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Protocol for Study M19-130

Systemic Lupus Erythematosus: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

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FULL TITLE: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

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1 SYNOPSIS

Title: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus	
Background and Rationale:	Elsubrutinib (ABBV-105) is a novel, covalent Bruton's tyrosine kinase (BTK) inhibitor being developed for the treatment of immune-mediated inflammatory diseases including systemic lupus erythematosus (SLE). Autoantibody generation by pathogenic B cells, which is dependent on B cell receptor signaling, is a hallmark of autoimmune diseases, such as RA and SLE. BTK is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of RA, SLE, and other autoimmune diseases. BTK is required for the propagation of pro-inflammatory signals downstream of immunoreceptors that promote autoimmune disease pathogenesis. The potential clinical value of BTK inhibition has been supported by studies in preclinical models of lupus. These have demonstrated marked reductions of proteinuria in mouse models of lupus, consistent with the effect of BTK inhibition on autoantibody production and/or myeloid cell activation. Upadacitinib (ABT-494), an oral Janus kinase (JAK) inhibitor that displays unique selectivity for the Janus kinase 1 (JAK1) receptor, is approved for the treatment of adult patients with RA and is being developed for Crohn's disease, ulcerative colitis, psoriatic arthritis, active axial spondyloarthritis, giant cell arteritis; adult and pediatric patients with moderate to severe atopic dermatitis; and pediatric patients with juvenile idiopathic arthritis. Elsubrutinib and upadacitinib given alone or in combination with each other (as the ABBV-599 [elsubrutinib/upadacitinib] combination therapy) are predicted to be effective in decreasing signs and symptoms associated with active SLE in patients.
Objective(s) and Endpoint(s):	The main objective is to evaluate the safety and efficacy of elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination vs placebo for the treatment of signs and symptoms of SLE at 24 and 48 weeks in subjects with moderately to severely active SLE and to define dose(s) for further development. **Efficacy Endpoints** Primary Endpoint: 1. Achievement of SLE Responder Index (SRI)-4 and steroid dose ≤ 10 mg prednisone equivalent once a day (QD) at Week 24 SLE Responder Index (SRI)-4 is defined as ≥ 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score without worsening of the overall condition (no worsening in Physician's Global Assessment [PhGA], < 0.3 point increase) or the development of

	significant disease activity in new organ systems (no new British Isles Lupus Assessment Group ([BILAG]) A or > 1 new BILAG B). Secondary Endpoints: 1. Achievement of SRI-4 at Week 24 2. Achievement of BILAG-Based Combined Lupus Assessment (BICLA) response at Week 24 3. Achievement of Lupus Low Disease Activity State (LLDAS) at Week 24 4. Steroid burden, assessed as change from Baseline at Week 24 5. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI Flare Index (SFI), assessed by number and types of flare per subject through Week 24 Additional Endpoints (for efficacy, at all visits unless otherwise noted): 1. Achievement of SRI-4 2. Achievement of SRI-5, -6, -7, -8 and steroid dose ≤ 10 mg prednisone equivalent QD at Weeks 24 and 48 3. Achievement of SRI-5, -6, -7, -8 4. Achievement of BICLA response 5. Achievement of LLDAS 6. Achievement of ≥ 4-point decrease in SLEDAI-2K from Baseline 7. Steroid burden, assessed as change from Baseline 8. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by SELENA SFI, assessed by number and types of flare per subject through Week 24 and Week 48 9. Time to first flare by SELENA SFI after first study drug administration up to Week 24 and Week 48 10. Achievement of 50% reduction of tender or swollen lupus joints defined as ≥ 50% decrease in either tender or swollen joints (of those starting with total ≥ 6 affected joints) 11. Achievement of 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score (of those starting with CLASI ≥ 10) 12. Change in SLEDAI-2K from Baseline 13. Change in BILAG from Baseline 14. Change in PhGA from Baseline 15. Change in Patient Global Assessment (PtGA) from Baseline 16. Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Weeks 2, 12, 24, and 48 17. Change from Baseline in 36-Item Short Form Health Survey (SF-36) at Weeks 2, 12, 24, and 48 18. Change from Baseline Lupus Quality of Life questionnaire (LupusQoL) at Weeks 2, 12, 24, and 48

	19. Change from Baseline Pain Numerical Rating Scale (NRS) at Weeks 2, 12, 24, and 48 **Safety Endpoints** Routine safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.
Investigator(s):	Multi-center
Study Site(s):	Approximately 140 sites worldwide
Study Population and Number of Subjects to be Enrolled:	Approximately 325 adult male or female subjects who are 18 to 65 years of age, inclusive, and have a clinical diagnosis of SLE at least 24 weeks prior to Screening, meeting at least 4 of the 11 revised Criteria for Classification of SLE according to the 1997 Update of the 1982 American College of Rheumatology (ACR) OR meeting at least 4 of the 2012 Systemic Lupus Erythematosus International Collaborating Clinics (SLICC) classification criteria, including at least 1 clinical criterion and 1 immunologic criterion. Subjects must have active SLE by SLEDAI-2K ≥ 6 as reported and independently adjudicated (clinical score ≥ 4, excluding lupus headache and/or organic brain syndrome) at Screening and Baseline. If 4 points of the required entry points are for arthritis, there must also be a minimum of 3 tender and 3 swollen joints.
Investigational Plan:	The study is designed to investigate the safety and efficacy of elsubrutinib and upadacitinib given alone or as ABBV-599 (elsubrutinib/upadacitinib) combination in subjects with moderately to severely active SLE despite standard of care therapy. The study duration will include a 42-day maximum screening period, a 48-week randomized, placebo-controlled, double-blind, parallel-group treatment period, and a 30-day follow-up phone call. The Week 24 Primary Analysis will be performed when all subjects have completed the Week 24 visit or have discontinued the study. Sites and subjects will remain blinded throughout the study. The study team will remain blinded until the Week 24 Primary Analysis. Study visits will be conducted at Screening, Baseline, and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48/Premature Discontinuation (PD). A 30-day follow-up phone call from the last dose of study drug should occur to determine the status of any ongoing adverse events (AEs)/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs. A long-term extension (LTE) study will be conducted under a separate protocol (LTE Study M20-186) at sites where it is permitted by the local Competent Authority and Ethics Committee. Subject rollover from the initial randomized portion of the study will occur at Week 48. A planned unblinded interim analysis was performed when 50% of the planned subjects completed their Week 24 assessments. The objective

	of this analysis was to reassess the treatment regimens in Study M19-130 and the benefit/risk for rollover into LTE Study M20-186. The interim analysis was performed by an independent team at AbbVie that is separate and apart from the blinded study team. The Study M19-130 team will remain blinded through the Week 24 Primary Analysis. An Interim Unblinding Plan (IUP) was developed separately describing the analyses to be performed and included execution logistics, an unblinded analysis team, and the data chain of custody to protect the integrity of the study. An Internal Executive Review Committee (IERC) reviewed the interim unblinded results as specified in the IERC charter and decided which treatment group(s) should be continued in Study M19-130 and for rollover into LTE Study M20-186. Study sites and subjects remained blinded to treatment assignment in Study M19-130 and LTE Study M20-186 throughout the studies.

Key Eligibility Criteria:	• Adult male or female, 18 to 65 years of age, inclusive, at Screening.
	• Clinical diagnosis of SLE at least 24 weeks prior to Screening, meeting at least 4 of the 11 revised Criteria for Classification of SLE according to the 1997 Update of the 1982 ACR OR meeting at least 4 of the 2012 SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion.
	• At Screening, must have at least one of the following:
	  • Anti-nuclear antibody test (ANA)+ (titer ≥ 1:80)
	  • Anti-double stranded DNA (anti-dsDNA)+
	  • anti-Smith+
	• SLEDAI-2K ≥ 6 despite background therapy as reported and independently adjudicated (clinical score ≥ 4, excluding lupus headache and/or organic brain syndrome) at Screening. If 4 points of the required entry points are for arthritis, there must also be a minimum of 3 tender and 3 swollen joints. If subject has rash and Principal Investigator (PI) considers it to be attributable to SLE, subject must consent to skin photograph collection for adjudication. Must be re-confirmed at Baseline visit.
	• PhGA ≥ 1 during screening period.
	• Must be on background treatment, stable for 30 days, at Baseline, and throughout the study, with prednisone (or prednisone equivalent) (≤ 20 mg), antimalarials, azathioprine (≤ 150 mg), mycophenolate (≤ 2 g), leflunomide (≤ 20 mg), cyclosporine, tacrolimus, and/or methotrexate (MTX) (≤ 20 mg).
	  • No combinations of the above with immunomodulators other than prednisone (or equivalents) and antimalarials.

