will be 1:4 matched to comparator pregnancies based on maternal age at cohort entry, gestational week of dispensing, indication, and calendar week. The frequency of pregnancy and infant outcomes among nemolizumab-exposed pregnancies and comparator pregnancies will be calculated. In the comparative analysis, pregnancies among patients with moderate to severe AD or PN who were

exposed to nemolizumab will be contrasted with the comparator groups using stabilized inverse probability of treatment weighting (IPTW) to adjust for potential confounding. RRs will be estimated using robust Poisson regression models and HRs using Cox proportional hazards models.

## 7.2 Data Sources

### 7.2.1 Optum Research Database (ORD)

The patients included in this study will be drawn from a proprietary research database containing eligibility and pharmacy and medical claims data from a large US health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US. As early as 1993, medical and pharmacy claims data are available for 68 million individuals with both medical and pharmacy benefit coverage. For 2023, data is available for approximately 11 million individuals with medical and pharmacy coverage.

Optum research activities use de-identified data from the research database. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified. All data access conforms to applicable Health Insurance Portability and Accountability Act laws.

Accessible information from the ORD includes demographics, pharmacy use, and all medical and facility claims, which provide data on services, procedures, and their accompanying diagnoses. The coding of medical claims conforms to insurance industry standards including:

- Use of designated claims forms (e.g., physicians use the Health Care Financing Agency-1500 format and hospitals use the uniform billing [UB]-04 or UB-92 format)
- International Classification of Diseases, 10th Revision (ICD-10) codes
- Current Procedural Terminology (CPT®) codes[1]
- Healthcare Common Procedure Coding System (HCPCS) codes
- Cost information
- De-identified patient and provider codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. Pharmacy claims data allowing for longitudinal tracking of medication refill patterns and changes in medications include:

- National Drug Code (NDC)
- Drug name

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- Dosage form
- Drug strength
- Fill date
- Days of supply
- Cost information
- De-identified patient and prescriber codes

An important advantage of the ORD is the large number of patients who can be studied because the data are routinely collected and maintained in computerized data files. The completeness of the data allows investigators to link any number of patient, physician, and treatment attributes, while maintaining the de-identified nature of the data. The database also captures a longitudinal record of medical services, irrespective of treatment site. The validity of the ORD for epidemiologic research (as compared with data abstracted from medical records) has been established (Dore et al., 2011; Eng et al., 2012; Loughlin et al., 2010).

#### 7.2.1.1 Optum Dynamic Assessment of Pregnancies and Infants (DAPI)

For analyses of pregnancy and infant outcomes, the cohorts for this study will employ the mother-child linkages established using DAPI, a proprietary process that includes a set of capabilities and established algorithms applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner within the ORD (Bertoia et al., 2022). There were approximately 170,000 new pregnancies identified in 2022 within the database. Approximately 85% of pregnancies resulting in live births can be linked to an infant. These linkages enable proactive monitoring of pregnancy outcomes to ascertain a range of outcome-specific risks associated with drug exposure during pregnancy.

##### 7.2.1.1.1 Pregnancy Identification

To identify pregnancies, Optum searches the administrative claims for combinations of diagnostic and procedure codes indicating a pregnancy, delivery, or pregnancy endpoint, as well as prenatal care. This process has been described previously by Bertoia et al. (2022). Women are required to have at least one pregnancy-related health insurance claim to be considered as having a pregnancy. The first pregnancy-related claim is identified a median of 74 days (range 1, 294; mean 114.3 [standard deviation 80.1]) after last menstrual period (LMP). If a woman has more than one eligible pregnancy during the study period, each of the qualifying pregnancies may be included. Analyses will account for the correlations between multiple pregnancies for a given woman. It should be noted that the first observed pregnancy per woman in the claims database might not be that woman's first pregnancy.

##### 7.2.1.1.2 Estimation of LMP and Date of Conception

The International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) coding system includes several codes (Z3A**) that describe the estimated gestational age of the fetus. For example, the ICD-10-CM code Z3A.12 represents 12 weeks of gestation and Z3A.23 represents 23 weeks of gestation. The date of the LMP is estimated by subtracting the number of weeks of gestation associated with the Z3A code from the corresponding date of service of that

claim. Validation of LMP date estimated using Z3A codes has indicated good performance, with a median difference of 4.0 days (interquartile range: 2.0 – 10.0) between LMP date based on Z3A codes and adjudicated (via medical record review) LMP date (Chomistek et al., 2023b). The LMP date corresponds to a gestational age of 0 weeks. Operationally, the start of pregnancy (the date of conception) is defined as gestational age equal to 2 weeks, 0 days.

Most pregnancies in the ORD include Z3A codes that permit LMP estimation for a pregnancy even before the pregnancy outcome is observed. However, there is a small fraction of pregnancies that do not include these Z3A codes; in these cases, Optum employs outcomes-based algorithms that estimate the LMP by counting back the number of weeks from the occurrence of the outcome, with different outcomes assigned different weeks of gestation (Hornbrook et al., 2007).

#### 7.2.1.1.3 Infant Linkage

The identification of infant outcomes, such as MCMs or SGA birth, relies on data from the infant's claims record rather than the mother's claims record. Mother and infant records will be linked through the presence of a common unique family insurance identifier. This number is used by health plans to identify all members of a family who are covered by the same insurance plan for the purposes of defining coverage, payment, and reimbursement, providing assurance that mother-infant pairs identified in this manner are accurate. In addition, claim(s) relating to the delivery must be within 7 days of the infant's birth date (or 32 days for multiples). This linkage has been used to address regulatory questions by pharmaceutical companies about the effects of drugs on pregnancy (Carman et al., 2007; Wyszynski et al., 2016).

The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being covered under a different health insurance from the mother. This may occur if the newborn were to be added to the other parent's plan (rather than the mother's), if the parents were to switch from individual plans to family health plans, or if the mother were covered under her parents' policy (in which case a separate plan would need to be purchased for the infant).

### 7.2.2 Optum's Market Clarity Data

Beginning with the 2029 PSUR, patients will also be identified within Optum's Market Clarity Data. This database integrates medical and pharmacy claims data with clinical data for approximately 80-85% of patients in Optum's EHR Research Database from January 2007 through the present. Market Clarity includes data on over 82 million patients as of March 2024, with over 68 million of those having eligibility information available.

Optum's EHR Research Database is a patient-level database that integrates multiple electronic medical record data systems with medical billing, prescription, and practice management data. The database incorporates relevant clinical data, as recorded during routine clinical practice, for patients in both ambulatory and inpatient settings. Data include medical records, laboratory results, and drug prescription (including number of refills) and administration data.

The database also includes data derived from free-text clinical notes relating to the medical encounters. Optum uses a generalized natural language processing (NLP) system developed to extract and organize concepts from free text into semi-structured fields. The database contains pertinent attributes, sentiments, and modifiers to the concepts. Re-examination of the source text

corresponding to the NLP-extracted observations is possible with appropriate permissions.

In Market Clarity, Optum's EHR data are supplemented with medical and pharmacy claims from the ORD and from third-party data sources. The availability of linked pharmacy claims data in Market Clarity provides the opportunity to augment the data on drug prescriptions available in the EHR, which enables more comprehensive identification of all drugs received by patients through pharmacy drug dispensings. This linkage will accordingly improve the ability to capture nemolizumab initiation and subsequent drug dispensings within the database.

## 7.3 Setting

### 7.3.1 Source Population

The source population for this study will include pregnancies that begin (based on ECD) between 12 August 2024 and 31 March 2032 (or most recent data available at the time of the last data extract).

### 7.3.2 Inclusion Criteria

Pregnancies among women who meet the following criteria will be eligible for inclusion in the study:

- An ECD between 12 August 2024 and 31 March 2032
- For claims data sources, continuous health plan enrollment with complete medical and pharmacy benefit coverage from 6 months before and including cohort entry (only applicable to the pregnant woman)
- For linked claims-EHR data sources:
    - Pharmacy (but not medical) coverage during the full pregnancy period (as described in Table 1) will be required to ensure dispensings of cohort defining drugs are captured. (A shorter period of continuous enrollment will be required for linked claims-EHR data sources compared with the claims databases because pharmacy claims will be used primarily for exposure assessment, while covariates will be assessed from the EHR data).
    - Presence of at least one outpatient clinical visit at least 6 months prior cohort entry (to establish a 6-month baseline period for assessment of AD and PN as well as clinical covariates).
- Evidence of moderate to severe AD or PN ascertained using appropriate algorithms

### 7.3.3 Exclusion Criteria

#### 7.3.3.1 JAK Inhibitors

Pregnancies among women exposed to oral JAK inhibitors indicated for moderate to severe AD or PN (i.e., abrocitinib, upadacitinib, baracitinib) from 5 half-lives (specific for each medication) prior to ECD through the end of pregnancy will be excluded because they are contraindicated

during pregnancy. This list may be updated if other JAK inhibitors are approved for moderate to severe AD or PN during the study period.

#### 7.3.3.2 Concurrent Exposure to Nemolizumab and Other AD/PN Treatments

Pregnancies among women with claims for both nemolizumab and another AD/PN Treatment during the relevant exposure window will be excluded.

#### 7.3.3.3 Exclusions for Analyses of MCMs

In the final report, analyses of MCMs will exclude the following:

- Pregnancies among women exposed to known teratogens from 5 half-lives (specific for each teratogen) prior to ECD through the end of pregnancy (Winterstein et al., 2024). A list of teratogens can be found in Appendix B.
- Pregnancies among women who are diagnosed with a TORCH infection (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19, human immunodeficiency virus {HIV}], rubella, cytomegalovirus, and herpes simplex) during pregnancy because they are known to cause congenital anomalies (Neu et al., 2015).
- Infants with syndromic or chromosomal anomalies identified during pregnancy or at birth (i.e., Down syndrome, trisomies 18 and 13, and other trisomies; monosomies and deletions from the autosomes; balanced re-arrangements and structural markers; and Turner's syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities).

Code lists for these exclusions will be provided in the statistical analysis plan (SAP).

### 7.3.4 Identification of Moderate to Severe AD

Women will be considered to have moderate to severe AD if they meet one of the following criteria between 12 months prior to ECD and the end of pregnancy:

1. ≥ 2 claims with an AD diagnosis code (ICD-10-CM: L20*), at least 30 days apart, from any physician and ≥ 1 dispensing of nemolizumab, dupilumab, abrocitinib, upadacitinib, baricitinib, tralokinumab, or lebrikizumab; OR
2. ≥ 2 claims with an AD diagnosis code, at least 30 days apart, from any physician and ≥ 2 dispensings on different days of high potency topical corticosteroids or systemic immunosuppressants; OR
3. ≥ 2 claims with an AD diagnosis code, at least 30 days apart, from a dermatologist or allergist and ≥ 3 dispensings on different days of medium potency topical corticosteroids, topical tacrolimus, phototherapy, or oral/parenteral corticosteroids.

In a validation study, a similar algorithm had a positive predictive value (PPV) of 76% (95% confidence interval [CI] 53%, 90%; Chomistek et al., 2023a). Nemolizumab, abrocitinib, upadacitinib, baricitinib, tralokinumab, and lebrikizumab were not included in the validation study because they were not approved for moderate to severe AD at the time of algorithm development. A full list of diagnosis codes and drugs included in this algorithm can be found in Appendix C.

