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Complete List of Authors:	MOSCA, MARTA; Azienda Ospedaliero Universitaria Pisana, ; University of Pisa, Department of Clinical and Experimental Medicine Chen, Samuel; AstraZeneca Carty, Lucy; AstraZeneca, Biostatistics Waratani, Miina; AstraZeneca, Immunology Seo, Caroline; AstraZeneca Sorrentino, Alessandro; AstraZeneca Emmas, Cathy; AstraZeneca Nan, Cassandra; AstraZeneca Sweden Stirnadel-Farrant, Heide A.; AstraZeneca Chen, Stephanie ; AstraZeneca R&D Gaithersburg, Global Medical Affair
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Study design for the international Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus receiving anifrolumab

Marta Mosca[1*], Cathy Emmas[2], Cassandra Nekeman-Nan[3], Heide Stirnadel-Farrant[4], Samuel Chen[5], Lucy Carty[6], Miina Waratani[7], Caroline Seo[8], Stephanie Chen[9], Alessandro Sorrentino[10]

[1]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Respiratory & Immunology Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [3]CVRM Evidence, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [4]Oncology Outcomes Research, Global Medical Affairs, AstraZeneca, Cambridge, UK; [5]Evidence Delivery, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [6]Biostatistics, AstraZeneca, Cambridge, UK; [7]Immunology, AstraZeneca, Cambridge, UK; [8]Patient Centered Science, BioPharmaceuticals Medical Evidence, AstraZeneca, Gaithersburg, MD, USA; [9]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [10]Global Medical Affairs, Respiratory & Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK

Corresponding author:

Marta Mosca

Clinical and Experimental Medicine

University of Pisa

Pisa, Italy

+393358309074

Email: marta.mosca@med.unipi.it

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a diverse clinical presentation that involves multiple organ systems and may lead to organ damage and increased risk of mortality. SLE is associated with a high burden of disease that can include loss of productivity and employment and reduced health-related quality of life. The current standard of care for SLE is primarily based on immunosuppression and glucocorticoids, is associated with risk of toxicities and poor tolerability. Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1, was recently approved as a new treatment for patients with moderate to severe SLE.

Methods and analysis: Here, we report the study design of the ongoing, multinational Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER; NCT05637112) that includes 3 years of follow-up beginning with the first infusion of anifrolumab and 1 year of retrospective baseline data. ASTER is targeting an enrollment of 500 adult patients receiving anifrolumab for SLE in Europe and North America. The key study objective is to describe the real-world effectiveness of anifrolumab in routine clinical practice, including clinician-reported disease activity and patient-reported outcomes collected via mobile application. This mobile application also includes a medication diary wherein patients report their prescription and nonprescription medication use for SLE on a weekly basis; these data will lend insights on treatment patterns for the study population.

Ethics and dissemination: The design of the ASTER study was informed through consultations with patients with SLE who provided important insights to help maximize patient engagement, retention, and the collection of key, patient-relevant endpoints. ASTER enrollment began in February 2023 and the study is expected to finish in 2029.

Registration details: Clinicaltrials.gov registration: NCT05637112.

Strengths and limitations of this study:

Strengths

- The ASTER study design provides detailed long-term information on SLE disease progression and risks and benefits of treatment with anifrolumab in clinical practice
- This is the first real-world multinational study where patient- and clinical-reported outcomes contribute to medication usage data
- Patients were involved in the study design, including endpoint selection, data collection, and advising on development of a patient-facing app

Limitations

- Enrollment requires treatment with anifrolumab, thereby limiting the patient population to those with moderate-to-severe SLE
- The single arm study does not allow for inferences into drug effectiveness; it can only provide information on how outcomes change among patients who start taking anifrolumab

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects females 30 to 50 years of age, with the highest rates occurring within Black, Hispanic, and Asian populations.[1] The clinical presentation of SLE is heterogeneous and can involve multiple organ systems including skin, kidneys, joints, and cardiovascular and central nervous systems; sequelae include premature cardiovascular disease, malignancies, and infection.[2] The course of SLE typically includes alternating periods of disease activity and remission, defined as Clinical SLEDAI = 0; evaluator's global assessment <0.5 (0-3); prednisone ≤5 mg/day; and stable antimalarials, immunosuppressives, and biologics,[3] with nearly half of patients incurring some form of organ damage and increased risk of mortality within 10 years of diagnosis.[4-6] The high burden of disease for SLE includes reduced life expectancy, poor health-related quality of life (HRQoL), reduced productivity and/or loss of employment, and high direct and indirect healthcare costs.[6-13]

Treatment for SLE should aim to increase life expectancy, prevent organ damage, and optimize HRQoL.[14] Standard-of-care (SoC) therapy for SLE is conventional immunosuppressive agents, typically beginning with hydroxychloroquine or other antimalarials, then proceeding to immunosuppressive drugs such as methotrexate, azathioprine, and/or systemic corticosteroids on the basis of symptom severity and treatment response.[4 15] However, this approach has limited effectiveness and chronic immunosuppressant use can have negative effects on physical health, including the risk of further organ damage with corticosteroid use.[16 17] Targeted therapies for SLE were introduced over 10 years ago, but have remained limited to belimumab (approved in 2011 and currently indicated for patients with active SLE receiving standard therapy), which inhibits B cell survival by selectively binding to the B lymphocyte stimulator protein,[18] and rituximab, which depletes circulating B cells by targeting the CD20 surface antigen[19] and is not yet approved but recommended for off-label use under certain conditions by clinical practice guidelines.[4 15 20]

The role of type I interferon (IFN-1) in SLE pathogenesis is well characterized[21-24] and has been the target of recent investigational drugs.[25] In 2021, anifrolumab, a fully human immunoglobulin G1 monoclonal antibody to type I interferon receptor subunit 1, became the first targeted type I

IFN inhibitor approved for the treatment of moderate to severe SLE and was added to the 2023 European League Against Rheumatism (EULAR) treatment recommendations.[26] By blocking the activity of type I IFN, anifrolumab results in the inhibition of downstream adaptive and innate immune effects mediated by a range of immune cell types.[27] In phase 3 trials, monthly intravenous administration of anifrolumab led to substantial decreases in SLE disease activity vs placebo and also allowed patients to reduce systemic corticosteroid usage, which was associated with improved HRQoL.[28-32]

The recent approval of anifrolumab and the eventual availability of other targeted agents could have important population-wide implications for patients with SLE by reducing the need for, and risks associated with, glucocorticoids and conventional immunosuppressives. However, proper assessment of the impacts of a new treatment class for disease management requires understanding its performance in the real-world setting. This is of particular importance in SLE, where the currently approved biologics are indicated as add-on therapies for patients already receiving standard treatment,[4 15] which they may also supplement with nonprescription medications to help manage daily symptoms and flares. To help address this need, we designed the Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) to better understand real-world treatment patterns and the associated impact on outcomes among patients with moderate to severe SLE initiating anifrolumab. It is noteworthy that this is the first real-world, multinational study to combine patient self-reporting with data from clinicians to provide a comprehensive and detailed understanding of everyday medication usage and how patient perceptions of disease activity and burden change while receiving treatment over several years. Here, we describe the design, methods, and potential implications of the ASTER study.

METHODS AND ANALYSIS

Study design

ASTER is a multinational, single-arm, observational, cohort study (clinicaltrials.gov registration: NCT05637112) that includes a 1 year retrospective baseline period followed by 3 years of follow-up to collect critical real-world evidence about the addition of anifrolumab to SoC therapy for SLE in routine clinical practice (**figure 1**).[33] Enrollment is on the basis of patients receiving their first anifrolumab prescription for SLE, with the first infusion defining the study

index date. Patients are expected to be followed for 3 years from anifrolumab initiation unless there is withdrawal of consent, loss to follow-up, or death. If patients discontinue anifrolumab before the study end date, relevant clinical and patient-reported data will continue to be collected unless the patient withdraws consent. ASTER has no control group or specific treatment assignment other than the qualifying anifrolumab infusion, and data collection is intended to take place in a manner that does not affect patient care.

The planned enrollment is 500 patients from Canada and Europe, with feasibility studies ongoing to determine the participation of individual countries. Enrollment began in February 2023, and the study is expected to remain ongoing through 18 months after the commercial launch of anifrolumab in each participating country, though it may be extended to reach enrollment targets. Study completion is anticipated for 2029.

Site and investigator selection

Study sites include academic, community, and hospital outpatient settings in each country, intended to recruit a study population that is highly representative of the SLE patient population at large. Enrollment will vary by country based on feasibility. Specific study sites were identified from lists of known clinical trial sites, previous study investigators, and key external experts, with input from payer networks when available. Nonacademic sites are being selected based on affiliations with local clinical networks and the availability of anifrolumab infusions. The investigator selection also considered prior experience with data collection for research studies and potential training to perform the clinical assessments required for ASTER.

Study participants

Patients eligible for ASTER are adults (≥18 years) who meet the 2019 EULAR/ACR criteria for SLE[34] and have received their first prescription of anifrolumab for the treatment of SLE according to the label and any local authorization requirements. Patients are not eligible if they have previously received any dose of anifrolumab, are currently enrolled in an interventional trial, or have a diagnosis of severe or rapidly progressive class III or IV glomerulonephritis requiring induction therapy, isolated class V lupus nephritis, active severe or unstable neuropsychiatric lupus, or any other condition that may limit a patient's ability to provide informed consent or perform study assessments. Patients without ≥12 months of medical records

for baseline data at the study may still enroll, provided that records can be requested from the previous healthcare facility.

Data collection

Study data for ASTER are being collected from both patients and clinicians. Patient-reported outcomes are being collected electronically using the MyReco® mobile application (AliraHealth, Framingham, MA), which includes questionnaires and diaries to assess symptoms, HRQoL, work productivity, medication use, and perceived health status. During enrollment, each patient downloads the MyReco® app on their personal device(s) and receives an activation code and setup instructions. The app will be used to complete all patient-reported outcomes assessments, including instruments and diaries, within prespecified window of availability. The user interface for the app includes an artificial intelligence virtual assistant that supports patients by providing notifications, reminders, and milestone badges at key time points to encourage completion of questionnaires and diary entries. Use of the virtual assistant was informed by prior research suggesting that virtual conversation agents have a positive effect on task and goal completion and that users find them less burdensome than data entry forms.[35 36] App design and features, such as study updates, milestone badges, thank you notes, and personal data monitoring over time were informed by key insights obtained from patients with SLE in the AstraZeneca Patient Partnership Program who were consulted during study design and emphasized the importance of ease of use, personalization, and acknowledgment/recognition for the time required to use the app (eg, thank you cards). The app is also integrated with the study network, allowing investigators to track patient compliance with data entry and data storage by a digital vendor until a transfer to the study database at prespecified intervals.