	• Must not be using intravenous (IV) or intramuscular (IM) corticosteroids greater than or equal to a 40 mg prednisone-equivalent bolus within 30 days of planned randomization.
Study Drug and Duration of Treatment:	Study drug will be taken orally as 3 capsules of elsubrutinib and/or matching placebo and 1 film-coated tablet of upadacitinib and/or matching placebo once daily with or without food for 48 weeks. Approximately 325 subjects who meet eligibility criteria will be randomized in a 1:1:1:1:1 ratio to one of 5 treatment groups, as follows Group 1: Elsubrutinib 60 mg QD and upadacitinib 30 mg QD (n = 65) Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD (n = 65) Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD (n = 65) Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD (n = 65) Group 5: Elsubrutinib placebo QD and upadacitinib placebo QD (n = 65)
Date of Protocol Synopsis:	25 October 2021

2 INTRODUCTION

2.1 Background and Rationale

Why This Study Is Being Conducted

The ABBV-599 (elsubrutinib/upadacitinib) combination is an innovative combination therapy that targets non-overlapping signaling pathways implicated in systemic lupus erythematosus (SLE). As described below, Janus kinase 1 (JAK1) inhibition via upadacitinib is expected to disrupt T cell activation and Type I interferon (IFN) signaling, whereas elsubrutinib (ABBV-105) is expected to inhibit B cell activation and immune complex-driven activation of dendritic cells (and neutrophils). As such, the ABBV-599 (elsubrutinib/upadacitinib) combination has the potential for differentiated efficacy in SLE through concurrent inhibition of multiple pathogenic nodes.

Autoantibody generation by pathogenic B cells, which is dependent on B cell receptor signaling, is a hallmark of autoimmune diseases, such as rheumatoid arthritis (RA) and SLE.[1]

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of RA, SLE, and other autoimmune diseases. BTK is required for the propagation of pro-inflammatory signals downstream of immunoreceptors that promote autoimmune disease pathogenesis.

The hematopoietic expression and signaling function of BTK downstream of numerous receptors has raised interest in pharmacologic targeting of BTK for immune-mediated inflammatory diseases including RA.[2] The potential clinical value of BTK inhibition has been supported by studies in preclinical models of arthritis and lupus.[3,4] These have demonstrated: 1) complete abrogation of arthritis in the collagen-induced arthritis model when initiated at disease onset, consistent with the effect of BTK inhibition on autoantibody production,[3,4] 2) efficacy in myeloid-mediated animal arthritis models, consistent with the effects of BTK inhibition on macrophage, mast cell, dendritic cell, and neutrophil activity,[3,4] and 3) marked reductions of proteinuria in mouse models of lupus, consistent with the effect of BTK inhibition on autoantibody production and/or myeloid cell activation.[5-7]

Upadacitinib (ABT-494), an oral Janus kinase (JAK) inhibitor that displays unique selectivity for the JAK1 receptor, was approved in 2019 under the brand name Rinvoq™ for the treatment of patients with RA in the United States (US), the European Union (EU), and Japan. Upadacitinib is currently being developed for the treatment of: adult patients with Crohn's disease (CD), ulcerative colitis (UC), psoriatic arthritis, active axial spondyloarthritis (axSpA), giant cell arteritis (GCA), adult and pediatric patients with moderate to severe atopic dermatitis, and pediatric patients with polyarticular course juvenile idiopathic arthritis (JIA).

Clinical Hypothesis

It is anticipated that inhibition of either JAK1 or BTK will result in amelioration of lupus disease activity with increased efficacy delivered by the ABBV-599 (elsubrutinib/upadacitinib) combination.

BTK inhibition by elsubrutinib and JAK1 inhibition by upadacitinib are expected to disrupt B cell activation, T cell activation, and Type I IFN signaling as well as block local immune complex-driven tissue

damage that contributes to inflammation. Given the diverse immunologic mechanisms at play in SLE, the ABBV-599 (elsubrutinib/upadacitinib) combination on background standard of care has the potential to provide greater clinical efficacy compared to current standard of care while maintaining an acceptable safety profile.

2.2 Benefits and Risks to Subjects

The ABBV-599 (elsubrutinib/upadacitinib) combination of BTK inhibition by elsubrutinib and JAK1 inhibition by upadacitinib has the potential to provide greater clinical efficacy when added to current standard of care while maintaining an acceptable safety profile.

Upadacitinib is approved as a single-ingredient agent for the treatment of RA and is being developed for the treatment of other inflammatory diseases, several of which are in Phase 3 development. Preclinical models and clinical samples from Phase 1 studies with upadacitinib have demonstrated that upadacitinib has minimal impact on the Janus kinase 2 (JAK2) and Janus kinase 3 (JAK3) at efficacious drug levels, in contrast to its inhibitory effects on JAK1. Review of the available safety data has determined the following common AEs (upper respiratory tract infection, increased blood creatine phosphokinase [CPK], herpes zoster, nausea, cough, herpes simplex, neutropenia, pneumonia, hypercholesterolemia, and pyrexia) to be possibly causally related to treatment with upadacitinib. Events of deep vein thrombosis and pulmonary embolism have been reported in patients receiving JAK inhibitors including upadacitinib. Phase 3 RA clinical data have determined the following as important identified risks for upadacitinib therapy: serious infections (including opportunistic infections and tuberculosis [TB]) and herpes zoster. Upadacitinib offers a favorable benefit/risk ratio in the treatment of adult RA, which supports further clinical development of upadacitinib in other immunoinflammatory indications (e.g., SLE, CD, UC, atopic dermatitis, psoriatic arthritis, axSpA, JIA, and GCA).

A detailed description of the preclinical toxicology, metabolism, and toxicology datasets can be found in the elsubrutinib[8] and upadacitinib[9] Investigator's Brochures. The results of genetic toxicology testing indicate that elsubrutinib and upadacitinib are not genotoxic. Preclinical embryofetal development studies indicate that elsubrutinib and/or upadacitinib are embryotoxic, fetotoxic, and/or teratogenic.

In Phase 1 Studies M16-356 (single doses of elsubrutinib ranging from 2 to 125 mg), M16-357 (multiple doses of elsubrutinib ranging from 3 to 60 mg), and M16-044 (co-administration of upadacitinib 30 mg with elsubrutinib ranging from 10 to 60 mg), elsubrutinib alone or elsubrutinib co-administration with upadacitinib was well-tolerated with no severe or serious adverse events (SAEs) observed in healthy adult subjects. The most common adverse event (AE) reported was headache, which was distributed evenly across cohorts including placebo and without apparent dose effect.

SLE patients are known to have an increased risk of thrombosis. Based on this and the potential risk of thrombosis with the use of JAK inhibitors, the use of estrogen-containing contraceptives may further increase the risk of thrombotic events; therefore, the choice of contraceptive should be carefully considered.

Taken together, the safety data from the Phase 1 program support further development of elsubrutinib given alone or in combination with upadacitinib (ABBV-599 [elsubrutinib/upadacitinib] combination) in Phase 2 in subjects with SLE.

In Study M19-130, routine safety evaluations of all treatment groups will be performed. These include assessments of deaths, SAEs, non-serious AEs, withdrawals, and pregnancies, as well as routine monitoring by physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory testing (hematology, chemistry, and urinalysis).