### 7.3.5 Identification of PN

Pregnant women will be considered to have PN if they have at least two ICD-10-CM diagnosis codes for PN (L28.1), at least 30 days apart, between 12 months prior to pregnancy and the end of pregnancy. In a validation study, this algorithm had a PPV of 87.9% (95% CI 81.5%, 94.3%; Roh et al., 2022).

Although nemolizumab is approved for the treatment of overall PN in the US, it is authorized for the treatment of moderate to severe PN in Europe. Currently, there is not a published, validated algorithm for moderate to severe PN. Optum will continue to search the published literature over the course of the study to see if a validated claims-based algorithm for moderate to severe PN is published. If a validated algorithm is found that has suitable performance characteristics, the methods for identifying PN may be modified.

### 7.3.6 Study Population

#### 7.3.6.1 Exposure Cohorts and Cohort Entry

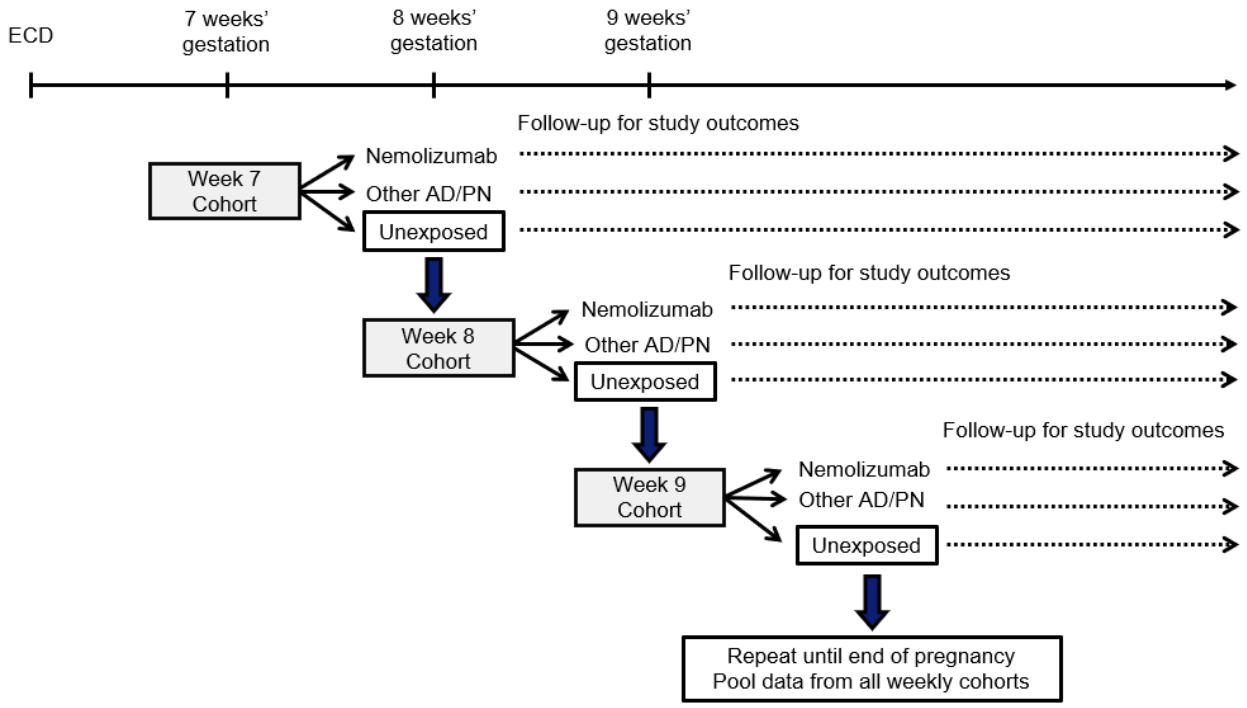
Based on the sequential cohort design, a series of study cohorts will be established for each gestational week of pregnancy (Caniglia et al., 2023; Hernández-Diaz S et al., 2023). To ensure capture of exposure to AD/PN treatments prior to the ECD but which remain in the body at ECD, the first gestational week of pregnancy will be extended (prior to ECD) by 5 times the half-life for each AD/PN treatment. For example, since nemolizumab has a half-life of 18.9 days (Nemluvio PI, 2025), the first gestational week for nemolizumab will begin 95 days (approximately 14 weeks) prior to ECD. The half-life for each AD/PN treatment is provided in Appendix D.

As nemolizumab and the comparator AD/PN treatments are injection drugs that are dispensed at a pharmacy for self-injection, treatment duration will be defined as date of dispensing plus 5 times the half-life of the therapy when a single pre-filled syringe, pen, or autoinjector is dispensed. When multiple units are dispensed, the days' supply will be calculated based on the quantity dispensed and recommended administration schedule; treatment duration will be calculated as the date of dispensing plus the days' supply plus 5 times the half-life of the therapy. A treatment will be considered to be overlapping with the first gestational week of pregnancy if there is at least one dispensing or dose received during the period 5 times the half-life prior to ECD through the end of the first gestational week. At each gestational week, we will first restrict to eligible pregnancies with no administrations or dispensings of nemolizumab or the other AD/PN treatments from 5 times the half-life of the corresponding treatment (e.g., 95 days, or approximately 14 weeks, for nemolizumab) before ECD through the end of the prior gestational week. We will then classify exposure status as exposed to nemolizumab, exposed to other AD/PN treatments, or unexposed based on the pregnancy's receipt of nemolizumab or other AD/PN treatments during that gestational week. Pregnancies among women with claims for both nemolizumab and another AD/PN treatment during the relevant exposure window will be excluded. For exposed pregnancies with more than one dose of the index treatment (e.g., two doses of nemolizumab) during pregnancy, cohort entry will align with the first dose.

Cohort entry will be set at the date of dispensing in the Nemolizumab Cohort (i.e., the earliest nemolizumab administration date during a pregnancy) and the Other AD/PN Treatment Cohort,

and the corresponding day of gestation among unexposed pregnancies, rounded down to the nearest week. For example, for pregnancies entering the Week 8 Cohort, we will first select all pregnancies with no nemolizumab or other AD/PN treatment from 5 times the half-life before ECD through 7 weeks' + 6 days' gestation. Then, we will assign the pregnancies that receive nemolizumab during Week 8 (8 weeks + 0 days through 8 weeks + 6 days) to the nemolizumab-exposed group, those that received another AD/PN treatment to the other treatment-exposed group, and those that did not receive nemolizumab or another AD/PN treatment during Week 8 to the unexposed group. Cohort entry among the Week 8 nemolizumab and comparator cohorts will be set to 8 weeks' + 0 days. The pregnancies in the Week 8 exposed cohort will no longer be eligible for inclusion in subsequent weekly cohorts. However, the pregnancies in the Week 8 unexposed group will go on to be eligible for inclusion in the Week 9 Cohort, at which point their exposure status would be reassessed during Week 9 (9 weeks + 0 days through 9 weeks + 6 days). A pictorial depiction of this process can be found in Figure 1 and key pregnancy dates can be found in Table 1. If the study size does not permit weekly sequential cohorts, the cohorts may be collapsed into longer (e.g., 2-week, 4-week) intervals as needed.

**Figure 1 Sequential cohort design, depicting an example of cohort entry for the Week 7 and Week 8 cohorts**




Abbreviations: AD, atopic dermatitis; ECD, estimated conception date; PN, prurigo nodularis

**Table 1 Pregnancy dates**

| Date | Definition |
|---|---|
| LMP | First day of last menstrual period<br>0 gestational weeks$^{0/7 \text{ days}}$ |
| Gestational age | Weeks of gestation<br>Anchored by LMP<br>Number of completed weeks elapsed after LMP |

| Date | Definition |
|---|---|
| ECD | Estimated as LMP + 14 days<br>2 gestational weeks$^{0/7 \text{ days}}$ |
| First trimester | Begins at ECD minus 5 times the half-life of the treatment<br>Ends at LMP + 97 days |
| Second trimester | Begins at LMP + 98 days<br>Ends at LMP + 195 days |
| Third trimester | Begins at LMP + 196 days<br>Ends at pregnancy outcome |
| Pregnancy period | Begins at ECD minus 5 times the half-life of the treatment<br>Ends at pregnancy outcome |

Abbreviations: ECD, estimated conception date; LMP, first day of last menstrual period

#### 7.3.6.2 Etiologically Relevant Windows for Exposure Assessment

For most study outcomes, the analysis will include weekly exposure cohorts that are formed throughout pregnancy (i.e., approximately 40 potential weekly cohorts beginning at Week 2 through Week 40 or the latest observed week of gestation). However, analyses of spontaneous abortion and elective termination will be restricted to the Week 2-19 Cohorts, because spontaneous abortion is defined as a pregnancy loss occurring before 20 weeks' gestation, and all pregnancies that are ongoing at Week 20 will be censored in these analyses. Analyses of preterm birth will be restricted to Weeks 2-36 Cohorts, because preterm birth is defined as a livebirth occurring before 37 weeks' gestation, and analyses of ectopic pregnancy and MCMs will be restricted to Weeks 2-13 Cohorts.

Table 2 depicts the potential gestational weeks of cohort entry for each study outcome relative to the timing of outcome assessment.

**Table 2 Etiologically relevant exposure windows for study outcomes**

| Study Outcome | Etiologically Relevant Exposure Window | Potential Cohort Entry of Pregnancy | Start of Follow-up[1] | Censoring Events[2] |
|---|---|---|---|---|
| Ectopic pregnancy | First trimester | Week 2 – Week 13 | Cohort entry | End of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| Elective termination | ECD through 19 weeks' gestation (19 weeks + 6 days) | Week 2 – Week 19 | Cohort entry | 20 weeks + 0 days, end of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| Live births | Entire pregnancy | Week 2 – Week 40 | Later of cohort entry or 20 weeks + 0 days | End of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| Preterm birth | ECD through 36 weeks' gestation (36 weeks + 6 days) | Week 2 – Week 36 | Later of cohort entry or 20 weeks + 0 days | 37 weeks + 0 days, end of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |

| Study Outcome | Etiologically Relevant Exposure Window | Potential Cohort Entry of Pregnancy | Start of Follow-up[1] | Censoring Events[2] |
|---|---|---|---|---|
| Spontaneous abortion | ECD through 19 weeks' gestation (19 weeks + 6 days) | Week 2 – Week 19 | Cohort entry | 20 weeks + 0 days, end of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| Stillbirth | Entire pregnancy | Week 2 – Week 40 | Later of cohort entry or 20 weeks + 0 days | End of pregnancy, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| MCM | First trimester | Week 2 – Week 13 | Delivery | First year of life, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |
| SGA birth | Entire pregnancy | Week 2 – Week 40 | Delivery | First year of life, disenrollment from the health plan/8 weeks of no clinical activity, or the end of the study period |

Abbreviations: ECD, estimated conception date; EHR, electronic health record; MCM, major congenital malformation; SGA, small for gestational age

[1] For individuals with a cohort entry date after the pre-specified start of follow-up, follow-up begins at cohort entry. For example, for cohorts beginning at 24 gestational weeks, follow-up for stillbirth will begin at 24 gestational weeks.

[2] For EHR and linked claims-EHR data sources, pregnancies will be censored at the end of 8 weeks of no clinical activity. Since pregnant women should regularly interact with the healthcare system, this censoring criterion will indicate loss to follow-up in the database.