Electronic case report forms (eCRFs) for clinical data collection by clinicians are accessed by designated, trained personnel or the study coordinator, through secure web-based portals that can be accessed via username and password. The eCRF guides the user through patient registration, data collection from medical records, and study management, to ensure data consistency between providers and study sites. Most data entered into the eCRF originate from routine health assessments, with the exception of COVID-19 vaccination data, which are collected directly into the eCRF. The data fields chosen for selection on the eCRF, such as medical/treatment history,

laboratory results, clinical assessments, adverse events and/or drug reactions, and medical events of interest, were guided by clinical practice guidelines for the management of SLE.[37,38] Immediately upon entry into the eCRF, data are saved to a secure central database and any changes are tracked to provide an auditable record. After data entry has been completed and reviewed, the eCRF will be signed electronically and dated and locked by the authorized personnel at the study site to prevent further editing.

Objectives and outcomes

ASTER study objectives and related measures are detailed in **table 1** and **figure 1**. The primary objective is to describe the clinical effectiveness and duration of effect of anifrolumab over time in routine clinical practice on the basis of the Physician's Global Assessment (PGA), the SLE Disease Activity Index 2000 (SLEDAI-2K), and the composite endpoint of lupus low disease activity state ate (LLDAS).[39] Secondary objectives include describing disease activity, treatment patterns, HRQoL, and healthcare resource utilization as detailed in **table 1**.

The secondary endpoint of SLE-related treatment patterns will be on the basis of medication data from pharmacy records and clinicians collected at baseline and every 6 months during the study, which will be supplemented by weekly reporting in medication diaries reported by the patients (**figure 1**). Related outcomes will include patterns of anifrolumab treatment, including adherence (defined as infusion intervals between 18-38 days on the basis of expected infusion every 4 weeks ± 10 days), persistence (proportion of expected infusions received), and discontinuation if applicable. Patterns of antimalarial, immunosuppressant, biologic, nonsteroidal anti-inflammatory drug, and corticosteroid usage will be reported for the baseline period on the basis of available records and tracked on an ongoing basis during and after (if applicable) anifrolumab treatment. Clinicians will report on eCRFs the number and type of treatments prescribed during the study, including dates of initiation and discontinuation, dosage, number of doses, and reasons for medication change when known. Patients will report (via medication diaries) usage patterns of prescribed corticosteroids and any over-the-counter medications to treat pain, inflammation, skin rashes, or insomnia. An exploratory endpoint is also included to examine potential differences in patient characteristics by the calendar year of anifrolumab initiation.

The selection of endpoints during study design was informed by consultation with patients in the AstraZeneca Patient Partnership Program (1 patient from Canada and 3 from the US). Key insights from the consultations included the importance of including endpoints that assess pain, fatigue, and sleep (**figure 1**), on the basis of the patients' experiences of these symptoms persisting even when disease activity measures and laboratory assessments appear stable.

Patient safety is being monitored continuously starting at the index date by recording all serious adverse events, adverse drug reactions (serious and nonserious), specific medical events of interest, and special situations (eg, exposure during pregnancies or breast-feeding, medication errors, overdose, product quality complaints, or any other valid individual case safety reports). Investigators are also encouraged to report to regulatory authorities any other safety data or adverse events not covered by the study reporting requirements.

Statistical analyses

A sample size of 500 patients is expected to allow for sufficient precision to effectively characterize the important endpoints using various analytical techniques on the selected study measures.

Outcomes will be analyzed and presented separately for all patients who initiate anifrolumab treatment and for all patients while on anifrolumab treatment. Categorical variables will be presented as frequencies and percentages with a 95% CI at different time points, and continuous variables as mean (SD) or median (with minimum, maximum, and/or interquartile range) for absolute values and changes between time points with a 95% CI. Graphical data representations will be generated where appropriate to visually explore potential trends. Outcomes may be stratified by country, relevant baseline and/or disease characteristics, baseline corticosteroid usage, and other variables as deemed necessary; for example, treatment line and prior biologic and immunosuppressant usage, time of enrollment, and adherence and persistence with anifrolumab will likely be of particular importance for subgroup analyses.

The number and percentage of missing data will also be presented for all variables, and multiple imputations may be considered (and used as sensitivity analyses) if the percentage of missing data in primary and secondary outcomes exceeds a prespecified threshold. Additionally, the feasibility of probabilistic matching of participants in ASTER, the Systemic Lupus

Erythematosus Prospective Observational Cohort Study (SPOCS) study, and patients included in patient support program datasets will be explored to potentially enrich datasets with additional time points and variables and to evaluate additional questions about patient disposition, treatment history, and anifrolumab use.

ETHICS AND DISSEMNATION

ASTER is being conducted in accordance with ethical principles consistent with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, and applicable legislation on noninterventional studies and/or observational studies. Study procedures will also adhere to regulations and guidelines governing medical practice and ethics in each participating country.

Patient participation is voluntary and requires signed and dated informed consent from each patient before any study procedures can be performed. The decision to prescribe anifrolumab, which is part of the patient qualifications for enrollment in ASTER, must occur prior to any study-related discussion. The investigator at each site must also ensure that the patient is provided full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study and has the time and opportunity to consider the information and ask questions. Patients must also be notified that they are free to discontinue the study at any time without consequences impacting their routine medical care.

The final version of the protocol, patient informed consent form, and patient-facing materials (eg, app functionality and questions, advertising for recruitment) have been approved in writing by an Institutional Review Board/Independent Ethics Committee (IRB/IEC), which will also be required for any future amendments to these materials.

All patient data are linked with a unique patient identification number, but stored in a pseudo-anonymized way. A nickname chosen by the patient will remain within the mobile app and will not be transferred to the study database or retained in the cloud. Minimal patient demographics will be collected and retained in the study database maintained by the digital vendor. Patients are required to review the application developer's terms and conditions, and must select a checkbox to indicate their agreement with the terms and conditions before using the app.

DISCUSSION

Here we have described the design of the observational ASTER study, which is intended to collect critical real-world evidence on the efficacy of adding anifrolumab to SoC therapy for SLE in routine clinical practice. The data to be generated by ASTER are ultimately intended to provide a comprehensive, longitudinal, and unique data source that can inform patients, physicians, and payers when making treatment decisions.

The observational design of ASTER is also important for providing real-world data to help inform future comparative effectiveness research, while also providing important context for findings from past and future controlled trials. A general advantage of real-world observational research is that enrollment criteria typically permit inclusion of most, if not all, patients eligible for the investigational treatment, who may otherwise be excluded by the more stringent entry criteria used in clinical trials; this key aspect of study eligibility is critical for anchoring clinical trial results to relevant effectiveness outcomes in routine clinical practice. Moreover, recruitment of large, multinational patient cohorts, like the population intended for ASTER, can contribute greatly to our understanding of the natural history and burden of disease and the range of possible treatment outcomes. This is particularly important for a disease like SLE, which varies by factors like ethnicity, geography, environmental exposure, and socioeconomic status, among others.[13]

Strengths of the ASTER design include the 3-year analysis period following a 12-month baseline period to provide detailed, long-term data on disease progression and the risks and benefits of anifrolumab treatment in clinical practice. Moreover, this is the first real-world, multinational study in which both patient-reported and clinician-reported outcomes contribute to the collection of medication usage data. This provides a distinct advantage over relying exclusively on data from prescription records or clinician reporting that occurs only during patient encounters. The weekly reporting of medication usage by patients will provide an opportunity to capture the patient's voice regarding medication usage and, from a data standpoint, a high-resolution picture of treatment adherence, corticosteroid usage/exposure, and supplementation of the prescribed regimen with nonprescription medications that may be used to manage daily symptoms and flares previously outside the clinician's knowledge. These data will be useful for cluster analyses

and/or rich data visualizations to improve our understanding of how treatment patterns affect patient outcomes in routine clinical practice.

Another strength of ASTER is that patients were involved in the study design, including the endpoint selection and data collection processes and advising on the development of the patient-facing app to ensure ease of use and a feeling of personalization akin to speaking with a peer with first-hand experience with SLE instead of a scientist or researcher. This is of particular importance in SLE, which is associated with a substantial "invisible" burden that can include fatigue, pain, negative body image, and detrimental effects on emotional health.[9 40 41]

ASTER also has some limitations that must be considered. First, enrollment requires treatment with anifrolumab, which limits the patient population to those with moderate to severe SLE (on the basis of the labeling indication) and those with access to anifrolumab, which may be limited by local treatment policies and/or availability of reimbursement. Second, the 3-year follow-up period allows for a substantial risk of patients withdrawing consent or becoming lost to follow-up during the study, which would affect the completeness of data, especially at later time points. However, during the study design process, the patient consultants noted that feelings of being heard and understood were key components for patient retention in a study of this length, which was considered during endpoint selection and design of the patient app. For example, there was an emphasis on components of "invisible" SLE burden (eg, fatigue and sleep disturbance) when selecting endpoints and app features intended to maximize engagement (eg, notifications, reminders, milestone badges, and study updates). Finally, the observational, single-arm study design does not allow for inferences into drug effectiveness per se and can only provide information on how outcomes change among patients who initiate treatment.

ASTER is currently ongoing and is expected to provide data that will improve our understanding of SLE natural history, disease activity, and treatment outcomes, including the real-world effects of anifrolumab as well as typical usage of other prescription and nonprescription medications that have yet to be systematically collected and analyzed for this patient population. The expected findings from ASTER are likely to be important for informing treatment decisions, clinical practice, and perhaps future guideline recommendations.

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Footnotes

Contributors: All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Competing Interests: CE, CN, HSF, SC, LC, MW, CS, SC, and AS are or were employees of AstraZeneca at the time of this study and may own stock. MM has received honoraria for consultancies/speaker from AbbVie, Astra Zeneca, GSK, Idorsia, Janssen, Lilly, Otsuka, and UCB.

