

# Strategic context:

**Standardized Medical Name:** Systemic Lupus Erythematosus (SLE) – Active, Moderate-to-Severe)

**Target Patient Profile:**

- **Temporality:** Prevalent
- **Disease Stage/State:** Active, Moderate-to-Severe SLE, inadequately controlled despite receiving standard background therapy (e.g., antimalarials, immunosuppressants, and/or corticosteroids).

**Strategic Rationale: Pharmaceutical Relevance (2025-2026):**

Systemic Lupus Erythematosus (SLE) represents a critical strategic focus for the pharmaceutical industry within the 2025-2026 horizon. Despite the availability of targeted biologics such as anifrolumab (Saphnelo) and belimumab (Benlysta), significant unmet needs persist across the moderate-to-severe population. The industry is intensely focused on developing therapies that achieve higher efficacy thresholds—namely remission or Lupus Low Disease Activity State (LLDAS)—while simultaneously enabling significant corticosteroid sparing, which remains a major driver of long-term morbidity.

The 2025-2026 agenda is defined by a diversification of mechanisms of action, a strong drive towards high-efficacy oral therapies, and the rapid emergence of potentially transformative cell therapies.

Evidence demonstrating high interest in the 2025-2026 horizon includes:

- **Novel Oral Therapies (TYK2 and JAK Inhibitors):** There is a significant push for effective oral options.
  - Bristol Myers Squibb's TYK2 inhibitor, deucravacitinib, is in Phase III (POETYS SLE trials), with readouts anticipated around early 2026.
  - Alumis is advancing ESK-001 (envudeucitinib; TYK2 inhibitor); the Phase 2b LUMUS trial completed enrollment in July 2025, with data expected in Q3 2026.
  - AbbVie's JAK1 inhibitor, upadacitinib (Rinvoq), is currently in the Phase III SELECT-SLE program, with data expected within the 2025-2026 timeframe.
- **Advanced Biologic Pathways:**
  - **Anti-CD40L:** UCB and Biogen are advancing dapirolizumab pegol. Following positive Phase III data (PHOENYCS GO) presented at EULAR 2025, a second pivotal trial (PHOENYCS FLY) is ongoing.

- **Anti-BDCA2:** Biogen's litifilimab, targeting plasmacytoid dendritic cells, is in the late stages of its Phase III TOPAZ program for SLE, with readouts expected around 2026.
- **Dual B-cell Targeting:** Novartis is progressing ianalumab (BAFF-R blockade and B-cell depletion) in the large-scale Phase III SIRIUS-SLE program.
- **B-Cell Depletion via T-Cell Engagers:** A new wave of therapies aiming for profound B-cell depletion is emerging. Cullinan Therapeutics (CLN-978) and Roche (RG6382) are developing CD19xCD3 T-cell engagers, with initial SLE data expected in Q4 2025 and H1 2026.
- **Transformative Cell Therapies (CAR-T):** The 2025-2026 period marks a significant acceleration in clinical development for CD19-targeted CAR-T therapies aiming for an "immune reset" and drug-free remission in refractory SLE. Multiple candidates are entering Phase I/II trials, supported by recent regulatory actions in 2025, including Cabaletta Bio's CABA-201, Adicet Bio's ADI-001 (Fast Track), Fate Therapeutics' FT819 (RMAT designation), and Allogene's ALLO-329 (Fast Track).

#### **Intended Clinical Application Research Utility:**

Epidemiological research characterizing the prevalent, active, moderate-to-severe SLE population is essential to support the commercialization and positioning of multiple novel oral agents (e.g., TYK2/JAK1 inhibitors) and advanced biologics entering the market in 2025-2026. This research will facilitate market access planning and health technology assessments (HTA) by establishing real-world benchmarks for disease activity, quantifying the inadequacy of current standard of care (including utilization of existing biologics and corticosteroid reliance), and generating comparative effectiveness data to differentiate emerging mechanisms.

# Phenotype Description: Systemic Lupus Erythematosus (SLE) – Active, Moderate-to-Severe, Inadequately Controlled

## 1. Clinical Condition

**Recommended Phenotype:** Systemic Lupus Erythematosus (SLE)

**Target Patient Profile:** Prevalent cases of active, moderate-to-severe SLE demonstrating inadequate control despite receiving standard background therapy (e.g., antimalarials, immunosuppressants, and/or corticosteroids).