#### 7.3.6.3 Nemolizumab Cohort

The Nemolizumab Cohort will include all pregnancies among women with moderate to severe AD or PN and at least one dispensing or dose of nemolizumab from 95 days (approximately 14 weeks) prior to ECD through the end of pregnancy. Cohort entry will be set at the date of the first nemolizumab dispensing, rounded down to the nearest week of gestation.

#### 7.3.6.4 Other AD/PN Treatment Cohort

The Other AD/PN Treatment Cohort will include all pregnancies among women with moderate to severe AD or PN and at least one dispensing/administration or dose of selected other AD or PN treatments from 5 times the half-life of the medication prior to ECD through the end of pregnancy. The cohort entry date will be set at the date of the first comparator treatment dispensing/administration, rounded down to the nearest week of gestation.

The following comparator treatments will define this cohort:

- Dupilumab (indicated for both moderate to severe AD and PN)
- Lebrikizumab (indicated for moderate to severe AD only)
- Tralokinumab (indicated for moderate to severe AD only)

These therapies are proposed because they are typically used in patients with moderate to severe AD or PN, similar to the expected population of patients using nemolizumab.

#### 7.3.6.5 Unexposed Cohort

The Unexposed Cohort will include all pregnancies among women with moderate to severe AD or PN who have no dispensings or administrations of nemolizumab or the other monoclonal antibody treatments used to defined the Other AD/PN Treatment Cohort (i.e., dupilumab, lebrikizumab, tralokinumab) from 5 times the half-life of each medication prior to ECD through the end of pregnancy. The cohort entry date will be matched to the date of nemolizumab dispensing, rounded down to the nearest week of gestation.

This cohort may include pregnancies among women who have dispensings or administrations of other treatments indicated for moderate to severe AD or PN (e.g., immunosuppressants, corticosteroids). Exposure to other treatments for moderate to severe AD or PN will be measured and adjustment for or stratification by use of these treatments may be considered during the analysis.

#### 7.3.6.6 Baseline Period

The 6 months (183 days; defined as an inclusion criteria) prior to and including the cohort entry date will be set as the baseline period. Recognizing that a narrower (for time-varying covariates, etc.) or a broader (for chronic conditions) window of assessment may better capture patient characteristics of interest, specific covariates may be assessed using alternative time period(s). For example, while patients are required to have 6 months of continuous medical and pharmacy coverage prior to cohort entry to be eligible for inclusion in the study, presence of AD and PN will be assessed up to 12 months prior to pregnancy, as data allow.

#### 7.3.6.7 Follow-up

For each weekly cohort, pregnancies will be followed from the date after cohort entry until the earliest of the end of pregnancy, disenrollment from the health plan (for claims databases), 8 weeks with no clinical activity recorded (for the linked claims-EHR database or EHR-only databases) or the end of the study period (31 March 2032 or latest data available). Each linked infant will be followed from delivery until the earliest of end of first year of life, disenrollment from the health plan (for claims databases), 8 weeks with no clinical activity recorded (for the linked claims-EHR database or EHR-only databases) or the end of the study period. Follow-up for spontaneous abortion and elective termination will be censored at 20 weeks' gestation, and follow-up for preterm birth will be censored at 37 weeks' gestation. The censoring events for each outcome are summarized in Table 2.

### 7.4 Variables

Variables will be assessed using a combination of CPT® codes, Hierarchical Ingredient Code List (HICL) codes, NDCs, ICD-10-CM codes, and HCPCS codes. HICL is a proprietary hierarchical coding system that groups therapies based on generic name. A combination of HCPCS, HICL, and NDCs will be used to identify medications assessed in this study.

### 7.4.1 Exposures

#### 7.4.1.1 Nemolizumab

Use of nemolizumab will be identified by the presence of the following NDC on the pharmacy claims:

- NDC 0299622015 Nemluvio 30 mg pen injector

This list will be updated annually, and additional NDCs will be included as they become available.

#### 7.4.1.2 Comparator AD and PN Treatments

Use of other AD and PN treatments will be identified using NDCs on pharmacy claims and drug administration codes on medical claims.

- Dupilumab
  - NDC 00024591100 Dupixent syringe 100mg/0.67 syringe
  - NDC 00024591102 Dupixent syringe 100mg/0.67 syringe
  - NDC 00024591400 Dupixent syringe 300 mg/2ml syringe
  - NDC 00024591401 Dupixent 300 mg/2ml syringe
  - NDC 00024591500 Dupixent pen 300 mg/2ml pen injector
  - NDC 00024591501 Dupixent pen 300 mg/2ml pen injector
  - NDC 00024591502 Dupixent pen 300 mg/2ml pen injector
  - NDC 00024591520 Dupixent pen 300 mg/2ml pen injector
  - NDC 00024591800 Dupixent syringe 200mg/1.14 syringe
  - NDC 00024591801 Dupixent 200mg/1.14 syringe
  - NDC 00024591802 Dupixent 200mg/1.14 syringe
  - NDC 00024591900 Dupixent pen 200mg /1.14 pen injector
  - NDC 00024591901 Dupixent pen 200mg /1.14 pen injector
  - NDC 00024591902 Dupixent pen 200mg /1.14 pen injector
  - NDC 00024591920 Dupixent pen 200mg /1.14 pen injector
- Lebrikizumab
  - NDC 00002777201 Ebglyss pen 250 mg /2ml pen injector
  - NDC 00002777211 Ebglyss pen 250 mg /2ml pen injector
  - NDC 00002779701 Ebglyss syringe 250 mg /2ml syringe
  - NDC 00002779711 Ebglyss syringe 250 mg /2ml syringe
- Tralokinumab

- NDC 50222034602 Adbry 150 mg /ml syringe
- NDC 50222034604 Adbry 150 mg /ml syringe
- NDC 50222034622 Adbry 150 mg /ml syringe
- NDC 50222034692 Adbry 150 mg /ml syringe
- NDC 50222035000 Adbry autoinjector 300 mg /2ml auto injector
- NDC 50222035001 Adbry autoinjector 300 mg /2ml auto injector
- NDC 50222035002 Adbry autoinjector 300 mg /2ml auto injector

The list of comparator treatments will be reviewed and updated prior to the final report.

### 7.4.2 Outcomes

During eligible follow-up, occurrence of pregnancy and infant outcomes will be identified through the presence of corresponding codes in the database. Published, validated algorithms will be used when available. The pregnancy outcomes will include ectopic pregnancy, elective termination, live birth, preterm birth, spontaneous abortion, and stillbirth, while infant outcomes are MCMs (primary outcome) and SGA birth. Code lists for all outcomes can be found in Appendix E.

#### 7.4.2.1 Pregnancy Outcomes

##### 7.4.2.1.1 Ectopic Pregnancy

Ectopic pregnancy is defined as the implantation of a fertilized egg in an anatomic location other than the uterus. It will be identified on the maternal record based on ICD-10-CM diagnosis and procedure codes found in Appendix E.

##### 7.4.2.1.2 Elective Termination

Elective termination is defined as an intervention to end a pregnancy prior to delivery. It will be identified on the maternal record based on diagnosis and procedure codes found in Appendix E.

##### 7.4.2.1.3 Live Birth

Live birth is defined as a delivered fetus with any sign of life (e.g., voluntary movement, heartbeat) regardless of gestational weeks. Live births will be identified on maternal records using ICD-10-CM diagnosis and procedure codes found in Appendix E.

##### 7.4.2.1.4 Preterm Birth

Preterm birth is defined as a live birth occurring before the 37$^{th}$ week of pregnancy based on LMP. It will be identified on maternal records based on ICD-10-CM O60.1* diagnosis codes and on infant records based on ICD-10-CM P07.2* and P07.3* codes, as described in Appendix E. Based on a validation study, a similar algorithm had a PPV of 92.3% (95% CI 82.1, 100.0; Chomistek et al., 2023b).

#### 7.4.2.1.5 Spontaneous Abortion

Spontaneous abortion or miscarriage is defined as pregnancy loss prior to 20 weeks of gestation. Ectopic and molar pregnancies will not be considered spontaneous abortions. Spontaneous abortion will be defined on maternal records as at least 1 ICD-10-CM diagnosis and/or procedure code found in Appendix E. In a validation study, this algorithm had a PPV of 84.7% (95% CI 78.3, 91.2; Chomistek et al., 2023b)

#### 7.4.2.1.6 Stillbirth

Stillbirth will be defined as foetal loss at or after 20 weeks of pregnancy. It will be identified on the maternal record using the following algorithm:

- Presence of an ICD-10-CM code for stillbirth or intrauterine foetal death and an ICD-10-CM code indicating a gestational age greater than or equal to 20 weeks recorded within the period 28 days before (and including) the date of the stillbirth or intrauterine foetal death

  PLUS

- At least two ICD-10-CM codes for stillbirth, intrauterine foetal death, or continuing pregnancy after intrauterine foetal death (unspecified trimester, second trimester, or third trimester) identified on or within 7 days

  OR

- No other pregnancy outcome ICD-10-CM code (e.g., for live births, spontaneous abortions, elective terminations) identified on the date of the stillbirth or intrauterine foetal death.

The list of ICD-10-CM diagnosis codes can be found in Appendix E. In a validation study, this algorithm had a PPV of 82.5% (95% CI 70.9, 91.0; Andrade et al., 2021).

### 7.4.2.2 Infant Outcomes

#### 7.4.2.2.1 MCM

MCMs will be defined based on guidelines from the New York State Department of Health Congenital Malformations Registry, National Birth Defects Prevention Network, and/or the European Surveillance of Congenital Malformations. Live births will be followed for up to one year to identify MCMs that may not be detected until after birth. All identified MCMs will be counted, overall, and classified by body system. Operational definitions may be modified to add or remove MCM-specific ICD-10-CM codes based on clinician input or newly identified algorithms in the literature. Minor congenital malformations will not be included in this definition. A list of ICD-10-CM diagnosis codes for MCMs can be found in Appendix E.

#### 7.4.2.2.2 SGA Birth

An SGA birth is defined as an infant with birthweight below the 10$^{th}$ percentile for their gestational age at birth. It will be identified on infant records based on the ICD-10-CM diagnosis codes found in Appendix E.

### 7.4.3 Covariates

Members of the study cohorts will be described according to baseline covariates, including demographics, healthcare utilization, comorbidities, pregnancy history and risk factors for the study outcomes, and AD and PN history and treatments. In the claims databases, characteristics will be assessed in the pharmacy and medical claims, while in Optum's Market Clarity Data patient characteristics will be assessed using the patient, procedure, and diagnosis tables from the EHR as well as the pharmacy and/or medical claims. Unless otherwise specified, diagnoses will be identified through the presence of ICD-10-CM codes, while prescription medications will be identified by NDCs through pharmacy dispensings. No over-the-counter medications will be assessed. Drug use and disease status will be categorized as yes (code present) or no (no code present). In addition to the covariates listed below, the 50 most common diagnoses, procedures, and medications will be described during the baseline period. Code lists for the covariates will be provided in the SAP.

#### 7.4.3.1 Demographics

The following demographic covariates will be assessed in the mother's record on cohort entry date (or for Optum's Market Clarity Data, the nearest visit to the cohort entry date):

- Age
- Calendar year
- Geographic region (Northeast, West, Midwest, South, unknown)

#### 7.4.3.2 Healthcare Utilization

Healthcare utilization will be assessed using data available up to 1 year prior to cohort entry unless otherwise noted.