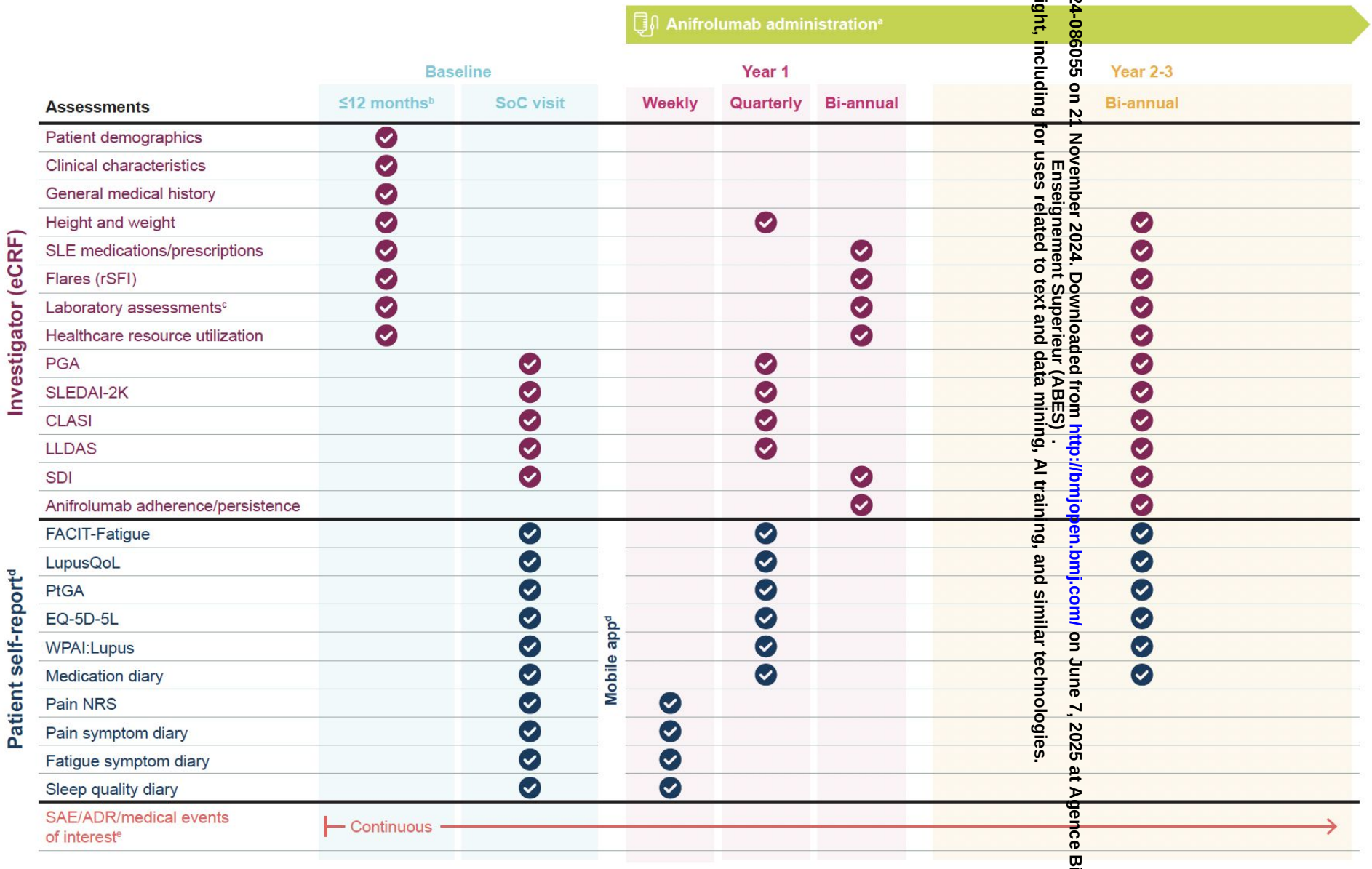
TABLES & FIGURES

Table 1. Summary of objectives and related endpoints in ASTER

Objective	Endpoints and definitions
Primary	Clinical effectiveness over time and duration of effect of anifrolumab in routine clinical practice on the basis of disease activity in individual patients according to PGA and SLEDAI-2K score; the proportion of patients attaining LLDAS[a]
Secondary	1. Clinical SLE manifestations over time in routine clinical practice on the basis of intensity, frequency, and rate of flares per rSFI and proportion of patients with irreversible organ damage per SDI 2. SLE treatment patterns prior to, concomitant with, and after anifrolumab, including use of antimalarials, immunosuppressants, biologics, NSAIDS, and/or corticosteroids; and adherence, persistence, and discontinuation of anifrolumab 3. Changes in patient-reported HRQoL, symptoms, and impairments on the basis of FACIT-Fatigue, Lupus QoL, PtGA, EQ-5D-5L, WPAI:Lupus, and pain NRS 4. SLE-related HCRU after anifrolumab initiation comprising outpatient hospital and emergency room visits and procedures; hospital admissions and inpatient hospital procedures (including reason and duration of stay, stratified by ICU vs non-ICU admission); rheumatologist visits and procedure (including laboratory tests); and dialysis
Exploratory	1. Extent of skin manifestations over time per (CLASI) in a subset of participating sites 2. Changes in patient-reported medication use, pain, fatigue, and sleep quality during the first year after anifrolumab initiation 3. Potential differences in patient characteristics by calendar year of anifrolumab initiation 4. Prevalence and/or incidence of anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and vaccination), MACE, malignancies, and pregnancy 5. Proportion and characteristics of patients who reach clinical remission[b]

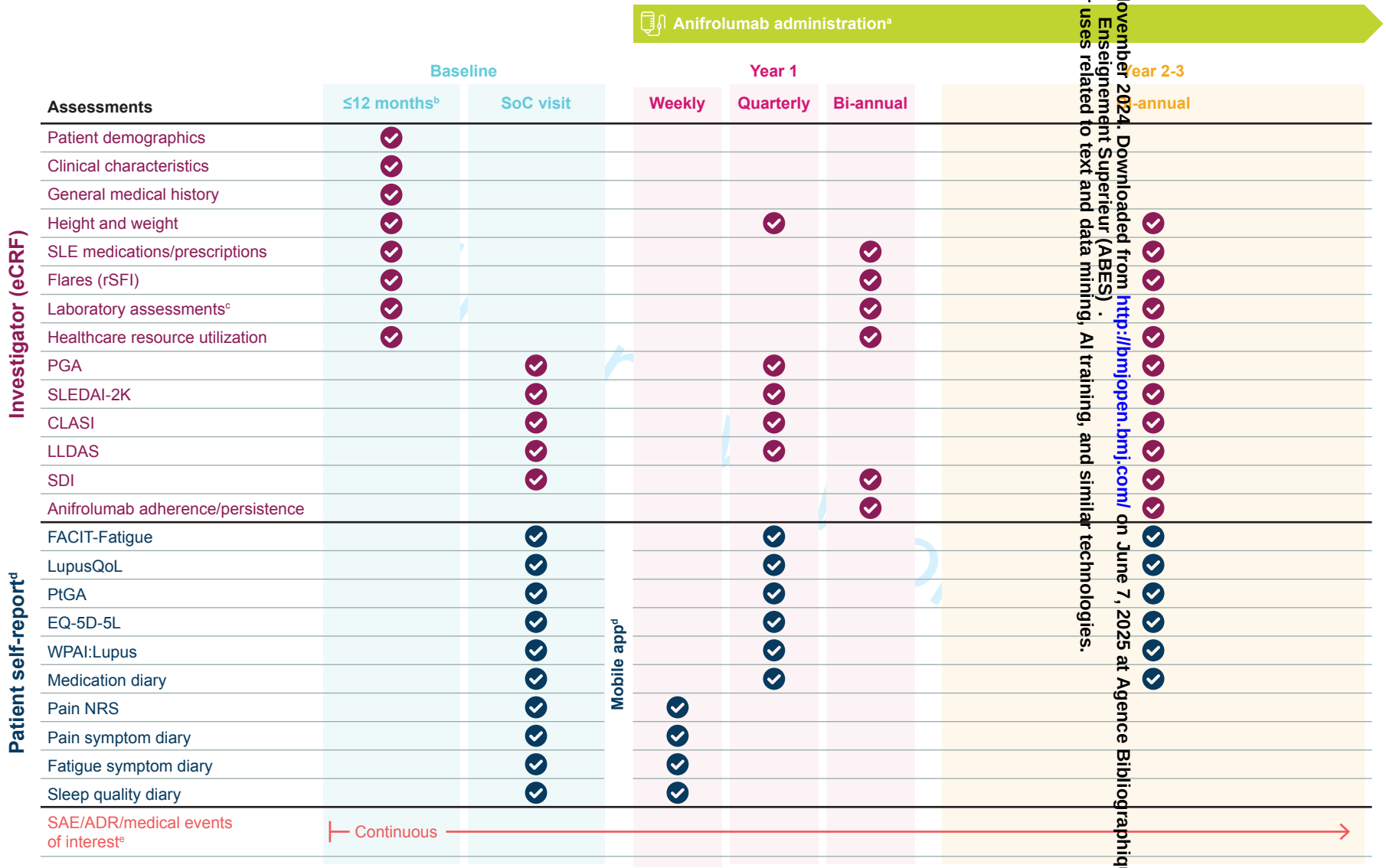
[a]Defined as: SLEDAI-2K ≤4 with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity; no new lupus disease activity since the previous assessment; PGA ≤1; current prednisone-equivalent dose ≤7.5mg/day; and standard maintenance dose of immunosuppressive drugs and biologics (if any) being well tolerated.
[b]Defined as: Clinical SLEDAI=0, Physician Global Assessment <0.5 (0-3), patients may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives, including biologics.[3]
CLASI, Cutaneous Lupus Disease Area and Severity Index; EQ-5D-5L, EuroQol 5-Dimension Health Questionnaire 5 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; ICU, intensive care unit; LLDAS, lupus low disease activity state; MACE, major adverse cardiovascular events; NRS, numerical rating scale; NSAIDS, nonsteroidal anti-inflammatory drugs; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised SELENA-SLEDAI flare index on the basis of SLEDAI-2K assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology SLE damage index; SELENA, Safety of Estrogens in Lupus National Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; WPAI, Work Productivity and Activity Impairment.

