STUDY REPORT SYNOPSIS

Systemic Lupus Erythematosus (SLE) Prospective Observational Cohort Study (SPOCS)

Prospective observational cohort of patients with moderate to severe SLE to characterize cross-sectional and longitudinal disease activity, treatment patterns and effectiveness, outcomes and comorbidities, healthcare resource utilization, and the impact of SLE on quality of life by type I interferon gene expression

Milestones:
Q1 2017: Final Protocol
Q2 2017: First Patient In
Q4 2017: Protocol Amendment 1
Q2 2019: Protocol Amendment 2
Q4 2019: Last Patient In
Q2 2020: First Patient Out
Q4 2022: Last Patient Out
Q3 2023: Final Report

Phase of development: N/A

Sponsor: AstraZeneca

Author: PPD

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

Background/rationale:

Systemic lupus erythematosus (SLE) is a chronic, multisystem, and often progressive autoimmune disorder with heterogeneous manifestations. Although the etiology remains unknown, the pathogenesis of SLE involves genetic, immunologic, hormonal, and environmental factors. The clinical manifestations of SLE range from minor mucocutaneous or musculoskeletal involvement to severe life-threatening damage to major organ systems, including the central nervous system (CNS), renal, cardiovascular (CV), and pulmonary systems.

The global incidence and prevalence of SLE vary widely, owing to inherent variation in population demographics, environmental exposures, and socioeconomic factors. The global incidence of SLE ranges between 1.5 and 11 per 100,000 person-years, and the global prevalence ranges from 13 to 7,713.5 per 100,000 individuals. Women and non-White populations are consistently more affected by SLE across international regions.

The burden of SLE is determined by disease severity, duration of flares, and resulting organ damage from disease activity, comorbidities, and/or SLE therapies. Disease manifestations lead to a significant reduction in physical function and health-related quality of life (HRQoL), with life expectancy reduced by approximately 10 years. SLE is also associated with substantial disease-related costs. Earlier diagnosis and treatment may improve health outcomes and reduce HCRU and costs.

In patients with SLE, activation of the type I interferon (type I IFN) pathway has been associated with disease activity and serologic activity, including the presence of autoantibodies and low complements. Peripheral blood cells from patients with SLE exhibit a striking pattern of upregulation of IFN-induced. These observations not only strongly suggest that the type I IFN pathway plays an important role in the pathogenesis of SLE, but they also highlight the role of the innate immune system in SLE. IFN levels can be difficult to measure directly and hence, type I IFN activity may be more reproducibly assessed by evaluating type I IFN-inducible gene expression, or evidence of genes that are induced or repressed by type I IFN.

Although there are established SLE registries, there is limited information on the type I IFN gene signature within these registries. Type I IFN gene signature is not collected per clinical practice and due to the specific testing methods required, there is lack of appropriately collected and stored blood samples for the analysis.

The SLE Prospective Observational Cohort Study (SPOCS) sought further understanding and characterization of the SLE patients and their journey with respect to disease activity, treatment patterns and effectiveness, SLE outcomes and comorbidities, HCRU, and the impact of SLE on quality of life. SPOCS collected blood samples to assess type I IFN gene signature distribution, including the longitudinal gene expression

Objectives:

Objectives are described at baseline and during follow-up, overall and by baseline type I IFN gene signature test status.

The Descriptive Objectives were to describe: Demographic and clinical characteristics, SLE disease components, Disease activity, Flares, HCRU, SLE medications used, Patient -Reported Outcomes, the prevalence of comorbidities (at baseline) and the incidence of medical events (during follow-up).

The Cross-sectional Objectives were to explore the associations between: baseline demographics and baseline type I IFN status; baseline comorbidities and baseline type I IFN status; baseline SLICC/ACR DI and baseline SLEDAI-2K total score; history of flares (SELENA-SLEDAI) prior to baseline and baseline SLEDAI-2K total score; baseline HCRU and baseline SLEDAI-2K total score; baseline medication including SLE medication, medication class and OCS cumulative dose and baseline SLEDAI-2K total score; baseline SLEDAI-2K score and organ system involvement, and baseline type I IFN status; baseline type I IFN status and baseline disease activity measures, including SLEDAI-2K total score, SLE flares and severity, and SLICC/ACR DI.