**Common Synonyms:** Lupus, SLE

## 2. Detailed Presentation

Systemic Lupus Erythematosus (SLE) is a chronic, heterogeneous autoimmune disease characterized by the production of autoantibodies directed against nuclear antigens, leading to immune complex formation, complement activation, and subsequent inflammation and damage across multiple organ systems. The clinical course is typically marked by periods of relapse (flares) and remission.

This phenotype specifically focuses on patients with established SLE exhibiting moderate-to-severe disease activity. This implies involvement of major organ systems or significant, persistent activity across multiple domains that necessitates substantial systemic immunosuppression.

**Clinical Presentation and Assessment:** The presentation of SLE is highly variable. Patients with moderate-to-severe disease often experience significant constitutional symptoms (profound fatigue, fever, weight loss) alongside specific organ involvement:

- **Renal (Lupus Nephritis):** A key driver of severity and morbidity. Manifestations include clinically significant proteinuria (often nephrotic range), active urinary sediment (hematuria, cellular casts), and/or impaired glomerular filtration rate.
- **Musculoskeletal:** Inflammatory arthritis (typically symmetric and non-erosive), myositis, or severe arthralgias.
- **Mucocutaneous:** Acute cutaneous lupus (e.g., malar "butterfly" rash), subacute or chronic (e.g., discoid) lesions, oral/nasal ulcerations, and alopecia.
- **Hematologic:** Clinically significant cytopenias, including thrombocytopenia, autoimmune hemolytic anemia, leukopenia, or lymphopenia.
- **Neuropsychiatric:** Severe manifestations such as seizures, psychosis, myelitis, or mononeuritis multiplex.
- **Serosal:** Pleuritis or pericarditis, often presenting with pleuritic chest pain and effusions.

While validated instruments (e.g., SLEDAI-2K, BILAG) are used in clinical trials to quantify activity, real-world assessment relies on physician documentation of these clinical manifestations and associated laboratory abnormalities.

**Diagnostic Criteria, Laboratory, and Imaging:** The diagnosis is established based on recognized classification criteria (e.g., EULAR/ACR 2019). Key laboratory findings supporting the diagnosis and indicating active disease that are reliably captured in RWD include:

- **Autoantibodies:** High titers of Antinuclear Antibodies (ANA). Specific autoantibodies such as anti-dsDNA (titers often elevate during flares, particularly with nephritis) and anti-Smith (anti-Sm).
- **Complement Levels:** Hypocomplementemia (low C3 and C4 levels), indicative of active immune complex consumption and disease activity.
- **Inflammatory Markers:** Elevated Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP).
- **Organ Function:** Complete blood counts (CBC) identifying cytopenias. Urinalysis abnormalities and quantification of proteinuria (e.g., urine protein-to-creatinine ratio). Renal biopsy is the gold standard for diagnosing and classifying Lupus Nephritis.

**Common Treatments and Inadequate Control:** Management aims to induce remission or Lupus Low Disease Activity State (LLDAS), prevent organ damage, and minimize drug toxicity. The target phenotype requires evidence of ongoing treatment, reflecting inadequate control.

- **Background Therapy:**
  - **Antimalarials:** Hydroxychloroquine (cornerstone therapy).
  - **Corticosteroids:** Prednisone or equivalent. Moderate-to-severe disease often leads to reliance on moderate-to-high doses. Minimizing long-term use (e.g., aiming for  $\leq 7.5$ mg/day) is a critical treatment goal.
  - **Immunosuppressants (csDMARDs):** Mycophenolate mofetil, Azathioprine, Methotrexate, or Calcineurin inhibitors (e.g., Tacrolimus, Voclosporin).
- **Targeted Biologics (bDMARDs):** Belimumab (anti-BAFF) or Anifrolumab (anti-Type I Interferon receptor).

**Inadequate control** is defined as persistent moderate-to-severe disease activity, frequent flares, or an inability to taper corticosteroids to acceptable low levels despite adequate trials of background immunosuppressants and/or biologics.