Figure 1. ASTER study design and outcomes



[a]Anifrolumab is administered according to country-specific labeling; the first dose defines the study index date for each patient. If anifrolumab is discontinued, data collection continues through year 3 unless the patient withdraws consent. [b]Baseline data are obtained from medical records covering 12 months prior to the index date and from clinician and patient-reported disease assessments at the final standard-of-care visit prior to the index date. [c]Clinical laboratory tests performed during routine clinical management may include hematology, clinical chemistry, urinalysis assessments, anti-dsDNA antibodies, hs-CRP, and serum component (C3 or C4). [d]Patient-reported data are collected at the final standard-of-care visit before the index date, after which patient reporting occurs via the mobile app. [e]Medical events of interest include anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and date(s) and type(s) of vaccination), major adverse cardiovascular events (including [cardiovascular] death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures, urgent cerebrovascular revascularization, arrhythmia [not associated with ischemia], peripheral arterial event, venous thromboembolic event, and other nonfatal cardiovascular events), malignancies, and pregnancy.

ADR, adverse drug reaction; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; eCRF, electronic case report form; EQ-5D-5L, EuroQol 5-Dimension 5-Health Questionnaire 5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; hs-CRP, high-sensitivity C-reactive protein; LupusQOL, Lupus Quality of Life; NRS, numerical rating scale; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised Safety of Estrogens in Lupus National Assessment-SLEDAI flare index; SAE, serious adverse event; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, Systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SoC, standard of care; WPAI:Lupus, Work Productivity and Activity Impairment–Lupus.



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Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study

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Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study

Marta Mosca[1], Cathy Emmas[2], Cassandra Nekeman-Nan[3], Heide Stirnadel-Farrant[4], Samuel Chen[5], Lucy Carty[6], Miina Waratani[7], Caroline Seo[8], Stephanie Chen[9], Alessandro Sorrentino[10*]

[1]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Respiratory & Immunology Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [3]CVRM Evidence, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [4]Oncology Outcomes Research, Global Medical Affairs, AstraZeneca, Cambridge, UK; [5]Evidence Delivery, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [6]Biostatistics, AstraZeneca, Cambridge, UK; [7]Immunology, AstraZeneca, Cambridge, UK; [8]Patient Centered Science, BioPharmaceuticals Medical Evidence, AstraZeneca, Gaithersburg, MD, USA; [9]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [10]Global Medical Affairs, Respiratory & Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK. *At the time of development

Corresponding author:

Marta Mosca

Clinical and Experimental Medicine

University of Pisa

Pisa, Italy

+393358309074

Email: marta.mosca@med.unipi.it

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a diverse clinical presentation that involves multiple organ systems and may lead to organ damage and increased risk of mortality. SLE is associated with a high burden of disease that can include loss of productivity and employment and reduced health-related quality of life. The current standard of care for SLE is primarily based on immunosuppression and glucocorticoids, is associated with risk of toxicities and poor tolerability. Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1, was recently approved as a new treatment for patients with moderate to severe SLE.

Methods and analysis: Here, we report the study design of the ongoing, multinational Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER; NCT05637112) that includes 3 years of follow-up beginning with the first infusion of anifrolumab and 1 year of retrospective baseline data. ASTER is targeting an enrollment of 500 adult patients receiving anifrolumab for SLE in Europe and Canada. The key study objective is to describe the real-world effectiveness of anifrolumab in routine clinical practice, including clinician-reported disease activity and patient-reported outcomes collected via mobile application. This mobile application also includes a medication diary wherein patients report their prescription and nonprescription medication use for SLE on a weekly basis; these data will lend insights on treatment patterns for the study population.

Ethics and dissemination: The design of the ASTER study was informed through consultations with patients with SLE who provided important insights to help maximize patient engagement, retention, and the collection of key, patient-relevant endpoints. ASTER enrollment began in February 2023 and the study is expected to finish in 2029.

Registration details: Clinicaltrials.gov registration: NCT05637112.

Strengths and limitations of this study:

- The ASTER study employs clinical assessments and patient-reported outcome data to obtain long-term information on SLE disease progression and risks and benefits of treatment with anifrolumab in clinical practice

- This study uses a multinational approach, incorporating both patient- and clinical-reported outcomes to assess medication usage
- Patients were involved in the study design, including endpoint selection, data collection, and advising on development of a patient-facing app
- Enrollment requires treatment with anifrolumab, thereby limiting the patient population to those with moderate-to-severe SLE
- The single arm study does not allow for inferences into drug effectiveness; it can only provide information on how outcomes change among patients who start taking anifrolumab

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects females 30 to 50 years of age, with the highest rates occurring within Black, Hispanic, and Asian populations.[1] The clinical presentation of SLE is heterogeneous and can involve multiple organ systems including skin, kidneys, joints, and cardiovascular and central nervous systems; sequelae include premature cardiovascular disease, malignancies, and infection.[2] The course of SLE typically includes alternating periods of disease activity and quiescence. However, quiescence does not necessarily equate to remission as defined by Definitions of Remission in SLE (DORIS) criteria (Clinical SLEDAI = 0; evaluator's global assessment <0.5 (0-3); prednisone ≤5 mg/day; and stable antimalarials, immunosuppressives, and biologics);[3] some patients may achieve low disease activity but may not meet the stringent requirements for DORIS remission. Nearly half of patients incur some form of organ damage and increased risk of mortality within 10 years of diagnosis.[4-6] The high burden of disease for SLE includes reduced life expectancy, poor health-related quality of life (HRQoL), reduced productivity and/or loss of employment, and high direct and indirect healthcare costs.[6-13]

Treatment for SLE should aim to increase life expectancy, prevent organ damage, and optimize HRQoL.[14] Standard-of-care (SoC) therapy for SLE is conventional immunosuppressive agents, typically beginning with hydroxychloroquine or other antimalarials, then proceeding to immunosuppressive drugs such as methotrexate, azathioprine, and/or systemic corticosteroids on the basis of symptom severity and treatment response.[4 15] However, this approach has limited effectiveness and chronic immunosuppressant use can have negative effects on physical health, including the risk of further organ damage with corticosteroid use.[16 17] Targeted therapies for SLE were introduced over 10 years ago, but have remained limited to belimumab, which inhibits B cell survival by selectively binding to the B lymphocyte stimulator protein,[18] and rituximab, which depletes circulating B cells by targeting the CD20 surface antigen.[19] Since its approval in 2011, belimumab has become an important component of SoC therapy; however, rituximab is not yet approved but recommended for off-label use under certain conditions by clinical practice guidelines.[4 15 20]

The role of type I interferon (IFN-1) in SLE pathogenesis is well characterized[21-24] and has been the target of recent investigational drugs.[25] In 2021, anifrolumab, a fully human immunoglobulin

G1 monoclonal antibody to type I interferon receptor subunit 1, became the first targeted type I IFN inhibitor approved for the treatment of moderate to severe SLE and was added to the 2023 European League Against Rheumatism (EULAR) treatment recommendations.[26] By blocking the activity of type I IFN, anifrolumab results in the inhibition of downstream adaptive and innate immune effects mediated by a range of immune cell types.[27] In phase 3 trials, monthly intravenous administration of anifrolumab led to substantial decreases in SLE disease activity vs placebo and also allowed patients to reduce systemic corticosteroid usage, which was associated with improved HRQoL.[28-32]

The recent approval of anifrolumab and the eventual availability of other targeted agents could have important population-wide implications for patients with SLE by reducing the need for, and risks associated with, glucocorticoids and conventional immunosuppressives. However, proper assessment of the impacts of a new treatment class for disease management requires understanding its performance in the real-world setting. This is of particular importance in SLE, where the currently approved biologics are indicated as add-on therapies for patients already receiving standard treatment,[4 15] which they may also supplement with nonprescription medications to help manage daily symptoms and flares. To help address this need, we designed the Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) to better understand real-world treatment patterns and the associated impact on outcomes among patients with moderate to severe SLE initiating anifrolumab. It is noteworthy that this is the first real-world, multinational study to combine patient self-reporting with data from clinicians to provide a comprehensive and detailed understanding of everyday medication usage and how patient perceptions of disease activity and burden change while receiving treatment over several years. Here, we describe the design, methods, and potential implications of the ASTER study.

METHODS AND ANALYSIS

Study design

ASTER is a multinational, single-arm, observational, cohort study (clinicaltrials.gov registration: NCT05637112) designed to collect critical real-world evidence about the addition of anifrolumab to SoC therapy for SLE in routine clinical practice (**figure 1**).[33] The date of anifrolumab initiation marks the study index date. Data will be collected for the 12 months prior to the index date to document disease activity, including the rate of flares. Patients are expected

to be followed for 3 years from anifrolumab initiation unless there is withdrawal of consent, loss to follow-up, or death. If patients discontinue anifrolumab before the study end date, relevant clinical and patient-reported data will continue to be collected unless the patient withdraws consent. ASTER has no control group or specific treatment assignment other than the qualifying anifrolumab infusion, and data collection is intended to take place in a manner that does not affect patient care.

The planned enrollment is 500 patients from Canada and Europe, with feasibility studies ongoing to determine the participation of individual countries. Enrollment began in February 2023, and the study is expected to remain ongoing through 18 months after the commercial launch of anifrolumab in each participating country, though it may be extended to reach enrollment targets. Study completion is anticipated for 2029. At the time of publication, the study has enrolled 271 patients from Austria, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Sweden, and the United Arab Emirates.

Site and investigator selection

Study sites include academic, community, and hospital outpatient settings in each country, intended to recruit a study population that is highly representative of the SLE patient population at large. Enrollment will vary by country based on feasibility. Specific study sites were identified from lists of known clinical trial sites, previous study investigators, and key external experts, with input from payer networks when available. Nonacademic sites are being selected based on affiliations with local clinical networks and the availability of anifrolumab infusions. The investigator selection also considered prior experience with data collection for research studies and potential training to perform the clinical assessments required for ASTER.

Study participants

Patients eligible for ASTER are adults (≥18 years) who meet the 2019 EULAR/ACR criteria for SLE[34] and have received their first prescription of anifrolumab for the treatment of SLE according to the approved country-specific label and any local authorization requirements. Patients are not eligible if they have previously received any dose of anifrolumab, are currently enrolled in an interventional trial, or have a diagnosis of severe or rapidly progressive class III or IV glomerulonephritis requiring induction therapy, isolated class V lupus nephritis, active severe

or unstable neuropsychiatric lupus, or any other condition that may limit a patient's ability to provide informed consent or perform study assessments. Patients without ≥12 months of medical records for baseline data at the study may still enroll, provided that records can be requested from the previous healthcare facility.