The Longitudinal Objectives were to explore the longitudinal association between:

- Change in disease activity outcomes (including SLEDAI-2K total score, clinical SLEDAI-2K total score, SLICC/ACR DI, PGA, and patient global assessment [PtGA]) from baseline to 6-, 12-, 18-, 24-, 30- and 36-month time points by baseline type I IFN gene signature status

- Baseline type I IFN gene signatures and disease activity outcomes (including SLEDAI-2K, SLE flares and severity, SLICC/ACR DI as binary variable) during follow-up

- The incidence of overall and HCRU (including SLE-related hospitalizations, emergency room visits, specialist visits, and general practitioner's visit) during follow-up by baseline SLEDAI-2K score categories

- Baseline medication of OCS cumulative dose (>0 to ≤7.5 mg/day vs >7.5 mg/day, and as a continuous variable [1 mg/day]) and occurrence of new organ damage (SLICC/ACR DI) during follow-up

- Baseline medication of OCS cumulative dose (>0 to ≤7.5 mg/day vs >7.5 mg/day) and occurrence of new organ damage (SLICC/ACR DI) during follow-up, but censoring when patient changes OCS dose category

- Baseline medication of OCS cumulative dose continuous and occurrence of new organ damage (SLICC/ACR DI) during follow-up, but censoring at the time of OCS dose change

- Baseline SLEDAI-2K and occurrence of new organ damage (SLICC/ACR DI) during follow-up

- The incidence of overall and HCRU (including SLE-related hospitalizations, emergency room visits, specialist visits, and general practitioner's visit) by each timepoint of interest during follow-up, by baseline flares (SELENA-SLEDAI)

- The costs of HCRU (including SLE-related hospitalizations, emergency room visits, specialist visits, and general practitioner's visit) at each timepoint of interest during follow-up, by baseline flares (SELENA-SLEDAI).

- Flares (SELENA-SLEDAI) at each timepoint of interest during follow-up, by LLDAS

- Flares (SELENA-SLEDAI) at each timepoint of interest during follow-up, by remission

- Change in HRQoL and health status, using the following instruments, from baseline to 6, 12, 18, 24, 30, and 36 months, by LLDAS at Month 6 as baseline:

    - Short Form Health Survey (SF-36) V2 (Physical Component Score [PCS], Mental Component Summary [MCS], and individual domain scores)

    - Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (total score and individual items)

    - EuroQol 5 Dimensions – 5 Levels (EQ-5D-5L) (index value, EuroQol 5 Visual Analogue Scale [EQ-VAS] value, and individual domains)

    - Lupus Quality of Life (LupusQoL) (individual domain scores)

    - PtGA (VAS score)

    - Work Productivity and Activity Impairment (WPAI) (domain scores)

    - Personal Health Questionnaire Depression Scale (PHQ-8) (total score and individual items)

- Change in HRQoL and health status (SF-36 V2, FACIT-F, EQ-5D-5L, LupusQoL, PtGA, PHQ-8) from baseline to 6, 12, 18, 24, 30, and 36 months, by remission at the 6-month timepoint as baseline.

Study design:

SPOCS was an international, multicenter, prospective, observational, cohort study of adult patients with moderate to severe SLE in Australia, Canada, France, Germany, Italy, Spain, United Kingdom (UK), and USA. The disease had to be confirmed by ACR or SLICC criteria, with at least one positive serology of ANA or dsDNA in a lifetime, as defined in local/country laboratory reference ranges, and a minimum of 6 months of systemic SLE treatment, beyond NSAIDs and analgesics.

The overall study period was planned for approximately 5 years, which included a 2-year enrollment period for active recruitment, and a maximum 3-year follow-up period for each patient. After the baseline visit, all patients continued in the study until a maximum of 3 years of follow-up, or were lost to follow-up or death, whichever occurred first.