**Differential Diagnoses and Comorbidities:** Differential diagnoses include other systemic autoimmune diseases (e.g., Sjögren's syndrome, Rheumatoid Arthritis, Mixed Connective Tissue Disease), vasculitis, and infections. Common comorbidities include accelerated cardiovascular disease, infections (due to immunosuppression), osteoporosis (exacerbated by corticosteroids), and antiphospholipid syndrome.

**Prognosis and Complications:** Persistent moderate-to-severe activity leads to irreversible organ damage (e.g., end-stage renal disease, stroke). Morbidity is driven by active inflammation, infections, and complications related to long-term corticosteroid use.

### 3. Phenotype Boundaries and Granularity

This phenotype is defined to capture a specific subset of SLE patients with high unmet medical need, characterized by significant disease burden and resistance to conventional therapies.

#### General Exclusions:

- Mild SLE (managed effectively with antimalarials alone or minimal immunosuppression).
- SLE currently in Remission or Lupus Low Disease Activity State (LLDAS).
- Isolated Cutaneous Lupus Erythematosus (CLE) without systemic involvement.
- Drug-Induced Lupus (DIL).
- Undifferentiated Connective Tissue Disease (UCTD) or overlap syndromes where SLE is not the primary driver of activity.

#### Temporal Context:

- **Prevalent:** Patients must have an established diagnosis of SLE.

#### Clinical Granularity:

- **Severity (Required):** Moderate-to-Severe. This must be identifiable through evidence of significant major organ involvement (e.g., nephritis, neuropsychiatric), elevated serological markers of activity (e.g., low complement, high anti-dsDNA), and/or the necessity of high-intensity therapy (e.g., high-dose corticosteroids, biologics, or multiple immunosuppressants).
- **Acuity (Required):** Active disease (current flare or chronic persistent activity). The presence of chronic damage without concurrent active inflammation is insufficient.
- **Etiology (Required):** Idiopathic/Primary SLE.
- **Manifestation (Preferred):** Identification of specific organ system involvement (e.g., renal, hematologic, musculoskeletal) is highly desirable.

#### Population Context:

- Primarily the adult population ( $\geq 18$  years).
- Patients must be currently receiving, or have recently failed, standard background therapy, confirming inadequate control.

### 4. Intended Clinical Application Research Utility

This phenotype is designed to support epidemiological research critical to the commercialization, positioning, and market access strategies for multiple novel therapeutic agents entering the SLE market in the 2025-2026 horizon. This research will facilitate Health

Technology Assessments (HTA) for emerging mechanisms aiming for high efficacy (remission/LLDAS) and significant corticosteroid sparing.

The relevant emerging therapies include:

- **Novel Oral Therapies:** TYK2 inhibitors (e.g., deucravacitinib, ESK-001) and JAK1 inhibitors (e.g., upadacitinib).
- **Advanced Biologics:** Agents targeting diverse pathways such as anti-CD40L (dapirolizumab pegol), anti-BDCA2 (litifilimab), dual B-cell targeting (ianalumab), and T-cell engagers (e.g., CLN-978, RG6382).
- **Transformative Cell Therapies:** CD19-targeted CAR-T therapies aiming for immune reset (e.g., CABA-201, ADI-001, FT819, ALLO-329).

The primary research utility is to characterize the prevalent, active, moderate-to-severe SLE population by:

1. Establishing real-world benchmarks for disease activity and progression in this high-need segment.
2. Quantifying the inadequacy of the current standard of care, including the utilization patterns and effectiveness of existing biologics (belimumab, anifrolumab).
3. Defining the extent of chronic corticosteroid reliance and associated morbidities, supporting the value proposition of steroid-sparing agents.
4. Generating comparative effectiveness data necessary to differentiate these emerging therapies.

# Clinical Description: Systemic Lupus Erythematosus (SLE) – Active, Moderate-to-Severe

**Synonyms:** Lupus, SLE

## 1. Clinical Case Definition

Systemic Lupus Erythematosus (SLE) is a chronic, heterogeneous autoimmune disease characterized by the production of autoantibodies directed against nuclear antigens. This process leads to immune complex formation, complement activation, and subsequent inflammation and damage across multiple organ systems. The clinical course is typically marked by periods of relapse (flares) and remission.