- Duration of continuous health plan enrollment before cohort entry (assessed in claims databases only using all available data prior to cohort entry, up to 5 years)
- Number of outpatient visits
- Number of emergency department visits
- Number of hospitalizations

#### 7.4.3.3 Comorbidities

All comorbidities will be assessed using diagnosis and procedure codes using all available data prior to cohort entry (up to 5 years).

- Allergic conjunctivitis (Thyssen et al., 2023)
- Allergic contact dermatitis (Thyssen et al., 2023)
- Allergic rhinitis (Thyssen et al., 2023)
- Alopecia areata (Thyssen et al., 2023)

- Anxiety (Huang et al., 2020b; Thyssen et al., 2023)
- Asthma (Thyssen et al., 2023)
- Attention-deficit/hyperactivity disorder (Thyssen et al., 2023)
- Depression (Huang et al., 2020b; Thyssen et al., 2023)
- Diabetes (Huang et al., 2020b)
- Eosinophilic esophagitis (Thyssen et al., 2023)
- Food allergies (Thyssen et al., 2023)
- HIV (Huang et al., 2020b)
- Hyperlipidemia (Huang et al., 2020b)
- Hypertension (Huang et al., 2020b; Thyssen et al., 2023)
- Inflammatory bowel disease (Thyssen et al., 2023)
- Obesity (Thyssen et al., 2023)
- Psoriasis (Huang et al., 2020b)
- Rheumatoid arthritis (Thyssen et al., 2023)
- Vitiligo (Thyssen et al., 2023)

#### 7.4.3.4 Pregnancy History and Risk Factors

Pregnancy history and risk factors will be assessed using diagnosis and procedure codes using all available data prior to cohort entry (up to 5 years).

- Gravidity, the number of pregnancies before the current pregnancy
- Parity, the number of vaginal deliveries or C-sections before the current pregnancy
- History of pregnancy complications
    - Spontaneous abortions
    - Elective terminations
    - Ectopic pregnancies
    - Preterm births
    - Stillbirths
    - Gestational hypertension
    - Gestational diabetes
    - Pre-eclampsia
    - Eclampsia
- Chronic kidney disease
- Other cardiovascular disease

- History of infertility
- Tobacco use
- Alcohol and drug-related diagnoses
- Maternal Comorbidity Score (Bateman et al., 2013)

#### 7.4.3.5 AD and PN History and Treatment

Covariates related to AD and PN history and treatment will be using all available data prior to the cohort entry (up to 5 years). The AD therapies include treatments that are for mild AD and are not included in the moderate to severe AD algorithm.

- AD
  - Number of AD diagnoses on unique days
- PN
  - Number of PN diagnoses on unique days
- Treatments for AD and/or PN
  - Abrocitinib
  - Dupilumab
  - Lebrikizumab
  - Tralokinumab
  - Upadacitinib
  - Baricitinib
  - Topical Tacrolimus
  - Crisaborole
  - Oral and parental corticosteroids
  - Phototherapy
  - Systemic immunosuppressants
    - Cyclosporine
    - Azathioprine
    - Methotrexate
    - Mycophenolate
    - Belimumab
    - Leflunomide
    - Interferon gamma
    - Rituximab

- Topical corticosteroids
  - High potency
  - Medium potency
  - Low potency
- Topical calcineurin inhibitors
- Topical tacrolimus, pimecrolimus
- Gabapentinoids (gabapentin, pregabalin)
- Cannabinoids
- Antidepressants (serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclic antidepressants)
- Topical ketamine/amitriptyline/lidocaine
- Topical calcipotriol

#### 7.4.3.6 Characteristics of Current Pregnancy

The following covariates will be assessed during the current pregnancy (ECD through end of pregnancy) and included in descriptive analyses only (not in propensity score models):

- Number and frequency of prenatal care visits
- Prenatal and delivery care markers (e.g., amniocentesis, ultrasound, antenatal screening)
- Receipt of Tdap vaccine
- Tobacco use
- Alcohol use
- Multiple pregnancy vs. singleton pregnancy
- Exposure to teratogens
- TORCH infections during pregnancy
- SARS-CoV-2 infection during pregnancy

#### 7.4.3.7 Infant Covariates

Infant covariates will be assessed during the first year of life and included in descriptive analyses only (not in propensity score models):

- Sex
- Multiple birth vs singleton birth
- Duration of continuous medical and pharmacy coverage (in claims databases only)

## 7.5 Study Size

Table 3 presents the minimum number of nemolizumab exposed pregnancies required to detect relative risks equal to or greater than 2.0, 2.5, or 3.0 for a comparative analysis of each of the study outcomes, assuming a ratio of 1:4 exposed to unexposed, 80% power, a 2-sided alpha of 0.05, and the referenced outcome prevalences. For infant outcomes, the minimum number of nemolizumab-exposed livebirths was calculated, and the number of nemolizumab-exposed pregnancies was derived from these counts based on the prevalence of live birth. For the primary outcome MCM, a study size of 214 live births with linked infants exposed to nemolizumab in the first trimester exposure window would provide an 80% power to detect a RR of 2.5, and 133 live births with linked infants exposed to nemolizumab in the first trimester exposure window would provide 80% power to detect a RR of 3. Assuming 80% of pregnancies have an observed outcome and 76% of observed outcomes are live births, an estimated 352 pregnancies exposed to nemolizumab during the first trimester would need to be accrued to detect a RR of 2.5 and 219 exposed pregnancies to detect a RR of 3. With a 1:4 ratio of exposed to unexposed, this corresponds to 1,408 pregnancies (for 2.5) or 876 (for 3) in each comparator group.

**Table 3 Sample size required for 80% power to detect effect estimates for pregnancy and infant outcomes, with 1:4 matching[1]**

| Outcome | Prevalence of Outcome | Relative Risk | Nemolizumab Exposed Pregnancies Needed | Nemolizumab Exposed Live Births Needed |
|---|---|---|---|---|
| MCM | 3%[2] | 2<br>2.5<br>3 | 709<br>352<br>219 | 431<br>214<br>133 |
| Ectopic pregnancy | 1-2% | 2<br>2.5<br>3 | 877<br>438<br>275 | N/A |
| Elective termination | 21% | 2<br>2.5<br>3 | 45<br>21<br>12 | N/A |
| Preterm birth, SGA birth | 10%[3,4] | 2<br>2.5<br>3 | 190<br>94<br>56 | 115<br>57<br>34 |
| Spontaneous abortion | 14%[5] | 2<br>2.5<br>3 | 77<br>37<br>22 | N/A |
| Stillbirth | 1%[6] | 2<br>2.5<br>3 | 1,324<br>662<br>415 | N/A |

Abbreviations: N/A, not applicable; SGA, small for gestational age

[1] Calculations were performed via www.OpenEpi.com using the Fleiss method, as described in Fleiss JL. Statistical Methods for Rates and Proportions. John Wiley & Sons, 1981.

[2] March of Dimes. Perinatal Data Snapshot: United States Birth Defects. 2015; http://www.marchofdimes.org/peristats/pdflib/999/pds_99_4.pdf.

[3] Centers for Disease Control and Prevention. Quick Stats: Percentage of Small for gestational-Age Births, by Race and Hispanic Ethnicity—United States, 2005. MMWR. 2008;57(50):1359. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5750a5.htm.

[4] National Vital Statistics Reports. Birth: Final Data for 2021. Volume 72, Number 1 (January 31, 2023). https://www.cdc.gov/nchs/data/nvsr/nvsr72/nvsr72-01.pdf.

[5] Yadava B. Jeve and William Davies. Evidence-based management of recurrent miscarriages. J Hum Reprod Sci. 2014 Jul-Sep; 7(3): 159–169.

[6] Food and Drug Administration. Guidance for Industry: Establishing Pregnancy Exposure Registries. United States Department of Health and Human Services, ed. Rockville, MD 2002.

Table 4 shows counts of pregnancies with at least 1 diagnosis code for AD or PN by year in the ORD. These counts are for informational purposes only. The sample size for the final study could increase or decrease depending on actual uptake and criteria applied during the conduct of the protocol.

**Table 4 Counts of pregnancies in the Optum Research Database with an AD or PN diagnosis code and a dispensing of dupilumab, 2020-2024**

| | 2020 | 2021 | 2022 | 2023 | 2024* | Total |
|---|---|---|---|---|---|---|
| Pregnancies with an AD code | 1,474 | 1,608 | 1,731 | 1,716 | 735 | 7,264 |
| Dupilumab dispensing | 38 | 44 | 48 | 55 | 24 | 209 |
| Pregnancies with a PN code | 26 | 59 | 52 | 58 | 12 | 207 |
| Dupilumab dispensing | 0 | 0 | 0 | 2 | 0 | 2 |

Abbreviations: AD, atopic dermatitis; PN, prurigo nodularis
* This indicates an incomplete year.

The PSURs will describe accrual of nemolizumab-exposed pregnancies and the feasibility of meeting the target study size. Additional data sources will be added after the feasibility report is conducted as part of 2029 PSUR.

### 7.6 Data Management

All reports and deliverables will contain aggregated results only and will not identify individual patients, physicians, or facilities. Optum Epidemiology and other potential research partners will conduct the analyses at their own sites, with Optum Epidemiology conducting the meta-analyses, and Galderma will not have access to individual level data.

For the ORD and Optum's Market Clarity data, high-level access to data platforms and data assets are controlled through an internal application that requires individuals to request individual access to specific environments and data. The ORD is maintained on a Teradata server with access to the database and individual project-specific folders controlled with an internal application, while Optum's Market Clarity data is stored in a secure Amazon Web Service S3 bucket within Optum's de-identified data warehouse. Project-specific data is extracted and downloaded to our Statistical Analysis System (SAS) Unix server where it is stored within project-specific folders with access limited to those on or supporting the project team. Users are required to complete ORD Privacy and Compliance training commensurate with their requested access role prior to gaining access, policy, or other appropriate means. Users are required to comply with any limits, qualifications, conditions, or restrictions set forth in the de-identification determination.

The data management team ensures that identification numbers are not derived from or related to other system or external IDs (such as social security number) or other information about the individual data subjects whose de-identified data is contained in the ORD, as set forth in 45 C.F.R. Section 164.514(b)(2)(i)(R). The Lockbox contains direct identifiers that may be used to re-identify an individual, but can only be accessed and used for re-identification after appropriate approvals are obtained.

## 7.7 Data Analysis

All analyses will be conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and SAS Enterprise Guide 6.1 or later.

### 7.7.1 Annual Monitoring

Optum will tabulate counts of pregnancies exposed to nemolizumab (from 95 days [i.e., 5 times the half-life], or approximately 14 weeks, before ECD through the end of pregnancy) as well as counts of live births from these pregnancies, and the results will be included in the PSURs. Women with nemolizumab-exposed pregnancy episodes will be described according to baseline demographic and clinical characteristics (a subset of those mentioned in Section 7.4.3). Additionally, the overall number of eligible pregnancies will be tabulated and described according to the same baseline demographic and clinical characteristics. All analyses will be descriptive, including the number of observations, mean, standard deviation, median, interquartile range, and range for all continuous variables and counts and percentages for each binary or categorical variable. Counts from Optum's Market Clarity Data will be added starting with the 2029 PSUR, and additional data partners will be added based on the results of the feasibility assessment to ensure sample size projections are met (as described in Section 7.7.2).

Outcome counts (except for live births), matching, propensity score estimation, meta-analyses, and sensitivity analyses will not be performed until the final report.