There were no visits or treatments mandated in the study. Patients were followed up according to local routine practice, and biannual (every 6 months) follow-up visits were expected. Clinical data were collected at each visit, with most data being part of guideline-recommended routine management of patients with SLE. It was acknowledged that some of the variables of interest in the study were not a part of each site/physician's standard practice. The PRO questionnaires were completed by patients during site visits, and blood samples were collected for type I IFN gene signature test (analyzed in the AZ-specified central laboratory), coinciding with a routine blood sample collection.

Data source:

Data for enrolled patients were obtained through a combination of primary collection methods, including electronic case report forms (eCRFs), PRO instruments, and laboratory assessments, as well as routinely collected existing data from the Australian Lupus Registry (ALR). Data were collected at study entry (at the baseline visit) and at biannual follow-up visits (approximately during the 3-year follow-up period). A total of 114 study sites across Australia, Canada, France, Germany, Italy, Spain, UK, and USA participated in the study (with 113 sites enrolling at least 1 patient).

Study population:

A total sample size of 1500 patients were initially planned and was deemed adequate to effectively characterize the main study outcomes. However, this sample size was amended to 900 patients because of slow accrual of eligible patients.

Inclusion criteria:

Patients enrolled in SPOCS had to meet the following criteria:

- Adult patients aged 18 years or older
- Physician confirmation that the patient met ACR or SLICC classification criteria for SLE
- Current or historic positive serology of ANA or dsDNA as defined in local/country laboratory reference ranges
- Minimum treatment duration of 6 months for active SLE with systemic SLE treatment beyond NSAIDs and analgesics
- Moderate to severe SLE; SLEDAI-2K criteria: modified SLEDAI-2K score ≥4 points, defined as the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results, including immunologic measures and lupus headache, or SLEDAI-2K total score ≥6 points
- Patients who understood the requirements of the study and provided written informed consent form (ICF)

Exclusion criteria:

Patients meeting any of the following criteria were ineligible for enrollment in SPOCS:

- Patients actively enrolled in interventional trials involving investigational agents
- Patients with active severe lupus nephritis, a history of a renal biopsy in the last year showing active class III or class IV ± class V lupus nephritis, and/or urine protein:creatinine ratio >1 mg/mg based on random urine collection at baseline visit
- Patients unable to complete study measures

Statistical methods:

Categorical variables were summarized as the number of patients and percentage (%) of patients within each category. Percentages were calculated over the number of subjects with available (non-missing) data. The count of missing observations was also reported. Continuous variables were summarized using the mean, standard deviation (SD), median, first and third quartiles, minimum, maximum, and the number of non-missing and missing observations. Unless otherwise specified in the description of the analyses, a two-sided 95% confidence interval (CI) was considered as a default (alpha=5%).

Univariable and multivariable linear regression models were used to assess the association between potential risk factors and continuous outcomes. The models estimated the regression coefficients associated with each risk factor and their 95% CI. Logistic regression models were used to assess the association between potential risk factors and dichotomous outcomes. The models estimated the odds ratio (OR) associated with each risk factor and its 95% CI.

The cumulative incidence of events of interest (%) and its 95% CI were computed at each time point using the Kaplan-Meier method in subgroups of interest. The median time to event, if available, and its 95% CI were provided for each group. The log-rank test was used to test whether there was a difference between groups. Patients were right censored at the end of study date.

Linear mixed effect models for repeated measures (MMRM) using PROC MIXED were used to assess the longitudinal association between potential risk factors and the continuous outcomes. Logistic generalized linear mixed models using PROC GLIMMIX were used to assess the longitudinal association between potential risk factors and the dichotomous outcomes. The covariance was adjusted using a _RESIDUAL_ under random statement. The models estimated the OR associated with each risk factor and its 95% CI. Negative binomial regression with offset variable models were used to assess the association between count outcomes and potential risk factors. The models estimated Incidence rate ratios associated with each risk factor and its 95% CI.

Gamma regression (using PROC GENMOD with log link and gamma distribution) models were used to assess the association between cost outcomes and potential risk factors. The models estimated the regression coefficient associated with each risk factor and its 95% CI.