For the safety of subjects, the following screening exclusions and ongoing assessments are included in the protocol:

- Exclusion of subjects with chronic or recent infections;
- Screen subjects for TB; exclude subjects with active TB or latent TB without history of appropriate prophylaxis [latent TB as assessed by IFN Gamma Release Assay (IGRA QuantiFERON TB Gold In-Tube Test or equivalent), and/or a purified protein derivative (tuberculin) (PPD) test (or both if required per local guidelines)].
    - If different national regulations exist for screening for latent TB while being on immunosuppressive treatment, these national regulations will be applied, respectively.
- Subjects will also be screened for human immunodeficiency virus (HIV) and hepatitis B (HB) and C infections.
- If a subject develops a serious infection (including coronavirus disease 2019 [COVID-19]) or serious opportunistic infection (excludes non-serious oropharyngeal candidiasis) with study treatment, study drug should be interrupted and appropriate treatment of the infection should be initiated.
- Review SAEs of infection on a real-time basis and query for additional information as clinically indicated.
- A supplemental herpes zoster form will be used to collect additional information for any herpes zoster events.

See Section 3.5 for detailed safety monitoring and information on the Data Monitoring Committee (DMC).

For further details, please see findings from completed studies, including safety data in the elsubrutinib[8] and upadacitinib[9] Investigator's Brochures.

In view of the COVID-19 pandemic, the benefit/risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of elsubrutinib and upadacitinib on the course of COVID-19 are not well-defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objective and Hypotheses

The main objective of this study is to evaluate the safety and efficacy of elsubrutinib, upadacitinib, and the ABBV-599 (elsubrutinib/upadacitinib) combination vs placebo for the treatment of signs and

symptoms of SLE at 24 and 48 weeks in subjects with moderately to severely active SLE and to define dose(s) for further development.

The hypotheses corresponding to the main objective are that elsubrutinib, upadacitinib, and the ABBV-599 (elsubrutinib/upadacitinib) combination are expected to provide better efficacy than placebo and to be well-tolerated in subjects with moderately to severely active SLE.

3.2 Primary Endpoint

The following is the primary efficacy endpoint:

1. Achievement of SLE Responder Index (SRI)-4 and steroid dose ≤ 10 mg prednisone equivalent once a day (QD) at Week 24

SLE Responder Index (SRI)-4 is defined as ≥ 4-point reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score without worsening of the overall condition (no worsening in Physician's Global Assessment [PhGA], < 0.3 point increase) or the development of significant disease activity in new organ systems (no new British Isles Lupus Assessment Group [BILAG] A or > 1 new BILAG B).

3.3 Secondary Endpoints

The following secondary efficacy endpoints will be evaluated:

1. Achievement of SRI-4 at Week 24
2. Achievement of BILAG-Based Combined Lupus Assessment (BICLA) response at Week 24
3. Achievement of Lupus Low Disease Activity State (LLDAS) at Week 24
4. Steroid burden, assessed as change from Baseline at Week 24
5. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI Flare Index (SFI), assessed by number and types of flare per subject through Week 24

3.4 Additional Efficacy Endpoints

The following additional efficacy endpoints will be evaluated at all visits unless otherwise noted:

1. Achievement of SRI-4
2. Achievement of SRI-5, -6, -7, -8 and steroid dose ≤ 10 mg prednisone equivalent QD at Weeks 24 and 48
3. Achievement of SRI-5, -6, -7, -8
4. Achievement of BICLA response

5. Achievement of LLDAS
6. Achievement of ≥ 4-point decrease in SLEDAI-2K from Baseline
7. Steroid burden, assessed as change from Baseline
8. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by SELENA SFI, assessed by number and types of flare per subject through Week 24 and Week 48.
9. Time to first flare by SELENA SFI after first study drug administration up to Week 24 and Week 48
10. Achievement of 50% reduction of tender or swollen lupus joints defined as ≥ 50% decrease in either tender or swollen joints (among those starting with total ≥ 6 affected joints)
11. Achievement of 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score (of those starting with CLASI ≥ 10)
12. Change in SLEDAI-2K from Baseline
13. Change in BILAG from Baseline
14. Change in PhGA from Baseline
15. Change in Patient Global Assessment (PtGA) from Baseline
16. Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue at Weeks 2, 12, 24, and 48
17. Change from Baseline in 36-Item Short Form Health Survey (SF-36) at Weeks 2, 12, 24, and 48
18. Change from Baseline Lupus Quality of Life questionnaire (LupusQoL) at Weeks 2, 12, 24, and 48
19. Change from Baseline Pain Numerical Rating Scale (NRS) at Weeks 2, 12, 24, and 48

3.5 Safety

Routine safety evaluations include AE monitoring, physical examinations, vital sign measurements, ECGs, and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

SAEs will be assessed at any dose that results in a death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly.

The following areas of safety interest will be routinely assessed to identify any major safety findings related to immunosuppression or potential risks associated with the individual classes of therapy: serious and/or opportunistic infections, herpes zoster, active TB, malignancies (all types), adjudicated gastrointestinal (GI) perforations, adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE]), anemia, neutropenia, lymphopenia, renal dysfunction, hepatic disorders, and adjudicated embolic and thromboembolic events (non-cardiac, non-central nervous system [CNS]) including venous thrombotic events defined as pulmonary embolism and deep vein thrombosis. Specific toxicity management measures will be utilized, as described in Section 6.2, for serious infections, serious GI events, cardiovascular events (MACE), malignancies, ECG abnormalities, and select laboratory

abnormalities. In addition, a 30-day follow-up phone call from the last dose of study drug should occur to determine the status of any ongoing AEs/SAEs, or the occurrence of any new AEs/SAEs.

An unblinded internal DMC will be established to ensure the overall integrity and conduct of the study. DMC reviews will be conducted at regular intervals (see Section 5.10 for more details). Regular systematic reviews of emerging safety data from all clinical studies with elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination will be conducted by AbbVie.

An independent external Cardiovascular Adjudication Committee (CAC) will adjudicate all blinded cardiovascular and cerebrovascular events, embolic/thrombotic events, and deaths, as defined in the CAC charter.

3.6 Pharmacokinetic Endpoints

Elsubrutinib and upadacitinib plasma concentrations will be summarized at each sampling time point (Appendix D) using descriptive statistics. A mixed-effects modeling approach may be used to estimate the population central value and the empirical Bayesian estimates of the individual values for elsubrutinib and upadacitinib oral clearance (CL/F) and volume of distribution (V_{ss}/F). Additional parameters and pharmacokinetic (PK)/pharmacodynamic relationships may be estimated if useful in the interpretation of the data.

3.7 Biomarker Research

Biospecimens (whole blood, peripheral blood mononuclear cells [PBMCs], plasma, and serum) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, RNA, DNA, and/or metabolites. The objective of this research is to analyze samples for biomarkers that will help to understand SLE, related conditions, and response to treatment with elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination or similar compounds. Research on samples collected in Germany will be limited to SLE, elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination. Biomarker samples will not be collected at sites in China as specified in Appendix D.

Type I IFN is a key driver of disease pathogenesis in lupus, and high IFN signature is associated with active SLE.[10,11] Approximately 60% of lupus patients express an elevated Type I IFN gene signature in the blood, suggesting higher Type I IFN activity in these individuals. JAK1 inhibition is expected to disrupt Type I IFN signaling; therefore, lupus patients expressing the Type I gene signature may be more likely to benefit from treatment with ABBV-599 (elsubrutinib/upadacitinib) combination. A Type I IFN RNA signature consisting of 4 genes (IFI6, IFI27, IFIT1, and MX1) will be evaluated using a validated assay with a cut point set at ≥ -0.25 for IFN high vs < -0.25 for IFN low (-0.25 is the upper limit of the cut point) using the Type I IFN Gene Expression Assay Score. In the event an IFN score cannot be collected or analyzed at Screening due to COVID-19 lab access, that subject will still be enrolled in the study and assigned a score of Not Applicable for the Screening visit. Samples drawn at the Week 4 and Week 24 visits may be used for analysis, if collected.