Data collection

Study data for ASTER are being collected from both patients and clinicians. Patient-reported outcomes are being collected electronically using the MyReco® mobile application (AliraHealth, Framingham, MA), which includes questionnaires and diaries to assess symptoms, HRQoL, work productivity, medication use, and perceived health status. Patients who do not have a smartphone or who are not willing to download the mobile application may still participate in the study without patient-reported outcome collection. During enrollment, each patient downloads the MyReco® app on their personal device(s) and receives an activation code and in-app setup instructions for how to use the application. The app will be used to complete all patient-reported outcomes assessments, including instruments and diaries, within prespecified window of availability. The user interface for the app includes an artificial intelligence virtual assistant that supports patients by providing notifications, reminders, and milestone badges at key time points to encourage completion of questionnaires and diary entries. Use of the virtual assistant was informed by prior research suggesting that virtual conversation agents have a positive effect on task and goal completion and that users find them less burdensome than data entry forms.[35 36] App design and features, such as study updates, milestone badges, thank you notes, and personal data monitoring over time were informed by key insights obtained from patients with SLE in the AstraZeneca Patient Partnership Program who were consulted during study design and emphasized the importance of ease of use, personalization, and acknowledgment/recognition for the time required to use the app (eg, thank you cards). The app is also integrated with the study network, allowing investigators to track patient compliance with data entry and data storage by a digital vendor until a transfer to the study database at prespecified intervals.

Electronic case report forms (eCRFs) for clinical data collection by clinicians are accessed by designated, trained personnel or the study coordinator, through secure web-based portals that can be accessed via username and password. The eCRF guides the user through patient registration, data collection from medical records, and study management, to ensure data consistency between

providers and study sites. Most data entered into the eCRF originate from routine health assessments, with the exception of COVID-19 vaccination data, which are collected directly into the eCRF. The data fields chosen for selection on the eCRF, such as medical/treatment history, laboratory results, clinical assessments, adverse events and/or drug reactions, and medical events of interest, were guided by clinical practice guidelines for the management of SLE.[37,38] Immediately upon entry into the eCRF, data are saved to a secure central database and any changes are tracked to provide an auditable record. After data entry has been completed and reviewed, the eCRF will be signed electronically and dated and locked by the authorized personnel at the study site to prevent further editing.

Objectives and outcomes

ASTER study objectives and related measures are detailed in **table 1** and **figure 1**. The primary objective is to describe the clinical effectiveness and duration of effect of anifrolumab over time in routine clinical practice on the basis of the Physician's Global Assessment (PGA), the SLE Disease Activity Index 2000 (SLEDAI-2K), and the composite endpoint of lupus low disease activity state ate (LLDAS).[39] Secondary objectives include describing disease activity, treatment patterns, HRQoL, and healthcare resource utilization as detailed in **table 1**.

The secondary endpoint of SLE-related treatment patterns will be on the basis of medication data from pharmacy records and clinicians collected at baseline and every 6 months during the study, which will be supplemented by weekly reporting in medication diaries reported by the patients (**figure 1**). Related outcomes will include patterns of anifrolumab treatment, including adherence (defined as infusion intervals between 18-38 days on the basis of expected infusion every 4 weeks ± 10 days), persistence (proportion of expected infusions received), and discontinuation if applicable. Patterns of antimalarial, immunosuppressant, biologic, nonsteroidal anti-inflammatory drug, and corticosteroid usage will be reported for the baseline period on the basis of available records and tracked on an ongoing basis during and after (if applicable) anifrolumab treatment. Clinicians will report on eCRFs the number and type of treatments prescribed during the study, including dates of initiation and discontinuation, dosage, number of doses, and reasons for medication change when known. Patients will report (via medication diaries) usage patterns of prescribed corticosteroids and any over-the-counter medications to treat pain, inflammation,

skin rashes, or insomnia. An exploratory endpoint is also included to examine potential differences in patient characteristics by the calendar year of anifrolumab initiation.

The selection of endpoints during study design was informed by consultation with patients in the AstraZeneca Patient Partnership Program (1 patient from Canada and 3 from the US). Key insights from the consultations included the importance of including endpoints that assess pain, fatigue, and sleep (**figure 1**), on the basis of the patients' experiences of these symptoms persisting even when disease activity measures and laboratory assessments appear stable.

Patient safety is being monitored continuously starting at the index date by recording all serious adverse events, adverse drug reactions (serious and nonserious), specific medical events of interest, and special situations (eg, exposure during pregnancies or breast-feeding, medication errors, overdose, product quality complaints, or any other valid individual case safety reports). Investigators are also encouraged to report to regulatory authorities any other safety data or adverse events not covered by the study reporting requirements.

Statistical analyses

A sample size of 500 patients is expected to allow for sufficient precision to effectively characterize the important endpoints using various analytical techniques on the selected study measures.

Outcomes will be analyzed and presented separately for all patients who initiate anifrolumab treatment and for all patients while on anifrolumab treatment. Categorical variables will be presented as frequencies and percentages with a 95% CI at different time points, and continuous variables as mean (SD) or median (with minimum, maximum, and/or interquartile range) for absolute values and changes between time points with a 95% CI. Graphical data representations will be generated where appropriate to visually explore potential trends. Outcomes may be stratified by country, relevant baseline and/or disease characteristics, baseline corticosteroid usage, and other variables as deemed necessary; for example, treatment line and prior biologic and immunosuppressant usage, time of enrollment, and adherence and persistence with anifrolumab will likely be of particular importance for subgroup analyses.

The number and percentage of missing data will also be presented for all variables, and multiple imputations may be considered (and used as sensitivity analyses) if the percentage of missing

data in primary and secondary outcomes exceeds a prespecified threshold. Additionally, the feasibility of probabilistic matching of participants in ASTER, the Systemic Lupus Erythematosus Prospective Observational Cohort Study (SPOCS) study, and patients included in patient support program datasets will be explored to potentially enrich datasets with additional time points and variables and to evaluate additional questions about patient disposition, treatment history, and anifrolumab use.

Patient and public involvement

Patients with SLE were involved in the study design, including endpoint selection, data collection, and advising on the development of the patient-facing mobile application.

ETHICS AND DISSEMINATION

ASTER is being conducted in accordance with ethical principles consistent with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, and applicable legislation on noninterventional studies and/or observational studies. Study procedures will also adhere to regulations and guidelines governing medical practice and ethics in each participating country. Trial results will be published in peer-reviewed journals and presented at national and international congresses.

Patient participation is voluntary and requires signed and dated informed consent from each patient before any study procedures can be performed. The decision to prescribe anifrolumab, which is part of the patient qualifications for enrollment in ASTER, must occur prior to any study-related discussion. The investigator at each site must also ensure that the patient is provided full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study and has the time and opportunity to consider the information and ask questions. Patients must also be notified that they are free to discontinue the study at any time without consequences impacting their routine medical care.

The final version of the protocol, patient informed consent form, and patient-facing materials (eg, app functionality and questions, advertising for recruitment) have been approved in writing by all applicable local Institutional Review Boards/Independent Ethics Committees (IRB/IEC), which will also be required for any future amendments to these materials.

All patient data are linked with a unique patient identification number, but stored in a pseudo-anonymized way. A nickname chosen by the patient will remain within the mobile app and will not be transferred to the study database or retained in the cloud. Minimal patient demographics will be collected and retained in the study database maintained by the digital vendor. Patients are required to review the application developer's terms and conditions, and must select a checkbox to indicate their agreement with the terms and conditions before using the app.

DISCUSSION

Here we have described the design of the observational ASTER study, which is intended to collect critical real-world evidence on the efficacy of adding anifrolumab to SoC therapy for SLE in routine clinical practice. The data to be generated by ASTER are ultimately intended to provide a comprehensive, longitudinal, and unique data source that can inform patients, physicians, and payers when making treatment decisions.

The observational design of ASTER is also important for providing real-world data to help inform future comparative effectiveness research, while also providing important context for findings from past and future controlled trials. A general advantage of real-world observational research is that enrollment criteria typically permit inclusion of most, if not all, patients eligible for the investigational treatment, who may otherwise be excluded by the more stringent entry criteria used in clinical trials; this key aspect of study eligibility is critical for anchoring clinical trial results to relevant effectiveness outcomes in routine clinical practice. Moreover, recruitment of large, multinational patient cohorts, like the population intended for ASTER, can contribute greatly to our understanding of the natural history and burden of disease and the range of possible treatment outcomes. This is particularly important for a disease like SLE, which varies by factors like ethnicity, geography, environmental exposure, and socioeconomic status, among others.[13]

Strengths of the ASTER design include the 3-year analysis period following a 12-month baseline period to provide detailed, long-term data on disease progression and the risks and benefits of anifrolumab treatment in clinical practice. Moreover, this is the first real-world, multinational study in which both patient-reported and clinician-reported outcomes contribute to the collection of medication usage data. This provides a distinct advantage over relying exclusively on data from prescription records or clinician reporting that occurs only during patient encounters. The

weekly reporting of medication usage by patients will provide an opportunity to capture the patient's voice regarding medication usage and, from a data standpoint, a high-resolution picture of treatment adherence, corticosteroid usage/exposure, and supplementation of the prescribed regimen with nonprescription medications that may be used to manage daily symptoms and flares previously outside the clinician's knowledge. These data will be useful for cluster analyses and/or rich data visualizations to improve our understanding of how treatment patterns affect patient outcomes in routine clinical practice.

Another strength of ASTER is that patients were involved in the study design, including the endpoint selection and data collection processes and advising on the development of the patient-facing app to ensure ease of use and a feeling of personalization akin to speaking with a peer with first-hand experience with SLE instead of a scientist or researcher. This is of particular importance in SLE, which is associated with a substantial "invisible" burden that can include fatigue, pain, negative body image, and detrimental effects on emotional health.[9 40 41]

ASTER also has some limitations that must be considered. First, enrollment requires treatment with anifrolumab, which limits the patient population to those with moderate to severe SLE (on the basis of the labeling indication) and those with access to anifrolumab, which may be limited by local treatment policies and/or availability of reimbursement. Additionally, patients must have a smartphone and be willing to download the mobile application in order to contribute patient-reported outcomes. Second, the 3-year follow-up period allows for a substantial risk of patients withdrawing consent or becoming lost to follow-up during the study, which would affect the completeness of data, especially at later time points. However, during the study design process, the patient consultants noted that feelings of being heard and understood were key components for patient retention in a study of this length, which was considered during endpoint selection and design of the patient app. For example, there was an emphasis on components of "invisible" SLE burden (eg, fatigue and sleep disturbance) when selecting endpoints and app features intended to maximize engagement (eg, notifications, reminders, milestone badges, and study updates). Finally, the observational, single-arm study design does not allow for inferences into drug effectiveness per se and can only provide information on how outcomes change among patients who initiate treatment.