Results:

Site descriptions and patient disposition:

Patients were enrolled between 28 June 2017 and 01 December 2019 and were followed for 3 years. A total of 1057 patients were screened for participation in the study and the final analysis included data from 826 patients (78.1% of the screened population). Among them, 309 (37.4%) were from USA which had a greater representation of patients than any other country. There were 85 patients (10.2%) who discontinued the study within the first 6 months of follow-up; at subsequent time points (every 6 months), the discontinuation rate remained below 10% among participants still enrolled in the study. Owing much to the COVID-19 pandemic, only 21.7% of the 826 enrolled patients completed the 7 planned follow-up study visits (ranging from 3.1% among the 96 patients in the UK, 37.8% among the 74 patients in Germany, and 60.8% among the 51 patients in Australia).

Overall, a total of 114 sites (28 in USA and 86 in Canada, Europe, and Australia) participated in the study. Sites with summary data (n=104) included university hospitals (n=60, 58.3%), general hospitals (n=20, 19.4%), private practices (n=18, 17.5%), centers of excellence (n=4, 3.9%), and 1 site classified as not-belonging to any of these categories.

Impact of the COVID-19 pandemic

Overall, 18 (2.2%) and 1 (0.1%) patient had at least one COVID-19 related major and minor protocol deviations. Overall, 109 (13.2%) patients had at least one remote visit due to COVID-19 pandemic and 59 (7.1%) patients discontinued due to "Global/Country" situation.

Patient demographics and baseline clinical characteristics

Most patients were female (n=770, 93.2%), and the mean (SD) age at study entry was 45.2 (13.91) years, ranging from 18 to 88 years; 135 (16.3%) patients were 60 years of age or older. The majority of the patients with available data were White (n=544, 65.9%), followed by Black or African American (n=123, 14.9%). BMI was available for 747 enrolled patients, with a mean (SD) BMI of 27.2 (7.09) kg/m^2; 203 (27.2%) patients had a BMI ≥30 kg/m^2 and were classified as obese. The overall mean (SD) systolic and diastolic blood pressure was 123.3 (17.06) mmHg and 76.3 (10.76) mmHg, respectively.

At baseline, 531 patients with available data (70.8%) expressed a high type I IFN gene signature and 219 (29.2%) expressed a low type I IFN gene signature. Among patients with a SLEDAI-2K total score, 344 had a score <10 (including 31 patients with SLEDAI-2K total score <6), and 247 had a score ≥10. Demographic and clinical characteristics were generally similar across SLEDAI-2K score categories. There were 768 (93.0%) patients with baseline data that allowed the estimation of average daily OCS prednisolone-equivalent doses, of whom 311 (40.5%) had no OCS use reported, and 457 (59.5%) had at least some daily OCS use data (>0 mg/day). Compared with patients reporting no OCS, patients with a total or average daily OCS prednisolone-equivalent dose >7.5 mg/day tended to be younger and have a lower percentage of White participants.

Medical history

Overall, 703 patients (85.1%) had at least 1 comorbidity reported at baseline, which included 268 patients from USA (with a country comorbidity prevalence of 86.7%) and 435 patients from non-USA countries (with a non-USA comorbidity prevalence of 84.1%). The condition that was most reported within the 12 months prior to study entry was SLE or non-SLE joint disease (n=515, 66.1%).

Most patients (62.3%) did not report any substance use (USA: n=197, 63.8%; and non-USA countries: n=288, 61.4%, including Australia: n=4, 100%). The percentage of patients reporting current or former alcohol consumption was comparable among patients in USA and non-USA countries (USA: n=56, 18.1%; non-USA countries: n=85, 16.4%). The percentage of current nicotine users was comparable by region (USA: n=17, 5.5%; non-USA countries: n=47, 9.1%).

SLE disease characteristics at baseline

Overall, most of the patients had either SLEDAI-2K total score ≥6 and <10 (53.0%) or ≥10 (41.8%) with median (Q1-Q3) 8.0 (6.0-12.0) at baseline. A total of 339 (44.1%) of patients had no OCS at baseline. The median (Q1-Q3) baseline total and average daily dose of OCS prednisolone-equivalent were 7.5 mg/day (5.0-12.5) and 5.0 mg/day (1.4-7.5), respectively. Most of the patients met ACR criteria (n=656, 89.6%) and SLICC criteria (n=496, 93.9%) and the SLE disease severity was moderate (n=313, 53.0%) or severe (n=247, 41.8%) at baseline.