These results robustly dichotomize the IFN high and low population. The assay will be performed on Screening samples and at subsequent time points unless precluded by local regulations or restrictions (IFN signature samples will not be collected at sites in China). Screening values will be used as a criterion for subject enrichment with the goal of enrolling 80% of the study subjects with high composite score. Stratifying the study to include approximately 80% high IFN score population will allow for increased confidence in the subject population.

Two assays to monitor BTK activity will be included. A BTK phosphorylation assay (BTK Y223) will be performed on whole blood from all subjects, and serial PBMC pellets will be isolated from a subset of subjects to monitor BTK occupancy. Whole blood will be collected for fluorescence-activated cell sorting B cell immunophenotyping as well as T lymphocyte, B lymphocyte, and natural killer lymphocyte (TBNK) measurement.

Research may also include analysis of genes, epigenetics, gene expression, and proteomic biomarkers that may associate with SLE, related conditions, or the subject's response to treatment. This research is exploratory in nature and the results may not be included with the clinical study report. Required biomarker samples will be collected and analyzed from all subjects, unless precluded by local regulations or restrictions (for such cases, optionality of collection/analysis is given through an appropriate Informed Consent Form).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, and placebo-controlled Phase 2 study, with a Week 24 primary endpoint, to investigate the safety and efficacy of elsubrutinib and upadacitinib given alone or in combination (ABBV-599 [elsubrutinib/upadacitinib] combination) in subjects with moderately to severely active SLE. The study will continue through Week 48 to further assess maintenance of efficacy and safety of each treatment beyond 24 weeks.

Approximately 325 male and female subjects, 18 to 65 years of age, inclusive, with a diagnosis of moderately to severely active SLE (clinical diagnosis of SLE at least 24 weeks prior to Screening, meeting at least 4 of the 11 revised Criteria for Classification of SLE according to the 1997 Update of the 1982 American College of Rheumatology [ACR] OR meeting at least 4 of the 2012 Systemic Lupus Erythematosus International Collaborating Clinics [SLICC] classification criteria, including at least 1 clinical criterion and 1 immunologic criterion) despite standard of care therapy will be randomized in a 1:1:1:1:1 ratio of 5 treatment groups, as follows:

- Group 1: Elsubrutinib 60 mg QD and upadacitinib 30 mg QD (n = 65)
- Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD (n = 65)
- Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD (n = 65)
- Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD (n = 65)
- Group 5: Elsubrutinib placebo QD and upadacitinib placebo QD (n = 65)

Randomization will be stratified based on the following factors:

- Baseline corticosteroid dose above 10 mg prednisone-equivalent (≤ 10 mg or > 10 mg)
- Screening SLEDAI-2K (< 10 or ≥ 10)
- High vs low vs not applicable IFN score (approximately 80% high) (this stratification factor does not apply to subjects in China)
- Baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, methotrexate [MTX], mycophenolate, or leflunomide) (yes/no)

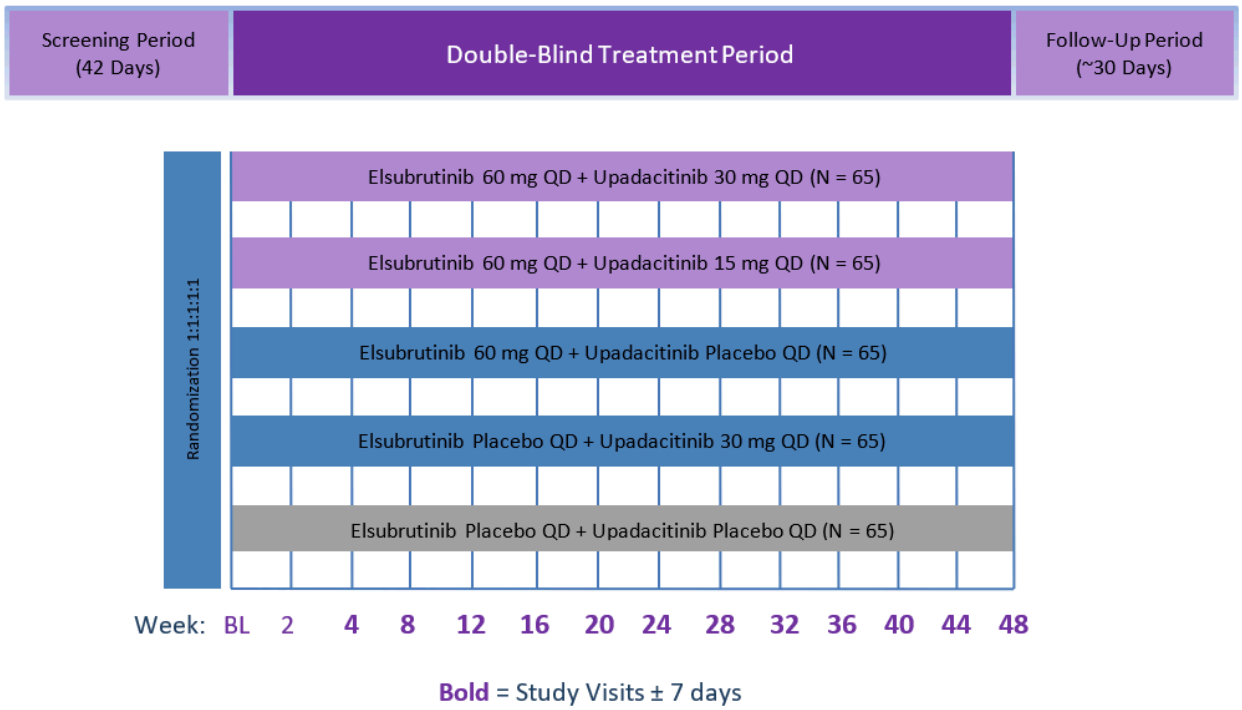
The study duration will include a 42-day maximum screening period and a 48-week randomized, placebo-controlled, double-blind, parallel-group treatment period with a 30-day follow-up phone call. Sites and subjects will remain blinded throughout the study. The Week 24 Primary Analysis will be performed when all subjects have completed the Week 24 visit or have discontinued the study. The study team will remain blinded until the Week 24 Primary Analysis. A 30-day follow-up phone call from the last dose of study drug should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

The schematic of the study is shown in Figure 1 Further details regarding study procedures are located in the Operations Manual. See Section 5 for information regarding eligibility criteria.

A long-term extension (LTE) study will be conducted under a separate protocol (LTE Study M20-186) at sites where it is permitted by the local Competent Authority and Ethics Committee. Subject rollover from the initial randomized portion of the study will occur at Week 48.

When 50% of the planned subjects completed the Week 24 assessments, an unblinded interim analysis was performed by an independent team at AbbVie. Details are provided in Section 7.5, Interim Analysis.

Figure 1. Study Schematic



BL = Baseline; QD = once a day

4.2 Discussion of Study Design

Choice of Control Group

This is a parallel-group study consisting of 5 treatment groups receiving elsubrutinib, upadacitinib, ABBV-599 (elsubrutinib/upadacitinib) combination, or matching placebo to assess the safety and efficacy of elsubrutinib or upadacitinib given alone or in combination (as the ABBV-599 [elsubrutinib/upadacitinib] combination) once daily for 48 weeks in subjects with moderately or severely active SLE. Placebo will serve as a reference for efficacy assessment while the additional efficacy of the ABBV-599 (elsubrutinib/upadacitinib) combination will utilize in-study comparison to the elsubrutinib and upadacitinib treatment groups.

Appropriateness of Measurements

All efficacy and safety measurements in this study are standard for assessing disease activity in subjects with SLE being treated with immunosuppressant therapies. The first safety evaluation is at Week 2, and at all subsequent visits. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Eligible for this study are adult male or female subjects, 18 to 65 years of age, inclusive, with a clinical diagnosis of SLE at least 24 weeks prior to Screening, meeting at least 4 of the 11 revised Criteria for

Classification of SLE according to the 1997 Update of the 1982 ACR OR meeting at least 4 of the 2012 SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion, and at least one of the following at Screening: positive antinuclear antibody (ANA) (titer ≥ 1:80), anti-double stranded DNA (dsDNA), or anti-Smith antibodies. The selection criteria identify individuals with active SLE that are the intended target population for treatment with elsubrutinib and/or upadacitinib, based on the current knowledge of these drugs.