### 7.7.2 Feasibility Assessment

As additional data sources will be needed to meet sample size projections for the study of rare pregnancy and infant outcomes, a feasibility assessment will be submitted as part of the 2029 PSUR. This assessment will consist of a count request and a questionnaire completed by potential data sources. All potential data sources will be asked to provide counts of nemolizumab-exposed pregnancies by year using the same methods employed by Optum for the counts included in the PSURs. Potential data sources will also be asked to complete a questionnaire that evaluates data quality and operational aspects needed to conduct the study. This survey will include questions regarding the ability to identify pregnancies and exposure to treatments, conduct mother-infant linkage, and identify outcomes of interest. There will also be questions regarding population size, geographic distribution, length of follow-up, data completeness, processes and timeline for data access and ethics approval, data lag time, and frequency of data updates. The feasibility assessment questionnaire will be included in the SAP.

### 7.7.3 Final Analysis

For the final study report, Optum will match nemolizumab-exposed pregnancies to the two comparator groups (Other AD/PN Treatment Cohort and Unexposed Cohort) in a 1:4 ratio based on maternal age at cohort entry, gestational week of dispensing, indication, and calendar week, separately within each data source. If the study size does not permit matching in these categories (or intervals), the sequential cohorts may be collapsed to 2-week intervals for gestational week at cohort entry or wider categories for maternal age at cohort entry and calendar time. A variable matching ratio of 1:up to 4 may also be considered.

#### 7.7.3.1 Propensity Score and IPTW

In the final study report, comparative analyses will be performed incorporating stabilized IPTW to adjust for potential confounding. The stabilized IPTW will be appropriately defined such that the causal estimate is the average treatment effect in the treated (ATT; Austin and Stuart, 2015). Briefly, to estimate the ATT, the weights are defined such that every nemolizumab-exposed pregnancy receives a weight of 1, while the comparator pregnancies receive weights that are a function of the propensity score. Each pregnancy's propensity score (the probability of receiving nemolizumab versus a comparator or no treatment, given membership in the study population and a set of covariates) will be estimated using a logistic regression model with exposure status as the outcome (dependent variable). A total of 2 propensity score models will be generated: one for the comparison of the Nemolizumab Cohort versus Other AD/PN Treatment Cohort and another for the comparison of the Nemolizumab Cohort versus the Unexposed Cohort. The covariates listed in Section 7.4.3 (excluding Sections 7.4.3.6 and 7.4.3.7) will be considered for inclusion in the model as independent (predictor) variables. The propensity score model will only include covariate information from cohort entry or earlier. In addition to the pre-specified variables in Section 7.4.3, the most common diagnoses, procedures, and medications observed prior to ECD will be evaluated to ensure no important confounders are missed.

If there are too many variables given the number of pregnancies exposed to nemolizumab (e.g., < 10 exposed pregnancies for every variable in the propensity score model), the number of variables may be reduced. For variable pairs that are highly correlated (e.g., correlation coefficient > 0.9), one may be eliminated.

Balance between the cohorts will be evaluated before and after weighting. Variables with an absolute standardized difference < 0.1 will be considered balanced. If a variable has an absolute standardized difference ≥ 0.1, the imbalanced covariate will be included in the outcome model. Overall balance between the cohorts, both before and after weighting, will be assessed via overlap (or lack thereof) in histograms of the propensity score. The distribution of weights will also be inspected. To address the impact of large weights on the analysis, truncation of weights greater than 10 will be considered.

#### 7.7.3.2 Descriptive Analysis

The final study report will include a flow chart that describes the number of pregnancies among women with moderate to severe AD or PN that meet all study eligibility criteria. The number of pregnancies included in each exposure window and in each study cohort, live births, linked infants and pregnancy and infant outcomes will be described.

Similar tables of study covariates will also be provided among the subset with pregnancy or infant outcomes of interest to identify likely risk factors for outcomes and compare mothers of linked infants to mothers of non-linked infants to evaluate the potential for selection bias in the analysis of infant outcomes that are by necessity restricted to pregnancies with linked infants.

The study population will be described by study cohort according to the characteristics listed in Section 7.4.3, before and after IPTW. Prevalence and a corresponding 95% confidence interval will be estimated for MCMs and SGA births. Prevalence will be estimated for these outcomes

because they develop during gestation but are only observable at birth; thus, only the prevalence at birth can be calculated. Incidence and a 95% confidence interval will be estimated for all other study outcomes, which are observable as they arise. For each outcome, the prevalence or incidence will be calculated before and after weighting. Analyses will be conducted on MCMs collectively as a whole, and among specific malformations or subgroups of malformations, as sample size allows. The number of pregnancies with each outcome will guide the analyses that are feasible.

#### 7.7.3.3 Comparative Analyses

Nemolizumab-exposed pregnancies will be matched to pregnancies in the two comparator groups in a 1:4 ratio based on maternal age at cohort entry, gestational week of dispensing, indication, and calendar week, separately within each data source. For all pregnancy and infant outcomes assessed at the end of pregnancy or during pregnancy, we will estimate RRs comparing the Nemolizumab Cohort to the comparator cohorts using robust Poisson regression models (for MCMs and SGA births) and HRs using Cox proportional hazards models (for all other outcomes). All comparative analyses will be performed incorporating stabilized IPTW to adjust for potential confounding. All analyses will be conducted by data source and then meta-analyzed (as described in Section 7.7.3.4).

#### 7.7.3.4 Meta-analysis

For the final report, all of the comparative analyses outlined in Section 7.7.3.3 will be conducted as meta-analyses. No individual-level data will be pooled across data sources. Standard software for combining estimates across data sources (e.g., Comprehensive Meta-Analysis or a similar package) will be utilized. This software package performs the meta-analyses and generates diagnostics for assessing heterogeneity along with tabular and graphical output (forest plot for display of results).

Database-specific estimates (HRs and CIs or exposure-specific events and person-time) will be analyzed using the software package and a summary of the data (tabular and forest plots) along with pooled estimates and CIs as well as diagnostic measures of heterogeneity will be provided. Results from both random effects and fixed effects meta-analysis will be reported. Additional details of the planned meta-analyses will be included in the SAP.

#### 7.7.3.5 Sensitivity Analyses

The following sensitivity analyses will only be conducted for the final report.

##### 7.7.3.5.1 Stratification by Maternal Age

Advanced maternal age pregnancies (pregnancies among individuals aged 35 years or older) have a greater risk of some of the study outcomes, such as spontaneous abortion. In a sensitivity analysis, the main study results will be stratified by maternal age at cohort entry. Age strata may include 17 years and younger, 18-34 years, and 35 years and older, as sample size allows.

##### 7.7.3.5.2 Restriction to Singleton Births

Given multiples have a higher risk of preterm birth and SGA birth, a sensitivity analysis will restrict to singleton pregnancies.

#### 7.7.3.5.3 Stratification by Indication (AD vs PN)

Since nemolizumab is indicated for both moderate to severe AD and PN, a sensitivity analysis will perform the comparative analyses stratified by indication. If the sample size for PN is too small, analyses will be restricted to those with moderate to severe AD only.

#### 7.7.3.5.4 Alternative Exposure Definition to Assess Exposure Misclassification

To assess potential exposure misclassification, we will perform four sensitivity analyses on the association between nemolizumab use and the study outcomes. First, exposure to nemolizumab and the other AD/PN treatments will be defined by dispensings/administrations during pregnancy (i.e., after ECD) only. Additionally, an analysis in which exposure is defined as the presence of 2 or more dispensings/administrations [to assess possible stockpiling] will be conducted. This dispensing-based sensitivity analysis may be more robust to potential misclassification of the exposure period, particularly for treatments with long half-lives. There will also be two exposure misclassification sensitivity analyses that change the beginning of the exposure window to 3 times and 1.5 times the half-life of the relevant treatment, respectively. The definitions of these windows can be found in Appendix D.

#### 7.7.3.5.5 Sensitivity Analysis to Exclude Systemic Treatments

In the primary analysis, pregnancies among women exposed to other, non-biologic systemic treatments for moderate to severe AD and PN were included in the study population. In a sensitivity analysis, pregnancies exposed to other systemic treatments for moderate to severe AD or PN (e.g., immunosuppressants, corticosteroids) will be excluded from all exposure cohorts.

#### 7.7.3.5.6 Quantitative Bias Analysis to Assess Unmeasured Confounding

A quantitative bias analysis (QBA) will be conducted to assess the degree of unmeasured confounding required to explain the observed RRs (i.e., the 'rule-out' approach). This method allows for a range of reasonable values of the prevalence of the unmeasured confounder and various magnitudes of association with risk of the study outcome (Schneeweiss, 2006).

#### 7.7.3.5.7 Quantitative Bias Analysis to Assess Outcome Misclassification

While published validation studies indicate that PPVs are high for many of the outcome algorithms used in this study, misclassification may result in biased measures of association if validity varies differentially by exposure status. Therefore, a QBA will be conducted to investigate the potential effect of differential outcome misclassification on the comparative analyses (Lash et al., 2014).

#### 7.7.3.5.8 Quantitative Bias Analysis for MCMs

A sensitivity analysis will be conducted to quantify potential MCMs that might not have been included in the main analysis because the pregnancies resulted in elective termination, spontaneous abortion, or stillbirth rather than live births. A quantitative bias analysis will be conducted to evaluate the impact of elective termination, spontaneous abortion, and stillbirth on prevalence estimates for MCM.

#### 7.7.3.5.9 Sensitivity Analysis Applying European Union (EU) Definitions of Adverse Pregnancy Outcomes

This study uses US databases and US definitions of adverse pregnancy outcomes based on ICD-10-CM codes. However, EU definitions of adverse pregnancy outcomes are slightly different, as early foetal death (before 22 completed weeks of gestation) is known as miscarriage, whereas late foetal death (after 22 completed weeks of gestation) is known as stillbirth. In this sensitivity analysis, we will reclassify pregnancies with a code for stillbirth prior to 22 completed weeks gestation as miscarriage and repeat the analyses for these two outcomes.

### 7.7.4 Missing Data

This study is based on an analysis of automated medical and prescription claims. Data collected for administrative purposes, such as age (or date of birth) and sex, are not expected to be missing, and records with this information missing will not be used for analysis.

Using the standard approach in claims data analyses, the presence of a medication or diagnosis claim will be assumed to indicate use of that medication or the presence of that condition. Conversely, the absence of a medication or diagnosis claim will indicate the absence of use of that medication or a diagnosis of the condition. Therefore, covariates related to drug use and disease status will be categorized as yes (code present) or no (no code present) and there will be no missing data for these variables.

Within Optum's Market Clarity, an integrated claims-EHR data source, clinical variables are missing for some individuals because of variation in care practices. Health care encounters with medical providers who do not contract with Optum will not be observed. Because the EHR database is an open system, some patients may only receive a fraction of their care through a provider captured in the data, and medical encounters outside of the networks contributing data to the EHR database will not be observed. To mitigate the potential for missingness in the data, we will require that the study cohorts have evidence of routine care (i.e., at least one outpatient visit at least 6 months prior to the index date) within the contributing EHR systems. Patients meeting this criterion likely have a reasonably high capture of medical encounters in the data. Additionally, the EHR data in Optum's Market Clarity are supplemented with medical and pharmacy claims, likely improving the capture of clinical variables for most patients.

## 7.8 Quality Control

### 7.8.1 Research Partner Sites

Each research partner site will follow a common protocol and SAP. Additionally, within each research partner site, Standard Operating Procedures (SOPs) or similar guidelines will be used for the conduct and reporting of the study. These procedures will include internal quality audits, rules for secure and confidential data, methods to maintain and archive project documents, quality control procedures for programming, and requirements for additional review and oversight throughout the project duration.