Disease Activity

At most of the time points, there was no difference in median PGA-VAS scores between patients expressing a high and a low baseline IFN gene signature, and minimal exceedance beyond the minimal clinically important difference (MCID) of 0.3 was observed. The majority of patients in either gene signature group reported a decrease in PGA-VAS score compared to baseline at most of the visits.

At all time points, the proportion of patients reporting a flare since preceding time point was higher for patients from USA compared with non-USA countries except at 6 months when it was similar in both regions. At most of the timepoints, the proportion of patients who experienced a total of 1 flare was higher in patients expressing a low type I IFN gene signature compared with patients expressing a high type I IFN gene signature.

At all time points, most of the patients did not achieve LLDAS and the 3 most common reasons for this included a PGA-VAS score >1, SLEDAI-2K score >4, and new lupus disease activity since previous assessment. At most of the time points, the proportion of patients achieving LLDAS was either higher in patients expressing a low type I IFN gene signature compared with patients expressing a high type I IFN gene signature or was similar in both groups. Less than 20% of patients achieved LLDAS and less than 15% achieved remission during the entire 36 months of follow-up.

Among the patients with missing type I IFN gene signature at baseline, the percentage of patients in the low type I IFN gene signature category was lower (with an approximate 35% vs 65% distribution) for most of the follow-up visits, except for the second year of follow-up (including the 18-month and the 24-month time points) where the distribution was reversed (to an approximate 60% vs 40% distribution). The distribution of low and high type I IFN gene signature categories for the patients in each of the medication classes remained stable over the follow-up period.

Organ damage burden

At most of the visits, the 5 most reported items of the SLICC/ACR DI were deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) and muscle atrophy or weakness from the musculoskeletal category, scarring chronic alopecia from the skin category, any cataract ever from the ocular disease category, and cognitive impairment from the neuropsychiatric category. The median SLICC/ACR DI score at most of the visits was high among patients expressing low than those with high type I IFN gene signatures (except 12-month). The mean SLICC/ACR DI score was high among patients expressing low than those with high type I IFN gene signatures at all visits. The mean (SD) change in SCLICC/ACR from baseline was similar in high and low type I IFN gene signature group at all visits.

At most of the time points, the 5 most frequently reported SLEDAI-2K components were arthritis, increased DNA binding, rash, low complement, and alopecia. The largest proportion of patients expressing a high or low type I IFN gene signature had a lower SLEDAI-2K total score at most of the visits.

SLE Medication

Most of the patients received more than 3 SLE medication types at each timepoint. Antimalarials, corticosteroids, and immunosuppressants were the 3 most prescribed classes of drugs. The proportion of patients who had discontinued at least 1 SLE medication within the 12 months prior to baseline was higher in non-USA countries than in USA. The proportion of patients prescribed at least 1 SLE medication was similar between patients expressing a high or low baseline type I IFN gene signature.

Healthcare resource utilization costs

The proportion of patients who had an SLE-related hospitalization was lower among patients in the USA than in patients from non-USA countries at most of the visits. Most patients who had been hospitalized, were discharged between baseline and the respective follow-up time point. At most of the time points, the median number of hospitalizations was similar for patients expressing high and low type I IFN gene signature at baseline, however, the median hospitalization duration was higher among patients expressing high type 1 IFN gene signature at baseline.

Patient-reported health outcomes

SF-36 V2

At most of the time points, median PCS and MCS scores differed by both region and by country, with non-USA countries having a higher score than the USA. At most of the time points, the median PCS score was lower in patients expressing a low type I IFN gene signature compared to

patients expressing a high type I IFN gene signature. However, the median MCS baseline score was similar in patients expressing a low and high type I IFN gene signature and across each timepoint. The median score changes for PCS and MCS were similar between the high and low type I IFN gene signature groups. Exceedances of MCID scores of 2.3 for PCS was observed at 24-, 30-, and 36-months follow-up and while MCID score of 2.3 for MCS was never observed.