ASTER is currently ongoing and is expected to provide data that will improve our understanding of SLE natural history, disease activity, and treatment outcomes, including the real-world effects of anifrolumab as well as typical usage of other prescription and nonprescription medications that have yet to be systematically collected and analyzed for this patient population. The expected findings from ASTER are likely to be important for informing treatment decisions, clinical practice, and perhaps future guideline recommendations.

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Footnotes

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TABLES & FIGURES

Table 1. Summary of objectives and related endpoints in ASTER

Objective	Endpoints and definitions
Primary	1. Disease activity assessed by the PGA and SLEDAI-2K 2. Proportion of patients attaining the composite endpoint of LLDAS[a]
Secondary	1. Clinical SLE flares assessment per rSFI 2. Proportion of patients with irreversible organ damage per SDI 3. SLE treatment patterns prior to, concomitant with, and after anifrolumab, including use of antimalarials, immunosuppressants, biologics, NSAIDS, and/or corticosteroids; and adherence, persistence, and discontinuation of anifrolumab 4. Changes in patient-reported HRQoL, symptoms, and impairments on the basis of FACIT-Fatigue, Lupus QoL, PtGA, EQ-5D-5L, WPAI:Lupus, and pain NRS 5. Number of outpatient hospital and emergency room visits and procedures; hospital admissions and inpatient hospital procedures (including reason and duration of stay, stratified by ICU vs non-ICU admission); rheumatologist visits and procedures (including SLE-related laboratory tests); and dialysis appointments
Exploratory	1. Extent of skin manifestations over time per (CLASI) in a subset of participating sites 2. Changes in patient-reported medication use, pain, fatigue, and sleep quality during the first year after anifrolumab initiation 3. Potential differences in patient characteristics by calendar year of anifrolumab initiation 4. Prevalence and/or incidence of anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and vaccination), MACE, malignancies, and pregnancy 5. Proportion and characteristics of patients who reach DORIS remission[b]

[a]Defined as: SLEDAI-2K ≤4 with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity; no new lupus disease activity since the previous assessment; PGA ≤1; current prednisone-equivalent dose ≤7.5mg/day; and standard maintenance dose of immunosuppressive drugs and biologics (if any) being well tolerated.
[b]Defined as: Clinical SLEDAI=0, Physician Global Assessment <0.5 (0-3), patients may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives, including biologics.[3]
CLASI, Cutaneous Lupus Disease Area and Severity Index; DORIS, Definition of Remission in Systemic Lupus Erythematosus; EQ-5D-5L, EuroQol 5-Dimension Health Questionnaire 5 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; ICU, intensive care unit; LLDAS, lupus low disease activity state; MACE, major adverse cardiovascular events; NRS, numerical rating scale; NSAIDS, nonsteroidal anti-inflammatory drugs; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised SELENA-SLEDAI flare index on the basis of SLEDAI-2K assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology SLE damage index; SELENA, Safety of Estrogens in Lupus National Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; WPAI, Work Productivity and Activity Impairment.

Figure 1. ASTER study design and outcomes

[a]Anifrolumab is administered according to country-specific labeling; the first dose defines the study index date for each patient. If anifrolumab is discontinued, data collection continues through year 3 unless the patient withdraws consent. [b]Baseline data are obtained from medical records covering 12 months prior to the index date and from clinician and patient-reported disease assessments at the final standard-of-care visit prior to the index date. [c]Clinical laboratory tests performed during routine clinical management may include hematology, clinical chemistry, urinalysis assessments, anti-dsDNA antibodies, hs-CRP, and serum component (C3 or C4). [d]Patient-reported data are collected at the final standard-of-care visit before the index date, after which patient reporting occurs via the mobile app. [e]Medical events of interest include anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and date(s) and type(s) of vaccination), major adverse cardiovascular events (including [cardiovascular] death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures, urgent cerebrovascular revascularization, arrhythmia [not associated with ischemia], peripheral arterial event, venous thromboembolic event, and other nonfatal cardiovascular events), malignancies, and pregnancy.

ADR, adverse drug reaction; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; eCRF, electronic case report form; EQ-5D-5L, EuroQol 5-Dimension 5-Health Questionnaire 5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; hs-CRP, high-sensitivity C-reactive protein; LupusQOL, Lupus Quality of Life; NRS, numerical rating scale; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised Safety of Estrogens in Lupus National Assessment-SLEDAI flare index; SAE, serious adverse event; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, Systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; WPAI:Lupus, Work Productivity and Activity Impairment: Lupus.

Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study

Marta Mosca[1], Cathy Emmas[2], Cassandra Nekeman-Nan[3], Heide Stirnadel-Farrant[4], Samuel Chen[5], Lucy Carty[6], Miina Waratani[7], Caroline Seo[8], Stephanie Chen[9], Alessandro Sorrentino[10*]

[1]Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Respiratory & Immunology Evidence, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [3]CVRM Evidence, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [4]Oncology Outcomes Research, Global Medical Affairs, AstraZeneca, Cambridge, UK; [5]Evidence Delivery, BioPharmaceuticals Medical, AstraZeneca, Mölndal, Sweden; [6]Biostatistics, AstraZeneca, Cambridge, UK; [7]Immunology, AstraZeneca, Cambridge, UK; [8]Patient Centered Science, BioPharmaceuticals Medical Evidence, AstraZeneca, Gaithersburg, MD, USA; [9]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [10]Global Medical Affairs, Respiratory & Immunology, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK. *At the time of development

Corresponding author:

Marta Mosca

Clinical and Experimental Medicine

University of Pisa

Pisa, Italy

+393358309074

Email: marta.mosca@med.unipi.it

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a diverse clinical presentation that involves multiple organ systems and may lead to organ damage and increased risk of mortality. SLE is associated with a high burden of disease that can include loss of productivity and employment and reduced health-related quality of life. The current standard of care for SLE is primarily based on immunosuppression and glucocorticoids, is associated with risk of toxicities and poor tolerability. Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1, was recently approved as a new treatment for patients with moderate to severe SLE.

Methods and analysis: Here, we report the study design of the ongoing, multinational Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER; NCT05637112) that includes 3 years of follow-up beginning with the first infusion of anifrolumab and 1 year of retrospective baseline data. ASTER is targeting an enrollment of 500 adult patients receiving anifrolumab for SLE in Europe and Canada. The key study objective is to describe the real-world effectiveness of anifrolumab in routine clinical practice, including clinician-reported disease activity and patient-reported outcomes collected via mobile application. This mobile application also includes a medication diary wherein patients report their prescription and nonprescription medication use for SLE on a weekly basis; these data will lend insights on treatment patterns for the study population.

Ethics and dissemination: The design of the ASTER study was informed through consultations with patients with SLE who provided important insights to help maximize patient engagement, retention, and the collection of key, patient-relevant endpoints. ASTER enrollment began in February 2023 and the study is expected to finish in 2029.

Registration details: Clinicaltrials.gov registration: NCT05637112.

Strengths and limitations of this study:

- The ASTER study employs clinical assessments and patient-reported outcome data to obtain long-term information on SLE disease progression and risks and benefits of treatment with anifrolumab in clinical practice

- This study uses a multinational approach, incorporating both patient- and clinical-reported outcomes to assess medication usage
- Patients were involved in the study design, including endpoint selection, data collection, and advising on development of a patient-facing app
- Enrollment requires treatment with anifrolumab, thereby limiting the patient population to those with moderate-to-severe SLE
- The single arm study does not allow for inferences into drug effectiveness; it can only provide information on how outcomes change among patients who start taking anifrolumab

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects females 30 to 50 years of age, with the highest rates occurring within Black, Hispanic, and Asian populations.[1] The clinical presentation of SLE is heterogeneous and can involve multiple organ systems including skin, kidneys, joints, and cardiovascular and central nervous systems; sequelae include premature cardiovascular disease, malignancies, and infection.[2] The course of SLE typically includes alternating periods of disease activity and quiescence. However, quiescence does not necessarily equate to remission as defined by Definitions of Remission in SLE (DORIS) criteria (Clinical SLEDAI = 0; evaluator's global assessment <0.5 (0-3); prednisone ≤5 mg/day; and stable antimalarials, immunosuppressives, and biologics);[3] some patients may achieve low disease activity but may not meet the stringent requirements for DORIS remission. Nearly half of patients incur some form of organ damage and increased risk of mortality within 10 years of diagnosis.[4-6] The high burden of disease for SLE includes reduced life expectancy, poor health-related quality of life (HRQoL), reduced productivity and/or loss of employment, and high direct and indirect healthcare costs.[6-13]

Treatment for SLE should aim to increase life expectancy, prevent organ damage, and optimize HRQoL.[14] Standard-of-care (SoC) therapy for SLE is conventional immunosuppressive agents, typically beginning with hydroxychloroquine or other antimalarials, then proceeding to immunosuppressive drugs such as methotrexate, azathioprine, and/or systemic corticosteroids on the basis of symptom severity and treatment response.[4 15] However, this approach has limited effectiveness and chronic immunosuppressant use can have negative effects on physical health, including the risk of further organ damage with corticosteroid use.[16 17] Targeted therapies for SLE were introduced over 10 years ago, but have remained limited to belimumab, which inhibits B cell survival by selectively binding to the B lymphocyte stimulator protein,[18] and rituximab, which depletes circulating B cells by targeting the CD20 surface antigen.[19] Since its approval in 2011, belimumab has become an important component of SoC therapy; however, rituximab is not yet approved but recommended for off-label use under certain conditions by clinical practice guidelines.[4 15 20]

The role of type I interferon (IFN-1) in SLE pathogenesis is well characterized[21-24] and has been the target of recent investigational drugs.[25] In 2021, anifrolumab, a fully human immunoglobulin

G1 monoclonal antibody to type I interferon receptor subunit 1, became the first targeted type I IFN inhibitor approved for the treatment of moderate to severe SLE and was added to the 2023 European League Against Rheumatism (EULAR) treatment recommendations.[26] By blocking the activity of type I IFN, anifrolumab results in the inhibition of downstream adaptive and innate immune effects mediated by a range of immune cell types.[27] In phase 3 trials, monthly intravenous administration of anifrolumab led to substantial decreases in SLE disease activity vs placebo and also allowed patients to reduce systemic corticosteroid usage, which was associated with improved HRQoL.[28-32]

The recent approval of anifrolumab and the eventual availability of other targeted agents could have important population-wide implications for patients with SLE by reducing the need for, and risks associated with, glucocorticoids and conventional immunosuppressives. However, proper assessment of the impacts of a new treatment class for disease management requires understanding its performance in the real-world setting. This is of particular importance in SLE, where the currently approved biologics are indicated as add-on therapies for patients already receiving standard treatment,[4 15] which they may also supplement with nonprescription medications to help manage daily symptoms and flares. To help address this need, we designed the Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) to better understand real-world treatment patterns and the associated impact on outcomes among patients with moderate to severe SLE initiating anifrolumab. It is noteworthy that this is the first real-world, multinational study to combine patient self-reporting with data from clinicians to provide a comprehensive and detailed understanding of everyday medication usage and how patient perceptions of disease activity and burden change while receiving treatment over several years. Here, we describe the design, methods, and potential implications of the ASTER study.