The protocol will be updated to incorporate other research partners and descriptions of their site-specific quality control measures.

### 7.8.2 Optum

Optum is responsible for site-specific analyses (annual counts, feasibility report, final report) as well as combining results from all research partner sites (annual counts starting in 2030 and final report). The conduct and reporting of this study follows Optum Epidemiology's SOPs that are consistent with the International Society for Pharmacoepidemiology (ISPE)'s Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE, 2015) as well as The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP): Guide on Methodological Standards in Pharmacoepidemiology and the EMA Guideline on Good Pharmacovigilance Practices: Module VIII – Post-authorization Safety Studies. For pregnancy safety studies such as this, the suggested study design and methodology are consistent with the FDA draft guidance document Postapproval Pregnancy Safety Studies Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation of analytic work typically involves a combination of a review of program logs and lists, independent coding, a review of program processes and documentation to ensure Optum SOPs are followed, and reconciliation of program code with the study protocol to ensure populations and results are consistent with what is needed for the study. Individual programs are documented and revised as needed until sign-off by a validation analyst using the validation/programming log.

The validity of the ORD for epidemiologic research (as compared with data abstracted from medical records) has been established (Dore et al., 2011; Eng et al., 2012; Loughlin et al., 2010).

## 7.9 Adverse Event Reporting

According to the EMA Guideline on Good Pharmacovigilance Practice: Module VI, there is no requirement for reporting of adverse drug reactions from secondary use of data such as electronic health care databases. In these data sources, it is not possible to identify a potential association between a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (identifiable patient, identifiable reporter, a suspect product, and event) cannot be met. Only aggregated safety results describing the overall association between an exposure and an outcome will be summarized in the study reports.

## 7.10 Limitations of the Research Methods

This proposed study is based on an analysis of claims and EHR databases. While these data sources are valuable, they have certain limitations because they are collected for the purpose of payment and patient management, not research. The presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Medications filled over the counter or provided as samples by the physician will not be observed in the claims data,

although this information may be available for some patients in the free-text clinical notes within Optum's Market Clarity database. The presence of a diagnosis code is not confirmation of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Duration of follow-up can be limited in the claims data due to individuals changing health insurance plans.

The study power will be limited until several years of cohort accrual have passed. Because accrual of nemolizumab initiators depends on actual use within the insured population that is the source for the study, divergence in numbers of users from sample size projections might affect how rapidly the study power reaches an adequate level.

While there are validated algorithms for moderate to severe AD and for PN (Chomistek et al., 2023a; Roh et al., 2022), there is currently no published algorithm for moderate to severe PN. The overall PN algorithm may lead to the inclusion of mild PN cases in our study population. During the study period, published literature will be searched for a validated claims-based algorithm to identify moderate to severe PN. If a validated algorithm is found that has suitable performance characteristics, the methods for identifying PN may be modified.

MCMs will be identified in live born infants, and study drug exposure will be assessed in the first trimester. However, the exact timing of the development of malformations is typically unknown. Additionally, while the use of ICD-10-CM Z3A codes to estimate LMP has been shown to be accurate (Chomistek et al., 2023b), not all pregnancies have Z3A codes, and some degree of measurement error is expected in estimating the beginning of pregnancy. The resulting exposure misclassification due to estimated LMP is not expected to be differential with respect to exposure. A sensitivity analysis will explore alternative exposure windows that are more conservative.

It is possible that selection bias may arise due to differential loss to follow-up (i.e., if pregnant women who receive nemolizumab are more or less likely to be lost to follow-up than those who are exposed to other AD/PN treatments or who are unexposed), though we expect censoring to be non-differential with respect to exposure and outcome status. To check this assumption, we will compare the baseline characteristics of pregnancies with an observed outcome versus those who were censored before the end of pregnancy. We will also describe the frequency of censoring events according to nemolizumab exposure status.

Residual confounding is always a concern in observational studies. While propensity score models can account for a large number of measured pre-specified and empirically derived variables, some variables may have a greater degree of misclassification, and some confounders may not be measured. For example, due to ICD-10 coding limitations, claims data tend to have incomplete capture of smoking status. However, the degree of residual confounding due to unmeasured factors may be reduced if proxies of unmeasured factors are included in the models (Guertin et al., 2016). A quantitative bias analysis will assess the impact of residual confounding on the observed results.

## 8. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, the conduct of this study will be governed by the Guidelines for Good Pharmacoepidemiology Practices issued by ISPE (ISPE, 2015). The research database is de-identified, and individual patient data is kept confidential and will not be shared

with Galderma. All analyses will be performed in accordance with applicable laws and regulations. All deliverables will contain aggregated results only and will not identify individual patients, physicians, facility, claims or medical records. The final table shells/analytic output are subject to change pursuant to Optum's standard statistical de-identification review process. For this reason, Optum may require certain modifications to the output layout to manage the statistical risk of re-identification.

### 8.1 Institutional Review Board Approval

The study protocol will be reviewed and approved by an Institutional Review Board (IRB) prior to the commencement of the study, ensuring that it meets all ethical and regulatory requirements and providing ongoing oversight throughout the study. Initial IRB approval will be sought following finalization of the study protocol. When additional research sites are added, each site will seek their own IRB approval. Each site will communicate directly with the IRB to address any questions and/or provide any additional information in connection with the reviews. Galderma will provide any necessary assistance or documents required for the submission to the IRB. Approval from an IRB for this study is not guaranteed. This study will be undertaken only after the study protocol and study documents have been reviewed by an IRB and sites are provided with an exemption/not human subject research determination letter. The IRB will monitor the study for the life of the project and may require formal re-review and approval on an annual basis. Changes to the project may also require re-review and approval by the IRB.

Optum internal review and approval processes are also required. Optum will provide general study information and a copy of the IRB approval and waiver documents for the relevant data sources for approval to utilize such data in the study, which is not guaranteed.

## 9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual counts and a final study report will be submitted to the study sponsor (as per Section 4), who will subsequently submit to the EMA. The study, including the final report, will also be registered in the ENCePP Registry. The study findings may also be submitted to a scientific congress and/or to a peer-reviewed journal.

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# 11. APPENDICES

## 11.1 Appendix A: ENCePP Checklist

**ENCePP Checklist for Study Protocols (Revision 4)**

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

**Study title:** Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Databases

**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[2] | ☒ | ☐ | ☐ | 4 |
| 1.1.2 End of data collection[3] | ☒ | ☐ | ☐ | 4 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | N/A |
| 1.1.4 Interim report(s) | ☐ | ☐ | ☒ | N/A |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 4 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 4 |

Comments:

| |
|---|
| |

| **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) | ☒ | ☐ | ☐ | 5 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 6 |
| 2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 7.3.6 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☒ | ☐ | ☐ | 6 |
| 2.1.5 If applicable, that there is no a priori hypothesis? | ☒ | ☐ | ☐ | 6 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 7.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 7.2 |

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

| Section 3: Study design | | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 7.7.3.2 |
| 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)) | ☒ | ☐ | ☐ | 7.7.3.3 |
| 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) | ☒ | ☐ | ☐ | 7.9 |

Comments:

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| |

| Section 4: Source and study populations | | Yes | No | N/A | Section Number |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 7.3.1 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 7.3.1 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 7.3.2 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 7.2.1 |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 7.3.4, 7.3.5 |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 7.3.6.7 |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 7.3.2, 7.3.3 |

Comments:

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| 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) | ☒ | ☐ | ☐ | 7.3.6.1, 7.3.6.2, 7.4.1 |
| 5.2 | Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 7.7.3.5.4 |
| 5.3 | Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 7.3.6.2 |
| 5.4 | Is intensity of exposure addressed? (e.g., dose, duration) | ☒ | ☐ | ☐ | 7.7.3.5.4 |
| 5.5 | Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |
| 5.6 | Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 7.3.6 |

Comments:

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| |

| **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? | ☒ | ☐ | ☐ | 7.4.2 |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 7.4.2 |
| 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) | ☒ | ☐ | ☐ | 7.4.2 |
| 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:

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| |

| **Section 7: Bias** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 7.1 | Does the protocol address ways to measure confounding? (e.g., confounding by indication) | ☒ | ☐ | ☐ | 7.7.3.1, 7.7.3.5.6 |
| 7.2 | Does the protocol address selection bias? (e.g., healthy user/adherer bias) | ☒ | ☐ | ☐ | 7.7.3.2 |
| 7.3 | Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 7.7.3.5.4 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 7.7.3.5 |

Comments:

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| |

| **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) | ☒ | ☐ | ☐ | 7.4.1 |
| 9.1.2 | Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 7.4.2 |
| 9.1.3 | Covariates and other characteristics? | ☒ | ☐ | ☐ | 7.4.3 |
| 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) | ☒ | ☐ | ☐ | 7.4.1 |
| 9.2.2 | Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 7.4.2 |
| 9.2.3 | Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 7.4.3 |
| 9.3 | Is a coding system described for: | | | | |
| 9.3.1 | Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 7.4.1 |
| 9.3.2 | Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 7.4.2 |
| 9.3.3 | Covariates and other characteristics? | ☒ | ☐ | ☐ | 7.4.3 |
| 9.4 | Is a linkage method between data sources described? (e.g., based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

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|---|
| |

| **Section 10: Analysis plan** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 10.1 | Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 7.7 |
| 10.2 | Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 7.5 |
| 10.3 | Are descriptive analyses included? | ☒ | ☐ | ☐ | 7.7.3.2 |
| 10.4 | Are stratified analyses included? | ☒ | ☐ | ☐ | 7.7.3.5.1, 7.7.3.5.3 |

| Section 10: Analysis plan | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 7.7.3.1 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☒ | ☐ | ☐ | 7.7.3.5.7 |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 7.7.4 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 7.7.3.5 |

Comments:

| |
|---|
| |

| Section 11: Data management and quality control | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 7.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 7.8 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 7.8, 9 |

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? | ☒ | ☐ | ☐ | 7.10 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 7.10 |
| 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). | ☒ | ☐ | ☐ | 7.10 |
| 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) | ☒ | ☐ | ☐ | 7.5 |

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? | ☒ | ☐ | ☐ | 8 |

| Section 13: Ethical/data protection issues | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 8 |

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? | ☒ | ☐ | ☐ | 3 |

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)? | ☒ | ☐ | ☐ | 4, 9 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 9 |

Comments:

| |
|---|
| |

## 11.2 Appendix B: List of Known Teratogens

- Acetohydroxamic Acid
- Acitretin
- Ambrisentan
- Amiodarone
- Angiotensin-converting-enzyme (ACE) inhibitors
- Angiotensin II receptor blocker
- Bexarotene
- Bosentan
- Carbamazepine
- Chemotherapeutic drugs for the treatment of cancer
- Danazol
- Dicumarol
- Dolutegravir
- Dronedarone
- Dutasteride
- Ethotoin
- Everolimus
- Finasteride
- Fluconazole
- Iodine-131
- Isotretinoin, Alitretinoin, Tretinoin
- Leflunomide
- Lithium
- Macitentan
- Methotrexate
- Methsuximide
- Methylene blue
- Misoprostol
- Mitoxantrone
- Mycophenolate
- Penicillamine