Selection of Doses in the Study

The dose selection in this study is based on analysis of PK, pharmacodynamics, safety, and efficacy (upadacitinib only), data from Phase 1 studies in healthy volunteers for elsubrutinib and ABBV-599 (elsubrutinib/upadacitinib) combination, Phase 2 and Phase 3 studies for upadacitinib in RA, as well as a published Phase 2 study of baricitinib in SLE.[8,9,12]

The 60 mg dose of elsubrutinib is intended to target exposures at or greater than those needed to achieve maximal peripheral BTK occupancy. Following once-daily dosing of elsubrutinib 60 mg, peak and trough BTK occupancy at steady-state are predicted to be 99% and 89%, respectively. Furthermore, the elsubrutinib dose of 60 mg (administered alone or with upadacitinib 30 mg) has been shown to be safe and well-tolerated in Phase 1 studies in healthy subjects.

The selected dosing regimens of upadacitinib are 15 mg and 30 mg QD (testing both dose levels in the ABBV-599 [elsubrutinib/upadacitinib] combination and only the higher dose in the upadacitinib monotherapy group). In addition to evaluation of upadacitinib 30 mg QD monotherapy, the selected ABBV-599 (elsubrutinib/upadacitinib) combination regimens will enable evaluation of upadacitinib dose response in combination with elsubrutinib. These doses are based on the demonstrated efficacy and well-tolerated safety profile of upadacitinib at these 2 doses in Phase 3 RA studies. Additionally, these doses are supported by extrapolation of data from a recently published Phase 2 study of baricitinib in SLE. In that study, the baricitinib 2 mg QD dosing regimen demonstrated negligible efficacy while the 4 mg QD regimen provided evidence of therapeutic benefit compared to placebo. *In vitro* cellular inhibition of Type I IFN signaling in CD3+ T cells and CD14+ monocytes showed comparable potency between upadacitinib and baricitinib (i.e., comparable concentration producing 50% inhibition [IC_{50}] values). Predicted plasma concentration-time profiles for upadacitinib and baricitinib indicate that the upadacitinib 15 mg QD dosing regimen is predicted to result in plasma concentrations that provide modestly higher inhibitory efficacy (e.g., time above IC_{50}) compared to the baricitinib 2 mg QD dosing regimen; whereas the upadacitinib 30 mg QD regimen is predicted to provide similar or higher inhibitory efficacy compared to the baricitinib 4 mg QD dosing regimen.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative (if required per local regulations) must understand and personally, voluntarily sign and date an informed consent, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures. In Japan, subjects under 20 years of age must voluntarily sign and date an informed consent, in addition to their parent or legal guardian. Legally authorized representation will not apply in the case of Germany and France, and protected persons such as minors, adults under guardianship, pregnant women, persons deprived of their liberty and persons incapable or unable to express their consent cannot be included in the study.

Demographic and Laboratory Assessments

- 2. Adult male or female, 18 to 65 years of age, inclusive, at Screening.
- 3. Must not have laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) > 2.0 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) > 2.0 × ULN;
  - Estimated glomerular filtration rate (GFR) by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula < 40 mL/min/1.73 m^2;
  - Absolute neutrophil count (ANC) < 1,000/µL;
  - Platelet count < 50,000/µL;
  - Hemoglobin < 9 g/dL.
- 4. Must not have positive titers for all 3 antiphospholipid antibodies known to be associated with venous thrombotic events at Screening: lupus anticoagulant, anti-beta 2 glycoprotein 1, and anticardiolipin antibody.
- 5. Are willing and able to comply with procedures required in this protocol.

Disease Activity

- 6. Clinical diagnosis of SLE at least 24 weeks prior to Screening, meeting at least 4 of the 11 revised Criteria for Classification of SLE according to the 1997 Update of the 1982 ACR OR meeting at least 4 of the 2012 SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion.
- 7. At Screening, must have at least one of the following:
  - ANA+ (titer ≥ 1:80)
  - anti-dsDNA+
  - anti-Smith+

- 8. SLEDAI-2K ≥ 6 despite background therapy as reported and independently adjudicated (clinical score ≥ 4, excluding lupus headache and/or organic brain syndrome) at Screening:
  - If 4 points of the required entry points are for arthritis, there must also be a minimum of 3 tender and 3 swollen joints.
  - If 4 points of the required clinical score are for proteinuria attributable to active lupus nephritis, it must be > 0.5 g/day equivalent (0.5 mg/mg).
  - If subject has rash and Principal Investigator (PI) considers it to be attributable to SLE, subject must consent to skin photograph collection for adjudication.
  - Score must be re-confirmed at the Baseline visit.
- 9. PhGA ≥ 1 during screening period.
- 10. The subject must be on background treatment throughout the study. The background treatment must be stable for 30 days prior to Baseline and throughout the study with
  - Antimalarial(s), prednisone (or prednisone-equivalent) (≤ 20 mg), azathioprine (≤ 150 mg), mycophenolate (≤ 2 g), leflunomide (≤ 20 mg), cyclosporine, tacrolimus, and/or MTX (≤ 20 mg).
  - The combination of background treatment with antimalarial(s) and/or prednisone (or equivalent) is permitted.
  - And a single, but not multiple, additional immunosuppressant from the list above, is permitted.

Subject History

- 11. Must not have active lupus nephritis (progressive Class IV or >1 g/day equivalent [1 mg/mg] proteinuria) or have undergone induction therapy within the last 6 months.
- 12. Must not be receiving hemodialysis (or other forms of renal replacement therapy).
- 13. Must not have active neuropsychiatric SLE as defined by the CNS portion of SLEDAI-2K or BILAG (excluding lupus headache).
- 14. Must not have any active, chronic, or recurrent viral or bacterial infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or HIV. Active HBV, HCV, and HIV are defined as:
  - HBV: hepatitis B surface antigen (HBs Ag) positive (+) or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive (+) subjects; (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects in China and Japan only);
  - HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).
  - HIV: confirmed positive anti-HIV antibody (HIV Ab) test.

- 15. Must not have active TB or latent TB and did not complete a full course of prophylaxis for latent TB.
- 16. Must not have a history of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in-situ (CIS) of the cervix.
- 17. Must not have a history of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.
- 18. Must not have a history of GI perforation (other than appendicitis or penetrating injury), diverticulitis, or significantly increased risk for GI perforation per investigator judgment.
- 19. Must not have any conditions that could interfere with drug absorption including but not limited to short bowel syndrome (e.g., subjects with a history of gastric bypass surgery are excluded). Subjects with a history of gastric banding/segmentation are not excluded.
- 20. Must not be a recipient of an organ transplant.
- 21. Must not have history of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
- 22. Must not have had an active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.
- 23. **Must not have confirmed COVID-19:** the Baseline visit must be at least 14 days from onset of signs/symptoms or positive SARS-CoV-2 test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 24. **Must not have suspected COVID-19:** subjects with signs/symptoms suggestive of COVID-19, known exposure, or high-risk behavior should undergo molecular (e.g., PCR) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure.
- 25. Must not have a history of an allergic reaction or significant sensitivity to constituents of the study drugs (and its excipients) and/or other products in the same class.
- 26. Must not have a history of any of the following cardiovascular conditions:
  - Recent history (within past 6 months) cerebrovascular accident (CVA), myocardial infarction (MI), coronary stenting, coronary bypass surgery.
  - Uncontrolled hypertension as defined by a persistent systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg. For subjects with known hypertension, the subject's BP must be stable for at least 30 days on current, stable anti-hypertensive medications.
  - Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.
- 27. Must not have any clinically relevant or significant ECG abnormalities at Screening, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 480 msec. In subjects with ventricular conduction delay (QRS > 120 msec), cardiologist consultation is required.
- 28. For Japan subjects only: must not have positive result of beta-D-glucan or 2 consecutive indeterminate results of beta-D-glucan (screening for *Pneumocystis jiroveci* infection).