FACIT-F

At most of the time points, fatigue median scores were higher in non-USA countries than in the USA. Within Europe, median scores were consistently lower in the UK and higher in Italy. No changes in absolute median fatigue scores from baseline to follow-up visits were seen for both high and low type I IFN gene signature patients whereas the MCID defined is 4 points. At most of the time points, median fatigue scores were lower in patients expressing a low baseline type I IFN gene signature compared to patients expressing a high baseline type I IFN gene signature.

EQ-5D-5L/ EQ-VAS

At most of the time points, for both EQ-VAS and EQ-5D-5L Index median scores, no regional differences were observed; however, EQ-VAS median scores showed variability between European countries, with UK having the lowest scores. At most of the visits, EQ-VAS and EQ-5D-5L Index median score was higher in patients with high type I IFN gene signature compared to patients with low type I IFN gene signature and the median changes between visits were consistent across regions/countries and type I IFN gene signature groups. The median score changes for EQ- VAS were differing beyond the MCID score of ≥10 points and it was 0 at all the time points against an MCID of 0.037 to 0.069 for EQ-5D-5L.

LupusQoL

At most of the time points, regional differences were observed, with a trend for higher median scores in non-USA countries compared to the USA; country differences within Europe were consistently observed as well, with the UK consistently having the lowest scores and Italy having the highest scores within the region for all LupusQoL domains. At most of the time points, median score value was higher for patients with high expression of type I IFN gene signature compared to patients with low expression of type I IFN gene signature for most of the LupusQoL domains. The overall median score change between visits was zero for all the domains and none of the domain's change score met the MCID cut-offs. These changes were consistent across regions/countries and type I IFN gene signature groups.

PtGA VAS

At most of the time points, no country or regional differences were observed. The median PtGA VAS score was lower among patients expressing a high type I IFN gene signature compared to patients expressing a low type I IFN gene signature. The median change in scores exceeded the MCID cut-off of ≥1 point (20%) at all timepoints during the follow-up.

WPAI

At most of the time points, median WPAI activity impairment differed between countries, with the highest impairment in the UK and lowest in Italy. WPAI activity impairment median scores were lower in patients expressing a high type I IFN gene signature than in patients with low baseline type I IFN gene signature. The median score changes between visits were zero for most WPAI domains. The median score changes between visits were not clinically significant for all WPAI domains, as the MCID is defined as 7%.

PHQ-8

At most of the time points, median PHQ-8 was the highest among UK patients and lowest among patients from Italy. The median PHQ-8 score was higher for low IFN gene signature patients compared to the median score for patients with high IFN gene signature. There were no differences observed in changes in PHQ-8 scores at different visits compared to baseline scores by region or IFN gene signature and differing beyond the MCID of 3 points defined for this PRO.

Medical events of special interest

No pattern or systematic difference in the cumulative incidence of any medical event was observed according to type I IFN gene signature status. The overall incidence and the incidence stratified by age categories tended to decrease over the study period, probably related to the reduction in the population still enrolled in the study and the censoring of the patients that had already experience one of the medical events.

Women´s health

Among the 770 enrolled female patients at baseline, there were 756 previous pregnancies. The median number of pregnancies per female patient was 2 (Q1-Q3: 0-3), with this number being the same in both the USA and non-USA patients. Overall, 224 (29.6%) females reported never having previously been pregnant, whilst 140 (18.5%), 173 (22.9%) and 219 (29.0%) females reported 1, 2 and ≥3 previous pregnancies.

Association analyses

At baseline, in adjusted analyses, the high type I IFN gene signature status was associated with younger age, Black or Asian racial makeup, being from a USA country, being obese, longer duration of SLE diagnosis, presence of renal disease, and absence of metabolic syndrome and SLE and non-SLE joint disease. In adjusted regression analyses, high type I IFN status at baseline was associated with reduced number of severe flares (OR 0.46; 95% CI 0.26, 0.83). In longitudinal analyses, high type I IFN status at baseline was associated with less organ damage (measured by the SLICC/ACR Damage Index) during follow-up (overall OR 0.61; 95% CI 0.38, 0.97).