This clinical description specifically defines active SLE exhibiting moderate-to-severe disease activity. This state implies the involvement of major organ systems or significant, persistent activity across multiple domains. Patients frequently present with constitutional symptoms, such as profound fatigue, fever, and weight loss, alongside specific organ involvement.

Key manifestations defining moderate-to-severe activity include:

- **Renal (Lupus Nephritis):** Characterized by clinically significant proteinuria, active urinary sediment (hematuria, cellular casts), and/or impaired glomerular filtration rate. Renal biopsy is the gold standard for diagnosis and classification.
- **Neuropsychiatric:** Severe central or peripheral nervous system involvement, such as seizures, psychosis, myelitis, or mononeuritis multiplex.
- **Hematologic:** Clinically significant cytopenias, including thrombocytopenia, autoimmune hemolytic anemia, leukopenia, or lymphopenia.
- **Serosal:** Pleuritis or pericarditis, often presenting with effusions.
- **Musculoskeletal:** Significant inflammatory arthritis, myositis, or severe arthralgias.
- **Mucocutaneous:** Extensive acute cutaneous lupus (e.g., malar rash), severe subacute or chronic lesions, oral/nasal ulcerations, and alopecia.

The diagnosis is established based on recognized clinical and immunological criteria. Key laboratory findings supporting the diagnosis and indicating active disease include high titers of Antinuclear Antibodies (ANA), specific autoantibodies such as anti-dsDNA and anti-Smith (anti-Sm), hypocomplementemia (low C3 and C4 levels indicating immune complex consumption), and elevated inflammatory markers (ESR or CRP).

## 2. Phenotype Scope & Granularity

- **Temporal Context:** Prevalent. Intended to identify patients with an established diagnosis of SLE.
- **Severity:** Moderate-to-Severe only. This scope is not inclusive of mild SLE.

- **Acuity / Chronicity:** Active disease (current flare or chronic persistent activity). This scope is not inclusive of SLE in Remission or Lupus Low Disease Activity State (LLDAS). The presence of chronic organ damage without concurrent active inflammation is insufficient.
- **Etiology:** Idiopathic/Primary SLE.
- **Population Context:** Primarily the adult population (≥18 years).

### 3. Related Conditions & Scope Boundaries

The following conditions represent related clinical entities, etiologies, or disease states that are not within the scope of this specific phenotype definition:

- **Drug-Induced Lupus (DIL):** This is a distinct etiology and is not within the scope of this idiopathic phenotype.
- **Isolated Cutaneous Lupus Erythematosus (CLE):** CLE without systemic involvement is outside the scope of this systemic phenotype.
- **Mild SLE:** Cases without major organ involvement or significant systemic activity are outside the scope of this moderate-to-severe definition.
- **Undifferentiated Connective Tissue Disease (UCTD) and Overlap Syndromes:** Conditions such as Mixed Connective Tissue Disease (MCTD), where SLE is not the primary diagnosis or driver of activity, are outside this scope.
- **Other Systemic Autoimmune Diseases:** Differential diagnoses such as Sjögren's syndrome, Rheumatoid Arthritis, and Vasculitis are related but distinct conditions.

### 4. Key Complications & Common Comorbidities

The following conditions are frequent complications or comorbidities of SLE and should be distinguished from the core definition of the active disease state itself:

- **Antiphospholipid Syndrome (APS)**
- **Accelerated Cardiovascular Disease**
- **Infections**
- **Osteoporosis**
- **Irreversible Organ Damage:** Including End-Stage Renal Disease (ESRD) and Stroke.

### 5. Intended Data Sources

This clinical description is intended for building concept sets against real-world administrative claims, electronic health record (EHR) databases, and patient registries. The target data should be standardized to the OMOP Common Data Model. Examples of licensable data sources where this concept set would be applied include:

- **Optum®** (Clinformatics® Data Mart, SES, Pan-Therapeutic)
- **Merative™** (MarketScan® Commercial Claims and Encounters)



- **Veradigm** (Health Verity, Practice Fusion EHR)
- **IQVIA** (AmbEMR, PharMetrics Plus)
- **HealthVerity**