METHODS AND ANALYSIS

Study design

ASTER is a multinational, single-arm, observational, cohort study (clinicaltrials.gov registration: NCT05637112) designed to collect critical real-world evidence about the addition of anifrolumab to SoC therapy for SLE in routine clinical practice (**figure 1**).[33] The date of anifrolumab initiation marks the study index date. Data will be collected for the 12 months prior to the index date to document disease activity, including the rate of flares. Patients are expected

to be followed for 3 years from anifrolumab initiation unless there is withdrawal of consent, loss to follow-up, or death. If patients discontinue anifrolumab before the study end date, relevant clinical and patient-reported data will continue to be collected unless the patient withdraws consent. ASTER has no control group or specific treatment assignment other than the qualifying anifrolumab infusion, and data collection is intended to take place in a manner that does not affect patient care.

The planned enrollment is 500 patients from Canada and Europe, with feasibility studies ongoing to determine the participation of individual countries. Enrollment began in February 2023, and the study is expected to remain ongoing through 18 months after the commercial launch of anifrolumab in each participating country, though it may be extended to reach enrollment targets. Study completion is anticipated for 2029. At the time of publication, the study has enrolled 271 patients from Austria, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Sweden, and the United Arab Emirates.

Site and investigator selection

Study sites include academic, community, and hospital outpatient settings in each country, intended to recruit a study population that is highly representative of the SLE patient population at large. Enrollment will vary by country based on feasibility. Specific study sites were identified from lists of known clinical trial sites, previous study investigators, and key external experts, with input from payer networks when available. Nonacademic sites are being selected based on affiliations with local clinical networks and the availability of anifrolumab infusions. The investigator selection also considered prior experience with data collection for research studies and potential training to perform the clinical assessments required for ASTER.

Study participants

Patients eligible for ASTER are adults (≥18 years) who meet the 2019 EULAR/ACR criteria for SLE[34] and have received their first prescription of anifrolumab for the treatment of SLE according to the approved country-specific label and any local authorization requirements. Patients are not eligible if they have previously received any dose of anifrolumab, are currently enrolled in an interventional trial, or have a diagnosis of severe or rapidly progressive class III or IV glomerulonephritis requiring induction therapy, isolated class V lupus nephritis, active severe

or unstable neuropsychiatric lupus, or any other condition that may limit a patient's ability to provide informed consent or perform study assessments. Patients without ≥12 months of medical records for baseline data at the study may still enroll, provided that records can be requested from the previous healthcare facility.

Data collection

Study data for ASTER are being collected from both patients and clinicians. Patient-reported outcomes are being collected electronically using the MyReco® mobile application (AliraHealth, Framingham, MA), which includes questionnaires and diaries to assess symptoms, HRQoL, work productivity, medication use, and perceived health status. Patients who do not have a smartphone or who are not willing to download the mobile application may still participate in the study without patient-reported outcome collection. During enrollment, each patient downloads the MyReco® app on their personal device(s) and receives an activation code and in-app setup instructions for how to use the application. The app will be used to complete all patient-reported outcomes assessments, including instruments and diaries, within prespecified window of availability. The user interface for the app includes an artificial intelligence virtual assistant that supports patients by providing notifications, reminders, and milestone badges at key time points to encourage completion of questionnaires and diary entries. Use of the virtual assistant was informed by prior research suggesting that virtual conversation agents have a positive effect on task and goal completion and that users find them less burdensome than data entry forms.[35 36] App design and features, such as study updates, milestone badges, thank you notes, and personal data monitoring over time were informed by key insights obtained from patients with SLE in the AstraZeneca Patient Partnership Program who were consulted during study design and emphasized the importance of ease of use, personalization, and acknowledgment/recognition for the time required to use the app (eg, thank you cards). The app is also integrated with the study network, allowing investigators to track patient compliance with data entry and data storage by a digital vendor until a transfer to the study database at prespecified intervals.

Electronic case report forms (eCRFs) for clinical data collection by clinicians are accessed by designated, trained personnel or the study coordinator, through secure web-based portals that can be accessed via username and password. The eCRF guides the user through patient registration, data collection from medical records, and study management, to ensure data consistency between

providers and study sites. Most data entered into the eCRF originate from routine health assessments, with the exception of COVID-19 vaccination data, which are collected directly into the eCRF. The data fields chosen for selection on the eCRF, such as medical/treatment history, laboratory results, clinical assessments, adverse events and/or drug reactions, and medical events of interest, were guided by clinical practice guidelines for the management of SLE.[37,38] Immediately upon entry into the eCRF, data are saved to a secure central database and any changes are tracked to provide an auditable record. After data entry has been completed and reviewed, the eCRF will be signed electronically and dated and locked by the authorized personnel at the study site to prevent further editing.

Objectives and outcomes

ASTER study objectives and related measures are detailed in **table 1** and **figure 1**. The primary objective is to describe the clinical effectiveness and duration of effect of anifrolumab over time in routine clinical practice on the basis of the Physician's Global Assessment (PGA), the SLE Disease Activity Index 2000 (SLEDAI-2K), and the composite endpoint of lupus low disease activity state ate (LLDAS).[39] Secondary objectives include describing disease activity, treatment patterns, HRQoL, and healthcare resource utilization as detailed in **table 1**.

The secondary endpoint of SLE-related treatment patterns will be on the basis of medication data from pharmacy records and clinicians collected at baseline and every 6 months during the study, which will be supplemented by weekly reporting in medication diaries reported by the patients (**figure 1**). Related outcomes will include patterns of anifrolumab treatment, including adherence (defined as infusion intervals between 18-38 days on the basis of expected infusion every 4 weeks ± 10 days), persistence (proportion of expected infusions received), and discontinuation if applicable. Patterns of antimalarial, immunosuppressant, biologic, nonsteroidal anti-inflammatory drug, and corticosteroid usage will be reported for the baseline period on the basis of available records and tracked on an ongoing basis during and after (if applicable) anifrolumab treatment. Clinicians will report on eCRFs the number and type of treatments prescribed during the study, including dates of initiation and discontinuation, dosage, number of doses, and reasons for medication change when known. Patients will report (via medication diaries) usage patterns of prescribed corticosteroids and any over-the-counter medications to treat pain, inflammation,

skin rashes, or insomnia. An exploratory endpoint is also included to examine potential differences in patient characteristics by the calendar year of anifrolumab initiation.

The selection of endpoints during study design was informed by consultation with patients in the AstraZeneca Patient Partnership Program (1 patient from Canada and 3 from the US). Key insights from the consultations included the importance of including endpoints that assess pain, fatigue, and sleep (**figure 1**), on the basis of the patients' experiences of these symptoms persisting even when disease activity measures and laboratory assessments appear stable.

Patient safety is being monitored continuously starting at the index date by recording all serious adverse events, adverse drug reactions (serious and nonserious), specific medical events of interest, and special situations (eg, exposure during pregnancies or breast-feeding, medication errors, overdose, product quality complaints, or any other valid individual case safety reports). Investigators are also encouraged to report to regulatory authorities any other safety data or adverse events not covered by the study reporting requirements.

Statistical analyses

A sample size of 500 patients is expected to allow for sufficient precision to effectively characterize the important endpoints using various analytical techniques on the selected study measures.

Outcomes will be analyzed and presented separately for all patients who initiate anifrolumab treatment and for all patients while on anifrolumab treatment. Categorical variables will be presented as frequencies and percentages with a 95% CI at different time points, and continuous variables as mean (SD) or median (with minimum, maximum, and/or interquartile range) for absolute values and changes between time points with a 95% CI. Graphical data representations will be generated where appropriate to visually explore potential trends. Outcomes may be stratified by country, relevant baseline and/or disease characteristics, baseline corticosteroid usage, and other variables as deemed necessary; for example, treatment line and prior biologic and immunosuppressant usage, time of enrollment, and adherence and persistence with anifrolumab will likely be of particular importance for subgroup analyses.

The number and percentage of missing data will also be presented for all variables, and multiple imputations may be considered (and used as sensitivity analyses) if the percentage of missing

data in primary and secondary outcomes exceeds a prespecified threshold. Additionally, the feasibility of probabilistic matching of participants in ASTER, the Systemic Lupus Erythematosus Prospective Observational Cohort Study (SPOCS) study, and patients included in patient support program datasets will be explored to potentially enrich datasets with additional time points and variables and to evaluate additional questions about patient disposition, treatment history, and anifrolumab use.

Patient and public involvement

Patients with SLE were involved in the study design, including endpoint selection, data collection, and advising on the development of the patient-facing mobile application.

ETHICS AND DISSEMINATION

ASTER is being conducted in accordance with ethical principles consistent with the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice Guidelines, International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices, and applicable legislation on noninterventional studies and/or observational studies. Study procedures will also adhere to regulations and guidelines governing medical practice and ethics in each participating country. Trial results will be published in peer-reviewed journals and presented at national and international congresses.

Patient participation is voluntary and requires signed and dated informed consent from each patient before any study procedures can be performed. The decision to prescribe anifrolumab, which is part of the patient qualifications for enrollment in ASTER, must occur prior to any study-related discussion. The investigator at each site must also ensure that the patient is provided full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study and has the time and opportunity to consider the information and ask questions. Patients must also be notified that they are free to discontinue the study at any time without consequences impacting their routine medical care.

The final version of the protocol, patient informed consent form, and patient-facing materials (eg, app functionality and questions, advertising for recruitment) have been approved in writing by all applicable local Institutional Review Boards/Independent Ethics Committees (IRB/IEC), which will also be required for any future amendments to these materials.