High type I IFN status at baseline was also associated with lower PtGA VAS scores during follow-up (overall estimate for the continuous score -7.62; 95% CI -11.74, -3.49; overall estimate for the continuous score adjusting for baseline PtGA VAS values -6.34; 95% CI -10.04, -2.65). The adjusted models for PGA-VAS did not reach statistical significance. Patients with high type I IFN status at baseline had increased likelihood of severe flares during follow-up (overall OR for baseline flare rate 2.52; 95% CI 1.00, 6.35).

When looking at association models between baseline OCS use and SLICC/ACR DI, the overall adjusted model estimated an OR 1.89 (95% CI 1.14, 3.15) for at least 1 organ damage during follow-up for the patients with >7.5 mg/day average daily OCS dose at baseline (compared to

>0- ≤7.5 mg/day). There was some evidence that having 1 or more flares reported at baseline increased the likelihood of an outpatient visit during follow-up, with an adjusted OR 1.23 (95% CI 0.99, 1.52).

Limitations:

Several factors should be considered in the interpretation of this study. Firstly, as this was an observational study without protocol-mandated visits, complete data at all timepoints could not be guaranteed. However, the availability of data over the follow-up period was further reduced due to a high dropout rate and COVID-19 pandemic disruptions, and it cannot be ruled out that longitudinal analyses may have been affected by selective dropout and/or survivor bias. Secondly, as SPOCS included a large proportion of USA patients, the overall study results are likely biased towards the SLE patient experience in the USA.

Regarding analytical methodology, the type I IFN gene signature was analyzed as a binary variable (high/low); a continuous gene expression variable could have been assessed, allowing for more flexible quantitative assessments. Additionally, baseline total SLEDAI-2K total scores were missing for about one third of the patients at baseline; this reduced the overall sample available for longitudinal analyses for the total score and created a "missing/unknown score" group (with potentially a more heterogeneous makeup) that was included as a separate category in all subgroup analyses. Finally, association analyses were purely exploratory, and p-values considered statistically significant ($p<0.05$) should be interpreted with caution given the multiple comparisons and large number of statistical tests performed.

Conclusion:

SPOCS enrolled 826 patients with moderate to severe SLE across North America, Europe and Australia. Approximately two-thirds of enrolled patients at baseline expressed high type I IFN gene signature. IFN gene signature status was relatively stable over time, with most of the population remaining in the same category over time. SLEDAI-2K, PGA-VAS, and PtGA values reduced during early follow-up but remained stable for the remainder of the follow-up. Disease activity patterns over time (as assessed by SLEDAI-2K, PGA-VAS, and PtGA) showed no clear differences between patients expressing high and low type I IFN gene signature. Nearly 20% of patients had new organ damage after 12 months. Organ damage data (SLICC/ ACR DI) showed higher damage in patients expressing low type I IFN gene signature compared to high type over each time point. Patients taking OCS average daily dose of >7.5 mg/day at baseline was associated with 89% increased risk of organ damage during the 3-year follow-up as compared to patients taking OCS average daily dose of >0 - ≤7.5 mg/day at baseline. Less than 20% of patients achieved LLDAS and less than 15% achieved remission during the entire 36 months of follow-up. The percentage of patients achieving LLDAS or remission during follow-up did not differ between type I IFN gene signature groups except at 24-month follow-up, where a

significantly higher percentage of patients achieved LLDAS in the low type I IFN gene signature group than in the high group

Patients with high type I IFN gene signatures at baseline had a higher probability of moderate/severe flares and a higher number of SLE-related hospitalizations during follow-up. The increase in mean daily OCS dose in the first 6 months was maintained through 36 months despite standard therapy, stable antimalarial use, and moderate increases in use of biologics and immunosuppressants. The proportion of OCS use was largely stable over time, those on OCS >7.5 mg/day increased initially and then declined but did not return to the baseline level. Patients with IFNGS-high status used more immunomodulatory therapy compared with those with IFNGS-low status. In general, patient-reported HRQoL measured by SF-36 V2, FACIT-F, EQ-5D-5L and LupusQoL showed better QoL measures in patients expressing high type 1 IFN signatures compared to those expressing low type across each timepoint.

Overall, SPOCS provided a wealth of real-world data on SLE patients and their outcomes over time.