Contraception

- 29. Women of childbearing potential (WOCBP) must not have a positive serum pregnancy test at the Screening visit and must have a negative urine pregnancy test at Baseline prior to the first dose of study drug. Note: Subjects with borderline serum pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of positive result.
- 30. If female, subject must be either postmenopausal, OR permanently surgically sterile OR for WOCBP practicing at least 1 protocol-specified method of birth control (Section 5.2), that is effective from Study Day 1 through at least 30 days after the last dose of study drug and in agreement with local regulations.
- 31. Women must not be pregnant, breastfeeding, or considering becoming pregnant during the study and for at least approximately 30 days after the last dose of study drug.

Prior/Concomitant Medications

- 32. Must not be using intravenous (IV) or intramuscular (IM) corticosteroids greater than or equal to a 40 mg prednisone-equivalent bolus within 30 days of planned randomization. Must not have been treated with intra-articular, trigger point or tender point, intra-bursa, or intra-tendon sheath corticosteroids in the preceding 8 weeks prior to the first dose of study drug.
- 33. Subjects must be naïve or have discontinued, if not currently benefiting from, the following prior to the first dose of study drug per the applicable washout period below or should be at least 5 times the mean terminal elimination half-life of a drug:
  - ≥ 6 months for plasmapheresis
  - ≥ 3 months for belimumab (Benlysta®)
  - ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to ≥ 50 B cells per microliter
  - ≥ 3 months for cyclophosphamide
  - ≥ 4 weeks for abatacept, any anti-tumor necrosis factor (TNF) therapy, and all other biologics
- 34. Subjects must not have received intravenous immunoglobulin (IVIG) within 30 days prior to the first dose of study drug.
- 35. Must not have prior exposure for 14 days or more or any prior intolerance to a JAK inhibitor (including but not limited to upadacitinib, tofacitinib, baricitinib, and filgotinib) or a BTK inhibitor. The washout period for JAK and BTK inhibitors prior to the first dose of study drug is ≥ 30 days or 5 times the half-life, whichever is longer.
- 36. To avoid combinations of immunosuppressive medications that are not permitted during the study (see criterion 10, above), subjects with prior exposure to the following medications may need to complete a washout period prior to enrollment as specified below or should be at least 5 times the mean terminal elimination half-life of a drug:
  - ≥ 4 weeks prior to first dose of study drug for MTX, azathioprine, tacrolimus, cyclosporine, mycophenolate.

- ≥ 8 weeks prior to first dose of study drug for leflunomide if no elimination procedure was followed, or adhere to an elimination procedure (i.e., 11 days with cholestyramine, or 30 days washout with activated charcoal or as per local label).

- 37. Must not have previous exposure to IFN kinoid vaccination.
- 38. Must not have prior exposure within 3 months of study Baseline to anti-IFN therapies, including anti-IFN and anti-IFN receptor.
- 39. Must not have been treated with any investigational drug within 30 days, or 5 half-lives of the drug (whichever is longer), prior to the first dose of study drug or be currently enrolled in another clinical study.
- 40. Subjects must have discontinued all high-potency opiates at least 1 week and traditional Chinese medicine for at least 30 days prior to the first dose of study drug.
- 41. Subjects must not have received any live vaccine within 30 days (56 days for Japan) prior to the first dose of study drug (see Section 5.3 for additional information on vaccines).

5.2 Contraception Recommendations

Contraception Requirements for Females

SLE patients are known to have an increased risk of thrombosis. There is a potential risk of thrombosis with the use of JAK inhibitors. The use of estrogen-containing contraceptives may further increase the risk of thrombotic events; therefore, the choice of contraceptive should be carefully considered.

Subjects must follow the following contraceptive guidelines as specified:

- Women, Non-Childbearing Potential

  Women do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Women of Childbearing Potential (WOCBP)

  WOCBP must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug. They must commit to one of the following **highly effective** methods of birth control with:

  - Combined (estrogen- and progestogen-containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure). For Japan: only bilateral tubal ligation.
- Vasectomized partner, provided the vasectomized partner has received medical confirmation of surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Practice true abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal] is not acceptable).

For the local requirements for contraception in Japan, please refer to Appendix F.

If required per local practices, WOCBP must commit to using 2 methods of contraception (either **2 highly effective** methods or **1 highly effective** method combined with **1 effective** method).

Effective methods of birth control are the following:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1.
- Male or female condom with or without spermicide.
- Cap, diaphragm, or sponge with spermicide.
- A combination of male condom with a cap, diaphragm, or sponge with spermicide (double-barrier method).

A condom is required in the following countries: United Kingdom (UK), Germany, and Spain.

If during the course of the study a woman becomes surgically sterile or post-menopausal (defined above) and complete documentation is available, contraceptive measures as defined above are no longer required.

It is important to note that the contraception requirements described above are specifically intended to prevent pregnancy during exposure to the investigational therapies (elsubrutinib and/or upadacitinib). For concomitant immunosuppressive agent(s) (i.e., MTX, azathioprine, mycophenolate, leflunomide, etc.) that have been prescribed per standard of care prior to study entry and are allowed to be continued during the study, contraception should continue while the subject is on the concomitant immunosuppressive agent(s). The duration of contraception after discontinuation of these immunosuppressive agent(s) should be based on the local product labelling. Urine pregnancy testing shall be performed at monthly intervals in the study activity schedule.

Additional local requirements may apply and should be followed accordingly.

Contraception Requirements for Males

There are no contraception recommendations for males participating in the study.

5.3 Prohibited Medications and Therapy

Medications and therapies with a washout period specified in Section 5.1 (eligibility criteria) are prohibited while subjects are on study drug.

In addition to the medications listed in the eligibility criteria, the following are prohibited while subjects are on study drug:

- Cyclophosphamide
- Belimumab
- Rituximab
- Granulocyte-colony stimulating factor (GCSF)
- IVIG
- Strong cytochrome P450 3A isoform subfamily (CYP3A) or cytochrome P450 1A2 isoform subfamily (CYP1A2) inhibitors and inducers (examples found in Table 1)
- Traditional Chinese medicines
- Elective surgery within the first 24 weeks. Further details regarding elective surgery are provided in Section 6.1 Complaints and Adverse Events.
- High-potency narcotics (unless administered during a hospitalization) including (but not limited to):
  - Oxycodone
  - Oxymorphone
  - Fentanyl
  - Levorphanol
  - Buprenorphine
  - Methadone
  - Hydromorphone
  - Morphine
  - Meperidine
- Of note, low-potency narcotics are permitted to optimize SLE medications (see Section 5.4 for more details).

Table 1. Examples of Commonly used Strong CYP3A or CYP1A2 Inhibitors and Inducers

Strong CYP3A Inhibitors	**Strong CYP3A Inducers**
Boceprevir Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Carbamazepine Phenytoin Rifampin Rifapentine St. John's Wort
Strong CYP1A2 Inhibitors	**Strong CYP1A2 Inducers**
Fluvoxamine Ciprofloxacin Enoxacin Zafirlukast	Rifampin

CYP3A = cytochrome P450 3A isoform subfamily; CYP1A2 = cytochrome P450 1A2 isoform subfamily

Vaccines

Although not mandated by the protocol, vaccines recommended by local guidelines should be considered. Live vaccines are not permitted during the study. If the subject and investigator choose to administer live vaccines, these vaccinations must be completed (per local label) 30 days (56 days for Japan) before first dose of study drug with appropriate precautions or administered at least 30 days after last dose of study drug.

Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster (i.e., Zostavax®);
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;

- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

Examples of common vaccines that are inactivated, toxoid or biosynthetic, include but are not limited to: injectable influenza vaccine, Shingrix™ (herpes zoster), pneumococcal, and pertussis (Tdap) vaccines.