- Phenobarbital
- Phenprocoumon
- Phenytoin
- Posaconazole
- Primidone
- Riociguat
- Sirolimus
- Statins
- Sulfamethoxazole & Trimethoprim
- Temsirolimus
- Teriflunomide
- Thalidomide (including analogs lenalidomide and pomalidomide)
- Trimethadione / Paramethadione
- Topiramate
- Valproic acid
- Vedolizumab
- Voriconazole
- Warfarin

## 11.3 Appendix C: Codes and Treatments Used for Identification of Moderate to Severe AD

### ICD-10 Codes for Identification of Atopic Dermatitis

| ICD-10 Code | Description |
|---|---|
| L20 | Atopic dermatitis |
| L20.0 | Besnier's prurigo |
| L20.8 | Other atopic dermatitis |
| L20.81 | Atopic neurodermatitis |
| L20.82 | Flexural eczema |
| L20.83 | Infantile (acute) (chronic) eczema |
| L20.84 | Intrinsic (allergic) eczema |
| L20.89 | Other atopic dermatitis |
| L20.9 | Atopic dermatitis, unspecified |

Abbreviation: ICD-10, International Classification of Diseases, 10th Revision

### Treatments Used for Identification of Moderate to Severe AD

| Biologics |
|---|
| Abrocitinib |
| Dupilumab |
| Lebrikizumab |
| Nemolizumab |
| Tralokinumab |

| JAK Inhibitors |
|---|
| Abrocitinib |
| Baricitinib |
| Upadacitinib |

Abbreviation: JAK, Janus kinase

| Systemic Immunosuppressants |
|---|
| Azathioprine |
| Cyclosporine |
| Methotrexate |
| Mycophenolate |

| High and Medium Potency Topical Corticosteroids | | |
|---|---|---|
| **Potency** | **Drug** | **Formulation** |
| High potency | Amcinonide | 0.1% cream/ointment/lotion |
| | Betamethasone dipropionate | 0.05% cream/ointment/foam |
| | Betamethasone valerate | 0.1% ointment, 0.12% foam |
| | Clobetasol propionate | 0.05% cream/ointment/solution/foam |
| | Desoximetasone | 0.25% cream/ointment |
| | Diflorasone diacetate | 0.05% ointment/cream/emollient |
| | Fluocinonide | 0.05% cream/gel/ointment/solution |
| | Halcinonide | 0.1% cream/ointment/solution |
| | Halobetasol propionate | 0.05% cream/ointment |
| | Mometasone furoate | 0.1% ointment |
| Medium potency | Betamethasone dipropionate | 0.02% lotion |
| | Betamethasone valerate | 0.1% foam/cream/lotion |
| | Clobetasone butyrate | 0.05% cream/ointment |
| | Desoximetasone | 0.05% cream |
| | Flucinolone acetonide | 0.025% ointment/cream |
| | Hydrocortisone butyrate | 0.1% lotion/cream/ointment |
| | Hydrocortisone valerate | 0.2% ointment/cream |
| | Mometasone furoate | 0.1% cream |
| | Prednicarbate | 0.1% cream |
| | Triamcinolone acetonide | 0.1% cream/ointment/lotion |

| Oral/Parenteral Corticosteroids |
|---|
| Beclomethasone Dipropionate |
| Flunisolide |
| Cortisone Acetate |
| Hydrocortisone Acetate |
| Hydrocortisone Cypionate |
| Hydrocortisone Sodium Phosphate |
| Hydrocortisone Sodium Succinate |
| Hydrocortisone |
| Prednisolone Acetate |
| Prednisolone Sodium Phosphate |
| Prednisolone |
| Methylprednisolone Acetate |
| Methylprednisolone Sodium Succinate |
| Methylprednisolone |
| Prednisone |
| Betamethasone Acetate/Betamethasone Sodium Phosphate |
| Betamethasone Sodium Phosphate |
| Betamethasone |
| Dexamethasone Acetate |

| **Oral/Parenteral Corticosteroids** |
|---|
| Dexamethasone Sodium Phosphate |
| Dexamethasone |
| Triamcinolone Acetonide |
| Triamcinolone Diacetate |
| Triamcinolone Hexacetonide |
| Triamcinolone |
| Fludrocortisone Acetate |
| Mometasone Furoate |
| Adrenal Cortex (Porcine) |
| Budesonide |
| Flunisolide/Menthol |
| Fluticasone Propionate |
| Dexamethasone Isonicotinate |
| Deflazacort |
| Betamethasone Acetate |
| Prasterone (Dhea) |
| Dexamethasone/Lidocaine Hcl |
| Triamcinolone/Lidocaine |
| Fluticasone/Salmeterol |
| Budesonide/Formoterol Fumarate |
| Ciclesonide |
| Dexamethasone, Micronized |
| Budesonide, Micronized |
| Dexamethasone Sodium Phosphate/Pf |
| Aldosterone |
| Methylprednisolone Sodium Succinate/Pf |
| Hydrocortisone Sodium Succinate/Pf |
| Mometasone/Formoterol |
| Prednisolone Sodium Phosphate/Peak Flow |
| Triamcinolone Hexacet, Micro |
| Methylprednisolone, Micronized |
| Prednisone Micronized |
| Dexamethasone Acetate, Micro |
| Dexamethasone In 0.9 % Nacl |
| Prednisolone, Micronized |
| Prednisolone Acetate, Micro |
| Methylprednisolone Acetate, Micro |
| Methylprednisolone/Bupivacaine |
| Triamcinolone Diacetate, Micro |
| Betamethasone Acetate, Micro |
| Fluticasone Propionate, Micro |
| Triamcinolone/Lidocaine/Priloc |
| Betamethasone/Norfluran/Pentflu |

| **Oral/Parenteral Corticosteroids** |
|---|
| Methylprednisolone /Norfluran/Hfc 245fa |
| Dexameth/Pf/Norflur/Hfc 245fa |
| Fluticasone/Umeclidin/Vilanter |
| Betamethasone Sodium Phosphate-Water |
| Methylprednisolone Acetate/Bupivac/Water |
| Methylprednisolone Acetate-Water |
| Triamcinolone Acetate/0.9%Nacl/Pf |
| Betamethasone Acetate, Sodium Phosphate/Water |
| Triamcinolone/Bupivacaine/Nacl |
| Dexamethasone Acetate, Sodium Phosphate/Water |
| Betamethasone Acetate, Sodium Phosphate/Water/Pf |
| Dexamethasone Acetate/Nacl, Iso-Osm |
| Methylprednisolone Acetate/Nacl, Iso-Os/Pf |
| Triamcinolone Acetonide/0.9% Nacl |
| Triamcinolone Diacetate/0.9% Nacl/Pf |

Oral corticosteroids: using the route description field in the claims data, limit to oral formulations only.
Parenteral corticosteroids: using the route description field in the claims data, limit to injection or intravenous only.

| **Other AD treatments** |
|---|
| Topical Tacrolimus |
| Phototherapy |

## 11.4 Appendix D: Half-lives for Cohort Defining Treatments

| Drug | Half-life | 5 times half-life* | 1.5 times half-life (sensitivity)* | 3 times half-life (sensitivity)* |
|---|---|---|---|---|
| Dupilumab | 2 weeks | 10 weeks | 3 weeks | 6 weeks |
| Lebrikizumab | 24.5 days | 123 days | 37 days | 74 days |
| Nemolizumab | 18.9 days | 95 days (approximately 14 weeks) | 29 days | 57 days |
| Tralokinumab | 3 weeks | 15 weeks | 32 days | 9 weeks |

*Numbers were rounded up to the nearest whole day.

## 11.5 Appendix E: Outcome Code Lists

| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| Ectopic Pregnancy | ICD-10-CM | O00*** | Ectopic pregnancy |
| Ectopic Pregnancy | ICD-10 Procedure | 10D27ZZ | Extraction of Products of Conception, Ectopic, Via Opening |
| Ectopic Pregnancy | ICD-10 Procedure | 10D28ZZ | Extraction of Products of Conception, Ectopic, Endo |
| Ectopic Pregnancy | ICD-10 Procedure | 10T20ZZ | Resection of Products of Conception, Ectopic, Open Approach |
| Ectopic Pregnancy | ICD-10 Procedure | 10T23ZZ | Resection of Products of Conception, Ectopic, Perc Approach |
| Ectopic Pregnancy | ICD-10 Procedure | 10T24ZZ | Resection of Ectopic POC, Perc Endo Approach |
| Ectopic Pregnancy | ICD-10 Procedure | 10T27ZZ | Resection of Products of Conception, Ectopic, Via Opening |
| Ectopic Pregnancy | ICD-10 Procedure | 10T28ZZ | Resection of Products of Conception, Ectopic, Endo |
| Ectopic Pregnancy | CPT®[4] | 59100 | Hysterotomy, abdominal (e.g., for hydatidiform mole, abortion) |
| Ectopic Pregnancy | CPT | 59120 | Surgical treatment of ectopic pregnancy; tubal or ovarian, requiring salpingectomy and/or oophorectomy, abdominal or vaginal approach |
| Ectopic Pregnancy | CPT | 59121 | Surgical treatment of ectopic pregnancy; tubal or ovarian, without salpingectomy and/or oophorectomy |
| Ectopic Pregnancy | CPT | 59130 | Surgical treatment of ectopic pregnancy; abdominal pregnancy |
| Ectopic Pregnancy | CPT | 59135 | Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy requiring total hysterectomy |
| Ectopic Pregnancy | CPT | 59136 | Surgical treatment of ectopic pregnancy; interstitial, uterine pregnancy with partial resection of uterus |
| Ectopic Pregnancy | CPT | 59140 | Surgical treatment of ectopic pregnancy; cervical, with evacuation |
| Ectopic Pregnancy | CPT | 59150 | Laparoscopic treatment of ectopic pregnancy; without salpingectomy and/or oophorectomy |
| Ectopic Pregnancy | CPT | 59151 | Laparoscopic treatment of ectopic pregnancy; with salpingectomy and/or oophorectomy |
| Ectopic Pregnancy | ICD-10-CM | O08** | Complications following ectopic and molar pregnancy |
| Elective termination | ICD-10-CM | O04** | Complications following (induced) termination of pregnancy |
| Elective termination | ICD-10-CM | O07** | Failed attempted termination of pregnancy |
| Elective termination | ICD-10-CM | Z33.2 | Encounter for elective termination of pregnancy |
| Elective termination | ICD-10 Procedure | 10A00ZZ | Abortion of Products of Conception, Open Approach |
| Elective termination | ICD-10 Procedure | 10A03ZZ | Abortion of Products of Conception, Percutaneous approach |