All patient data are linked with a unique patient identification number, but stored in a pseudo-anonymized way. A nickname chosen by the patient will remain within the mobile app and will not be transferred to the study database or retained in the cloud. Minimal patient demographics will be collected and retained in the study database maintained by the digital vendor. Patients are required to review the application developer's terms and conditions, and must select a checkbox to indicate their agreement with the terms and conditions before using the app.

DISCUSSION

Here we have described the design of the observational ASTER study, which is intended to collect critical real-world evidence on the efficacy of adding anifrolumab to SoC therapy for SLE in routine clinical practice. The data to be generated by ASTER are ultimately intended to provide a comprehensive, longitudinal, and unique data source that can inform patients, physicians, and payers when making treatment decisions.

The observational design of ASTER is also important for providing real-world data to help inform future comparative effectiveness research, while also providing important context for findings from past and future controlled trials. A general advantage of real-world observational research is that enrollment criteria typically permit inclusion of most, if not all, patients eligible for the investigational treatment, who may otherwise be excluded by the more stringent entry criteria used in clinical trials; this key aspect of study eligibility is critical for anchoring clinical trial results to relevant effectiveness outcomes in routine clinical practice. Moreover, recruitment of large, multinational patient cohorts, like the population intended for ASTER, can contribute greatly to our understanding of the natural history and burden of disease and the range of possible treatment outcomes. This is particularly important for a disease like SLE, which varies by factors like ethnicity, geography, environmental exposure, and socioeconomic status, among others.[13]

Strengths of the ASTER design include the 3-year analysis period following a 12-month baseline period to provide detailed, long-term data on disease progression and the risks and benefits of anifrolumab treatment in clinical practice. Moreover, this is the first real-world, multinational study in which both patient-reported and clinician-reported outcomes contribute to the collection of medication usage data. This provides a distinct advantage over relying exclusively on data from prescription records or clinician reporting that occurs only during patient encounters. The

weekly reporting of medication usage by patients will provide an opportunity to capture the patient's voice regarding medication usage and, from a data standpoint, a high-resolution picture of treatment adherence, corticosteroid usage/exposure, and supplementation of the prescribed regimen with nonprescription medications that may be used to manage daily symptoms and flares previously outside the clinician's knowledge. These data will be useful for cluster analyses and/or rich data visualizations to improve our understanding of how treatment patterns affect patient outcomes in routine clinical practice.

Another strength of ASTER is that patients were involved in the study design, including the endpoint selection and data collection processes and advising on the development of the patient-facing app to ensure ease of use and a feeling of personalization akin to speaking with a peer with first-hand experience with SLE instead of a scientist or researcher. This is of particular importance in SLE, which is associated with a substantial "invisible" burden that can include fatigue, pain, negative body image, and detrimental effects on emotional health.[9 40 41]

ASTER also has some limitations that must be considered. First, enrollment requires treatment with anifrolumab, which limits the patient population to those with moderate to severe SLE (on the basis of the labeling indication) and those with access to anifrolumab, which may be limited by local treatment policies and/or availability of reimbursement. Additionally, patients must have a smartphone and be willing to download the mobile application in order to contribute patient-reported outcomes. Second, the 3-year follow-up period allows for a substantial risk of patients withdrawing consent or becoming lost to follow-up during the study, which would affect the completeness of data, especially at later time points. However, during the study design process, the patient consultants noted that feelings of being heard and understood were key components for patient retention in a study of this length, which was considered during endpoint selection and design of the patient app. For example, there was an emphasis on components of "invisible" SLE burden (eg, fatigue and sleep disturbance) when selecting endpoints and app features intended to maximize engagement (eg, notifications, reminders, milestone badges, and study updates). Finally, the observational, single-arm study design does not allow for inferences into drug effectiveness per se and can only provide information on how outcomes change among patients who initiate treatment.

ASTER is currently ongoing and is expected to provide data that will improve our understanding of SLE natural history, disease activity, and treatment outcomes, including the real-world effects of anifrolumab as well as typical usage of other prescription and nonprescription medications that have yet to be systematically collected and analyzed for this patient population. The expected findings from ASTER are likely to be important for informing treatment decisions, clinical practice, and perhaps future guideline recommendations.

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Footnotes

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TABLES & FIGURES

Table 1. Summary of objectives and related endpoints in ASTER

Objective	Endpoints and definitions
Primary	1. Disease activity assessed by the PGA and SLEDAI-2K 2. Proportion of patients attaining the composite endpoint of LLDAS[a]
Secondary	1. Clinical SLE flares assessment per rSFI 2. Proportion of patients with irreversible organ damage per SDI 3. SLE treatment patterns prior to, concomitant with, and after anifrolumab, including use of antimalarials, immunosuppressants, biologics, NSAIDS, and/or corticosteroids; and adherence, persistence, and discontinuation of anifrolumab 4. Changes in patient-reported HRQoL, symptoms, and impairments on the basis of FACIT-Fatigue, Lupus QoL, PtGA, EQ-5D-5L, WPAI:Lupus, and pain NRS 5. Number of outpatient hospital and emergency room visits and procedures; hospital admissions and inpatient hospital procedures (including reason and duration of stay, stratified by ICU vs non-ICU admission); rheumatologist visits and procedures (including SLE-related laboratory tests); and dialysis appointments
Exploratory	1. Extent of skin manifestations over time per (CLASI) in a subset of participating sites 2. Changes in patient-reported medication use, pain, fatigue, and sleep quality during the first year after anifrolumab initiation 3. Potential differences in patient characteristics by calendar year of anifrolumab initiation 4. Prevalence and/or incidence of anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and vaccination), MACE, malignancies, and pregnancy 5. Proportion and characteristics of patients who reach DORIS remission[b]

[a]Defined as: SLEDAI-2K ≤4 with no activity in major organ systems and no hemolytic anemia or gastrointestinal activity; no new lupus disease activity since the previous assessment; PGA ≤1; current prednisone-equivalent dose ≤7.5mg/day; and standard maintenance dose of immunosuppressive drugs and biologics (if any) being well tolerated.
[b]Defined as: Clinical SLEDAI=0, Physician Global Assessment <0.5 (0-3), patients may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives, including biologics.[3]
CLASI, Cutaneous Lupus Disease Area and Severity Index; DORIS, Definition of Remission in Systemic Lupus Erythematosus; EQ-5D-5L, EuroQol 5-Dimension Health Questionnaire 5 Level; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, health-related quality of life; ICU, intensive care unit; LLDAS, lupus low disease activity state; MACE, major adverse cardiovascular events; NRS, numerical rating scale; NSAIDS, nonsteroidal anti-inflammatory drugs; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised SELENA-SLEDAI flare index on the basis of SLEDAI-2K assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology SLE damage index; SELENA, Safety of Estrogens in Lupus National Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; WPAI, Work Productivity and Activity Impairment.

Figure 1. ASTER study design and outcomes

[a]Anifrolumab is administered according to country-specific labeling; the first dose defines the study index date for each patient. If anifrolumab is discontinued, data collection continues through year 3 unless the patient withdraws consent. [b]Baseline data are obtained from medical records covering 12 months prior to the index date and from clinician and patient-reported disease assessments at the final standard-of-care visit prior to the index date. [c]Clinical laboratory tests performed during routine clinical management may include hematology, clinical chemistry, urinalysis assessments, anti-dsDNA antibodies, hs-CRP, and serum component (C3 or C4). [d]Patient-reported data are collected at the final standard-of-care visit before the index date, after which patient reporting occurs via the mobile app. [e]Medical events of interest include anaphylaxis following anifrolumab treatment, herpes zoster (and vaccination), serious infections, COVID-19 infection (and date(s) and type(s) of vaccination), major adverse cardiovascular events (including [cardiovascular] death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures, urgent cerebrovascular revascularization, arrhythmia [not associated with ischemia], peripheral arterial event, venous thromboembolic event, and other nonfatal cardiovascular events), malignancies, and pregnancy.

ADR, adverse drug reaction; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; eCRF, electronic case report form; EQ-5D-5L, EuroQol 5-Dimension 5-Health Questionnaire 5 Level; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; hs-CRP, high-sensitivity C-reactive protein; LupusQOL, Lupus Quality of Life; NRS, numerical rating scale; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; rSFI, revised Safety of Estrogens in Lupus National Assessment-SLEDAI flare index; SAE, serious adverse event; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, Systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; WPAI:Lupus, Work Productivity and Activity Impairment: Lupus.

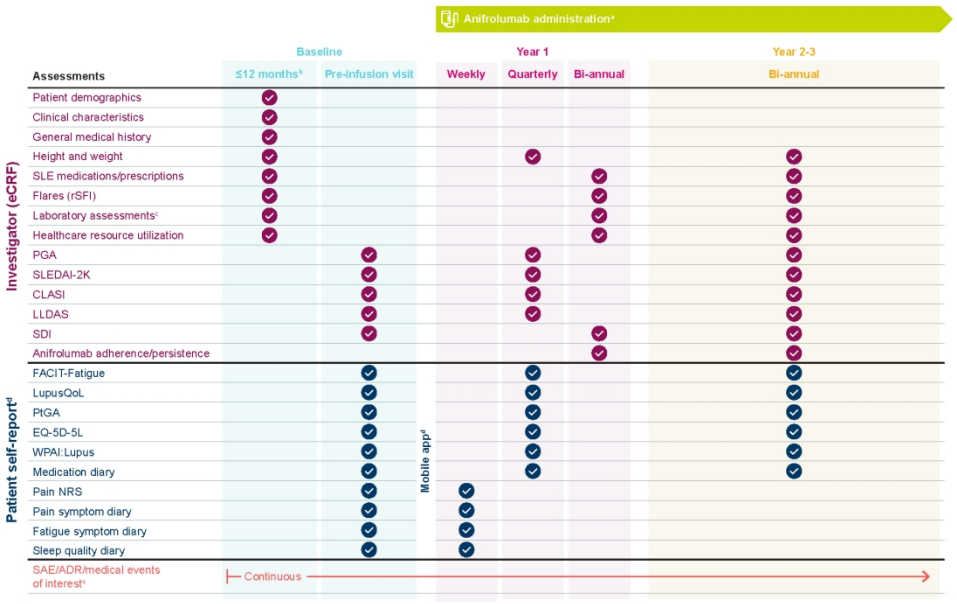

Figure 1

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