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| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| Elective termination | ICD-10 Procedure | 10A04ZZ | Abortion of Products of Conception, Perc Endo Approach |
| Elective termination | ICD-10 Procedure | 10A07Z6 | Abortion of Products of Conception, Vacuum, Via Opening |
| Elective termination | ICD-10 Procedure | 10A07ZW | Abortion of Products of Conception, Laminaria, Via Opening |
| Elective termination | ICD-10 Procedure | 10A07ZX | Abortion of POC, Abortifacient, Via Opening |
| Elective termination | ICD-10 Procedure | 10A07ZZ | Abortion of Products of Conception, Via Opening |
| Elective termination | ICD-10 Procedure | 10A08ZZ | Abortion of Products of Conception, Endo |
| Elective termination | HCPCS | S0190 | Mifepristone Oral 200mg |
| Elective termination | HCPCS | S0191 | Misoprostol, oral, 200 mcg |
| Elective termination | HCPCS | S0199 | Medically induced abortion by oral ingestion of medication including all associated services and supplies (e.g., patient counseling, office visits, confirmation of pregnancy by HCG, ultrasound to confirm duration of pregnancy, ultrasound to confirm completion of abortion) except drugs |
| Elective termination | HCPCS | S2260 | Induced abortion, 17-24 weeks |
| Elective termination | HCPCS | S2265 | Induced abortion, 25-28 weeks |
| Elective termination | HCPCS | S2266 | Induced abortion, 29-31 weeks |
| Elective termination | HCPCS | S2267 | Induced abortion, 32 weeks/greater |
| Elective termination | CPT[5] | 01965 | Anesthesia for incomplete or missed abortion procedures |
| Elective termination | CPT | 01966 | Anesthesia for induced abortion procedures |
| Elective termination | CPT | 59840 | Induced abortion, by dilation and curettage |
| Elective termination | CPT | 59841 | Induced abortion, by dilation and evacuation |
| Elective termination | CPT | 59850 | Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; |
| Elective termination | CPT | 59851 | Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation |
| Elective termination | CPT | 59852 | Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection) |
| Elective termination | CPT | 59855 | Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; |

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| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| Elective termination | CPT[6] | 59856 | Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation |
| Elective termination | CPT | 59857 | Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation) |
| Live births | ICD-10-CM | Z37.0 | Single live birth |
| Live births | ICD-10-CM | Z37.2 | Twins, both liveborn |
| Live births | ICD-10-CM | Z37.3 | Twins, one liveborn and one stillborn |
| Live births | ICD-10-CM | Z37.5* | Other multiple births, all liveborn |
| Live births | ICD-10-CM | Z37.6* | Other multiple births, some liveborn |
| Live births | ICD-10-CM | Z38** | Liveborn infants according to place of birth and type of delivery |
| MCM | ICD-10-CM | Q00* | Anencephaly and similar malformations |
| MCM | ICD-10-CM | Q01* | Encephalocele |
| MCM | ICD-10-CM | Q02 | Microcephaly |
| MCM | ICD-10-CM | Q03* | Congenital hydrocephalus |
| MCM | ICD-10-CM | Q04* | Other congenital malformations of brain |
| MCM | ICD-10-CM | Q05* | Spina bifida |
| MCM | ICD-10-CM | Q06* | Other congenital malformations of spinal cord |
| MCM | ICD-10-CM | Q07** | Other congenital malformations of nervous system |
| MCM | ICD-10-CM | Q10* | Congenital malformations of eyelid, lacrimal apparatus and orbit |
| MCM | ICD-10-CM | Q11* | Anophthalmos, microphthalmos and microphthalmos |
| MCM | ICD-10-CM | Q12* | Congenital lens malformations |
| MCM | ICD-10-CM | Q13** | Congenital malformations of anterior segment of eye |
| MCM | ICD-10-CM | Q14* | Congenital malformations of posterior segment of eye |
| MCM | ICD-10-CM | Q15* | Other congenital malformations of eye |
| MCM | ICD-10-CM | Q16* | Congenital malformations of ear causing impairment of hearing |
| MCM | ICD-10-CM | Q17* | Other congenital malformations of ear |
| MCM | ICD-10-CM | Q18* | Other congenital malformations of face and neck |
| MCM | ICD-10-CM | Q20* | Congenital malformations of cardiac chambers and connections |
| MCM | ICD-10-CM | Q21** | Congenital malformations of cardiac septa |
| MCM | ICD-10-CM | Q22* | Congenital malformations of pulmonary and tricuspid valves |
| MCM | ICD-10-CM | Q23* | Congenital malformations of aortic and mitral valves |

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| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| MCM | ICD-10-CM | Q24* | Other congenital malformations of heart |
| MCM | ICD-10-CM | Q25** | Congenital malformations of great arteries |
| MCM | ICD-10-CM | Q26* | Congenital malformations of great veins |
| MCM | ICD-10-CM | Q27** | Other congenital malformations of peripheral vascular system |
| MCM | ICD-10-CM | Q28* | Other congenital malformations of circulatory system |
| MCM | ICD-10-CM | Q30* | Congenital malformations of nose |
| MCM | ICD-10-CM | Q31* | Congenital malformations of larynx |
| MCM | ICD-10-CM | Q32* | Congenital malformations of trachea and bronchus |
| MCM | ICD-10-CM | Q33* | Congenital malformations of lung |
| MCM | ICD-10-CM | Q34* | Other congenital malformations of respiratory system |
| MCM | ICD-10-CM | Q35* | Cleft palate |
| MCM | ICD-10-CM | Q36* | Cleft lip |
| MCM | ICD-10-CM | Q37* | Cleft palate with cleft lip |
| MCM | ICD-10-CM | Q38* | Other congenital malformations of tongue, mouth and pharynx |
| MCM | ICD-10-CM | Q39* | Congenital malformations of esophagus |
| MCM | ICD-10-CM | Q40* | Other congenital malformations of upper alimentary tract |
| MCM | ICD-10-CM | Q41* | Congenital absence, atresia and stenosis of small intestine |
| MCM | ICD-10-CM | Q42* | Congenital absence, atresia and stenosis of large intestine |
| MCM | ICD-10-CM | Q43* | Other congenital malformations of intestine |
| MCM | ICD-10-CM | Q44* | Congenital malformations of gallbladder, bile ducts and liver |
| MCM | ICD-10-CM | Q45* | Other congenital malformations of digestive system |
| MCM | ICD-10-CM | Q50** | Congenital malformations of ovaries, fallopian tubes and broad ligaments |
| MCM | ICD-10-CM | Q51*** | Congenital malformations of uterus and cervix |
| MCM | ICD-10-CM | Q52*** | Other congenital malformations of female genitalia |
| MCM | ICD-10-CM | Q53*** | Undescended and ectopic testicle |
| MCM | ICD-10-CM | Q54* | Hypospadias |
| MCM | ICD-10-CM | Q55** | Other congenital malformations of male genital organs |
| MCM | ICD-10-CM | Q56* | Indeterminate sex and pseudohermaphroditism |
| MCM | ICD-10-CM | Q60* | Renal agenesis and other reduction defects of kidney |
| MCM | ICD-10-CM | Q61** | Cystic kidney disease |
| MCM | ICD-10-CM | Q62** | Congenital obstructive defects of renal pelvis and congenital malformations of ureter |
| MCM | ICD-10-CM | Q63* | Other congenital malformations of kidney |
| MCM | ICD-10-CM | Q64** | Other congenital malformations of urinary system |
| MCM | ICD-10-CM | Q65** | Congenital deformities of hip |
| MCM | ICD-10-CM | Q66*** | Congenital deformities of feet |

| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| MCM | ICD-10-CM | Q67* | Congenital musculoskeletal deformities of head, face, spine and chest |
| MCM | ICD-10-CM | Q68* | Other congenital musculoskeletal deformities |
| MCM | ICD-10-CM | Q69* | Polydactyly |
| MCM | ICD-10-CM | Q70** | Syndactyly |
| MCM | ICD-10-CM | Q71*** | Reduction defects of upper limb |
| MCM | ICD-10-CM | Q72*** | Reduction defects of lower limb |
| MCM | ICD-10-CM | Q73* | Reduction defects of unspecified limb |
| MCM | ICD-10-CM | Q74* | Other congenital malformations of limb(s) |
| MCM | ICD-10-CM | Q75* | Other congenital malformations of skull and face bones |
| MCM | ICD-10-CM | Q76*** | Congenital malformations of spine and bony thorax |
| MCM | ICD-10-CM | Q77* | Osteochondrodysplasia with defects of growth of tubular bones and spine |
| MCM | ICD-10-CM | Q78* | Other osteochondrodysplasias |
| MCM | ICD-10-CM | Q79** | Congenital malformations of musculoskeletal system, not elsewhere classified |
| MCM | ICD-10-CM | Q80* | Congenital ichthyosis |
| MCM | ICD-10-CM | Q81* | Epidermolysis bullosa |
| MCM | ICD-10-CM | Q82* | Other congenital malformations of skin |
| MCM | ICD-10-CM | Q83* | Congenital malformations of breast |
| MCM | ICD-10-CM | Q84* | Other congenital malformations of integument |
| MCM | ICD-10-CM | Q85** | Phakomatoses, not elsewhere classified |
| MCM | ICD-10-CM | Q86* | Congenital malformation syndromes due to known exogenous causes, not elsewhere classified |
| MCM | ICD-10-CM | Q87*** | Other specified congenital malformation syndromes affecting multiple systems |
| MCM | ICD-10-CM | Q89** | Other congenital malformations, not elsewhere classified |
| Preterm birth | ICD-10-CM | O60.10** | Preterm labor with preterm delivery |
| Preterm birth | ICD-10-CM | O60.12** | Preterm labor second trimester with preterm delivery second trimester |
| Preterm birth | ICD-10-CM | O60.13** | Preterm labor second trimester with preterm delivery third trimester |
| Preterm birth | ICD-10-CM | O60.14** | Preterm labor third trimester with preterm delivery third trimester |
| Preterm birth | ICD-10-CM | P07.2* | Extreme immaturity of newborn |
| Preterm birth | ICD-10-CM | P07.3* | Preterm [premature] newborn [other] |
| SGA | ICD-10-CM | P05.0* | Newborn light for gestational age |
| SGA | ICD-10-CM | P05.1* | Newborn small for gestational age |
| Spontaneous abortion | ICD-10-CM | O02.1 | Missed abortion |
| Spontaneous abortion | ICD-10-CM | O03** | Spontaneous abortion |
| Spontaneous abortion | CPT[7] | 01965 | Anesthesia for incomplete or missed abortion procedures |
| Spontaneous abortion | CPT | 59800 | Treatment Of Spontaneous Abortion, First Trimester |
| Spontaneous abortion | CPT | 59801 | Treatment Of Spontaneous Abortion, First Trimester |

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| Outcome | Type | Code(s) | Code Description |
|---|---|---|---|
| Spontaneous abortion | CPT[8] | 59810 | Treatment Of Spontaneous Abortion, Second Trimester |
| Spontaneous abortion | CPT | 59811 | Treatment Of Spontaneous Abortion, Second Trimester |
| Stillbirth | ICD-10-CM | Z37.1 | Single stillbirth |
| Stillbirth | ICD-10-CM | Z37.3 | Twins, one liveborn and one stillborn |
| Stillbirth | ICD-10-CM | Z37.6* | Other multiple births, some liveborn |
| Stillbirth | ICD-10-CM | Z37.4 | Twins, both stillborn |
| Stillbirth | ICD-10-CM | Z37.7 | Other multiple births, all stillborn |
| Stillbirth | ICD-10-CM | O31.00 | Papyraceous fetus, unspecified trimester |
| Stillbirth | ICD-10-CM | O31.02 | Papyraceous fetus, second trimester |
| Stillbirth | ICD-10-CM | O3103X0 | Papyraceous fetus, third trimester, not applicable or unsp |
| Stillbirth | ICD-10-CM | P95 | Stillbirth |
| Stillbirth | ICD-10-CM | O36.4 | Maternal care for intrauterine death |

Abbreviations: CPT, Current Procedural Terminology codes; HICL, Hierarchical Ingredient Code List
ICD-10, International Classification of Diseases, 10th Revision;
ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification;
MCM, major congenital malformation; SGA, small for gestational age
Subcodes for minor congenital malformations will be removed from the definition of MCM.
* Indicates how many additional decimal places should be included in the wildcard for billable codes only.