5.4 Concomitant Therapy

Subjects taking the following concomitant medications/therapy are required to follow the directives below:

Allowed Concomitant Medications/Therapy	**Comments/Notes**
Methotrexate	≤ 20 mg/wk with concomitant folic acid ≥ 5 mg/wk
Azathioprine	≤ 150 mg/day
Mycophenolate mofetil	≤ 2,000 mg/day
Mycophenolate sodium	≤ 1,440 mg/day
Hydroxychloroquine	≤ 400 mg/day
Chloroquine	≤ 500 mg/day
Quinacrine	≤ 100 mg/day
Leflunomide	≤ 20 mg/day
Cyclosporine	Dosed by serum levels
Tacrolimus	Dosed by serum levels
Corticosteroids (prednisone-equivalent)	≤ 20 mg/day, decrease no faster than 5 mg QD per week

Rescue Concomitant Medications/Therapy	**Comments/Notes**
Corticosteroids (prednisone-equivalent)	Increase of no more than 5 mg QD per week regardless of Baseline dose, maximum dose of 25 mg, through Week 8

[redacted]

[redacted]

Subject must remain on their background therapy throughout the entirety of the study. The only permitted change of background therapy is steroid tapering. If applicable, subjects should continue on their stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and low-potency narcotics. For NSAIDs, acetaminophen/paracetamol, tramadol, codeine, hydrocodone, and propoxyphene that are part of background therapy, changes in dose, including initiation, are not allowed, with the exception of protocol-defined rescue therapy. The following medications taken as needed (PRN) are allowed but should not be taken within the 24 hours prior to any study visit: NSAIDs, acetaminophen/paracetamol, tramadol, codeine, hydrocodone, and propoxyphene. In the event of tolerability (or other safety) issues, the doses of NSAID and/or acetaminophen may be decreased or discontinued with substitution of another NSAID.

Note: If medication supply issues result in a change in background therapy due to pandemic changes, substitutions meeting protocol requirements are permitted and must be approved by the AbbVie Therapeutic Area Medical Director (TA MD).

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through the post-treatment visit (30-day follow-up phone call).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie TA MD. Information regarding potential drug interactions with elsubrutinib and/or upadacitinib can be located in the individual elsubrutinib and upadacitinib Investigator's Brochures.

Subjects must be able to safely discontinue any prohibited medications 30 days prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study

Subjects can request to be discontinued from participating in the study at any time for any reason including but not limited to disease progression or lack of response to treatment. The Investigator may discontinue any subject's study treatment at any time for any reason, including but not limited to disease progression, lack of response to treatment, safety concerns, or failure to comply with the protocol. See Section 6.2 on Toxicity Management for toxicity management criteria.

At Week 24, the Investigator must assess and document in source if continuing in the study is in the best interest of the subject.

Subjects will be discontinued from study drug immediately if any of the following occur:

- Development or worsening of lupus manifestation requiring introduction of certain prohibited medications or dosages when continuation of the study drug would place the subject at risk, as determined by the AbbVie TA MD. The following will require discontinuation of study drug immediately:
  - Cyclophosphamide
  - Belimumab
  - Rituximab
  - More than one of the following in combination: azathioprine, mycophenolate, leflunomide, MTX, cyclosporine, or tacrolimus;
  - Plasmapheresis
  - High-dose corticosteroids (≥ 60 mg prednisone equivalent oral or parenteral)
  - IVIG
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Serious infections (e.g., pneumonia, sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk for continued participation in the trial, as determined by the Investigator or the AbbVie TA MD.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from study drug or the study, or the Sponsor decides to discontinue 1 or more treatment groups after the interim analysis.
- Inclusion or exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Subject develops an ECG change considered clinically significant and with reasonable possibility of relationship to study drug or a confirmed absolute QTcF value > 500 msec or confirmed increase of ≥ 60 msec from Baseline.
  - Subject's QTcF increases from Baseline ≥ 60 msec, the investigator will evaluate, confirm the value, and treatment should be stopped.
- Subject develops active or latent TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or CIS of the cervix.
- Subject is significantly non-compliant with study procedures, including inconsistent study drug dosing, which would put the subject at risk for continued participation in the trial as determined by the Investigator or the AbbVie TA MD.
- Subject develops a GI perforation.
- If a diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis is confirmed.

- Subject develops active neuropsychiatric SLE (excluding lupus headache) as defined by the CNS portion of SLEDAI-2K or BILAG.
- Subject develops Class IV lupus nephritis (confirmed by biopsy).

In order to minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should:

- Continue in the study without receiving study drug
- Have all procedures performed outlined in the Premature Discontinuation (PD) visit, preferably within 2 weeks of study drug discontinuation
- Continue with their regular study visit schedule

No PK or biomarker samples should be collected after the PD visit.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely at any time, either in its entirety or partially (discontinue 1 or more treatment groups), at any site. The study may be discontinued or terminated in case of an unacceptable risk, relevant toxicity, or a negative change in the benefit/risk assessment including the occurrence of AEs of which the character, severity, or frequency is new in comparison to the existing risk profile. In addition, data deriving from other clinical trials or toxicological studies which negatively influence the benefit/risk assessment might cause discontinuation or termination of the study. In the event the study is partially terminated, all subjects in the terminated arm(s) will be asked to return for a PD visit and to perform a 30-day follow-up phone call after the last dose of study drug. These subjects are not eligible for the LTE Study M20-186. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

Discontinuation of Study Drug and Continuation of Study Participation

During the study, subjects may discontinue study drug treatment but may choose to continue to participate in the study. Subjects who prematurely discontinue study drug should complete a PD visit as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in Appendix D and Section 2.1 of the Operations Manual, and adhere to all study

procedures except for dispensing study drug. As the subject has discontinued study drug, all rescue and efficacy discontinuation criteria no longer apply. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required. Subjects who discontinue study drug treatment are not eligible for the LTE Study M20-186.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks, and preferably prior to initiation of another therapy. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

If a subject withdraws from study follow up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected, and the samples will be destroyed. Data generated from biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Elsubrutinib, upadacitinib, or matching placebo manufactured by AbbVie (Table 2) will be administered on Day 1 (Baseline) and should be taken at approximately the same time each day. Subjects will be instructed to take study drugs orally, which includes only 1 capsule of elsubrutinib or placebo from each of the 3 dispensed bottles per day, with or without food, and only 1 tablet of upadacitinib or placebo from the dispensed bottle per day, with or without food. Subjects will be instructed to take only 1 capsule or tablet from each dispensed bottle per day. If subjects should forget to take their elsubrutinib, upadacitinib, or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 10 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

Subject dosing will be recorded on a subject dosing diary. The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. Study site personnel will document compliance.

Medications other than elsubrutinib, upadacitinib, or matching placebo will not be provided by AbbVie. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Elsubrutinib, upadacitinib, and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Table 2. Study Drug

	Investigational Product	**Investigational Product**	**Investigational Product Placebo**	**Investigational Product Placebo**
Investigational product name	Elsubrutinib (ABBV-105)	Upadacitinib (ABT-494)	Elsubrutinib (ABBV-105) Placebo	Upadacitinib (ABT-494) Placebo
Active ingredient	Elsubrutinib (ABBV-105)	Upadacitinib (ABT-494)	N/A	N/A
Mode/Route of Administration (ROA)	Oral	Oral	Oral	Oral
Dosage Form	Capsule	Film-Coated Tablet	Capsule	Film-Coated Tablet
Dose and units	20 mg	15 mg, 30 mg	N/A	N/A
Frequency of administration	Daily	Daily	Daily	Daily
Storage Conditions	Room temperature (15 - 25°C) Protect from freezing	Room temperature (15 - 25°C)	Room temperature (15 - 25°C) Protect from freezing	Room temperature (15 - 25°C)

N/A = not applicable

5.8 Randomization/Drug Assignment

Approximately 325 subjects who meet eligibility criteria will be randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment groups:

- Group 1: Elsubrutinib 60 mg QD and upadacitinib 30 mg QD (n = 65)
- Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD (n = 65)
- Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD (n = 65)
- Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD (n = 65)
- Group 5: Elsubrutinib placebo QD and upadacitinib placebo QD (n = 65)

All subjects will be assigned a unique identification number by the IRT at the Screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening visit should be

used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Randomization will be stratified based on the following factors:

- Baseline corticosteroid dose above 10 mg prednisone-equivalent (≤ 10 mg or > 10 mg)
- Screening SLEDAI-2K (< 10 or ≥ 10).
- High vs low vs not applicable IFN score (approximately 80% high)
  - This stratification factor does not apply to subjects in China.
- Baseline immunosuppressant (azathioprine, tacrolimus, cyclosporine, MTX, mycophenolate, or leflunomide) (yes/no)

Once approximately 20% of total subjects have been randomized who are IFN signature low, further enrollment of such subjects may be suspended. Please refer to rationale in Section 3.7.

The investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded through Week 24 and will become unblinded only after the primary efficacy analysis at Week 24 is completed. To maintain the blind, the elsubrutinib capsules and matching placebo capsules and upadacitinib tablets and matching placebo tablets provided for the study will be identical in appearance.

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie TA MD prior to breaking the blind as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the Investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/help-desk/. In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. Also, the date and reason that the blind was broken must be recorded in the source documents and electronic case report form (eCRF), as applicable.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

In Japan, the investigator will record all the protocol deviations in the appropriate medical records at the site.

5.10 Data Monitoring Committee

An internal DMC will be composed of persons independent of the Study M19-130 protocol and with relevant expertise in their field who will review unblinded safety data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study. When needed, high-level unblinded efficacy data may also be requested by the DMC and reviewed so that the DMC can assess benefit/risk of any emerging safety differences. A separate DMC charter will be prepared outside of the protocol before the first subject is enrolled in the study and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications. Communications from the DMC to the study team will not contain information that could potentially unblind the study team to subject treatment assignments.

AbbVie utilizes an internal DMC charter template which closely follows that used for external DMCs and applies the same rigor describing DMC roles and responsibilities, DMC procedures, and the maintenance of data integrity. Each internal DMC will be appropriately constituted with DMC members who have relevant expertise in SLE and have no involvement in the development of compound(s) that are the subject of the study to ensure objective decision making. Specifically, all DMC members of Study M19-130 will be well-versed in safety aspects of drug development with years of experience in the pharmaceutical industry. As described in the DMC charter for Study M19-130, the DMC's sole remit is to safeguard the interests of trial subjects and make recommendations regarding study continuation, study modification, or study termination.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from the use of the drug as stipulated in the protocol, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or the investigator considers them to be AEs. Worsening SLE including flares will be captured and analyzed via the disease activity forms (SLEDAI, BILAG, CLASI, and SELENA SLEDAI Flare Index) and will be analyzed as part of efficacy. As such, worsening SLE and flares will not be captured as AEs unless they result in serious outcomes.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. Elective surgery is not permitted during the study until the primary endpoint has been assessed. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE. If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. For both elective and emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

If any of the following events are reported (Table 3), then the following supplemental report must be completed.

Table 3. Adverse Events Requiring Supplemental Reports

Adverse Events	Supplemental Report
Cardiovascular AE	Cardiovascular (Cardiac) AE eCRF Myocardial Infarction (MI) and Unstable Angina AE eCRF Heart Failure eCRF Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF Embolic and Thrombotic Event (Non-cardiac, Non-central nervous system eCRF)
Hepatic Disorders AE	Hepatic Supplemental Local Labs eCRF Hepatic Supplemental Procedure eCRF (Non-SAE Non-Protocol Diagnostic/Therapeutic Procedures) Hepatic Abnormal Laboratory Value Supplemental
Herpes zoster	Herpes zoster eCRF
Elevated CPK	Increased CPK Supplemental eCRF
Renal Dysfunction	Renal Supplemental Local Labs eCRF Renal Supplemental Procedure eCRF Renal Abnormal Laboratory Value Supplemental eCRF
COVID-19 Infection	COVID-19 Supplemental Signs/Symptoms eCRF COVID-19 Status Form eCRF
Death	Death eCRF

AE = adverse event; COVID-19 = coronavirus disease - 2019; CPK = creatine phosphokinase; eCRF = electronic case report form; SAE = serious adverse event

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse Event Collection

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or are a congenital anomaly or birth defect.
SUSAR	A suspected unexpected SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is not listed is the applicable Reference Safety Information (RSI), and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following adverse events of special interest (AESI) will be monitored during the study:

- Serious infections
- Opportunistic infections
- Herpes zoster
- Active TB
- Malignancy (all types)
- Adjudicated GI perforations
- Adjudicated cardiovascular events (e.g, MACE)
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorders
- Adjudicated embolic and thrombotic events (non-cardiac, non-CNS) including venous thromboembolic events defined as pulmonary embolism and deep vein thrombosis.

Adverse Event Severity and Relationship to Study Drug

Investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5, which can be accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf.

If no specific grading criteria are provided for the reported event, then the event should be as follows:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Moderate (Grade 2): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.);
- Severe (Grade 3 - 5):
    - Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);

- Grade 4: Life-threatening consequences; urgent intervention indicated;
- Grade 5: Death related to AE.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to the study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the SAE.

In Japan, the PI will provide documentation of all SAEs to the Director of the investigative site and to the Sponsor.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued from study drug (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partner will be collected from the date of the first dose through 30 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

The toxicity management of the AEs including AESI consists of safety monitoring (review of AEs on an ongoing basis, and periodic/ad hoc unblinded review of safety issues by an internal safety DMC), interruption of study drug dosing with appropriate clinical management if applicable, and discontinuation of the subjects from study drug.

The management of specific AEs and laboratory parameters is discussed below and described in Table 4. This includes AEs of serious infections, opportunistic infections, GI perforations, cardiovascular events (MACE), thromboembolic events, malignancies, and ECG abnormalities. This also includes the following laboratory abnormalities: hemoglobin, ANC, platelet count, ALT or AST, serum creatinine, CPK, lymphocyte count, total white blood cell (WBC) count, and urine protein to creatinine ratio (UPCR).

For all other AEs or laboratory-related AEs, study drug will be interrupted immediately if a subject experiences a confirmed severe (Grade 3) clinical AE or SAE for which the investigator considers the relationship to the study drug to be a reasonable possibility. For confirmed Grade 4 AEs for which the investigator considers the relationship to the study drug to be a reasonable possibility and the event does not improve back to at least Grade 2, then the study drug must be discontinued.

Product complaints concerning the investigational product must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Management of Serious Infections

Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection (including COVID-19) or a serious opportunistic infection (excludes non-serious oropharyngeal candidiasis). A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active or latent TB must be discontinued from the study drug.

Canada only: Investigators should be advised to follow local public health guidelines in order to prevent subjects enrolled in these trials from acquiring TB.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The appropriate COVID-19 eCRFs should be completed. If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator must contact the AbbVie TA MD before reintroducing study drug.

Management of Herpes Zoster

If a subject develops herpes zoster, the Investigator should consider temporarily interrupting study drug until the episode resolves.

Management of Serious Gastrointestinal Events

Subjects presenting with the onset of signs or symptoms of a serious GI event should be evaluated promptly for early diagnosis and treatment. If the diagnosis of GI perforation is confirmed, the subject must be discontinued from the study drug.

Management of Cardiovascular Events

Subjects presenting with potential cardiovascular events should be appropriately assessed and carefully monitored. These events will be reviewed and adjudicated by an independent CAC in a blinded manner.

Management of Malignancy

Subjects who develop malignancy other than NMSC or CIS of the cervix must be discontinued from the study drug. Information including histopathological results should be queried for the confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

Management of ECG Abnormality

Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug OR a confirmed absolute Fridericia's correction formula (QTcF) value > 500 msec or confirmed increase of ≥ 60 msec from Baseline.

Management of Muscle-Related Symptoms

If a subject experiences symptoms suggestive of myositis or rhabdomyolysis, CPK and aldolase measurements should be requested and will be provided after review by the TA MD with clinical management and/or study drug interruption as deemed appropriate by the treating physician. Please refer to Table 4 below for further instructions.

Management of Thrombosis Events

Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

Management of Select Laboratory Abnormalities

For any given laboratory abnormality, the investigator should assess the subject and apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 4 and may require a supplemental eCRF to be completed (see Section 6.1 Complaints and Adverse Events). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 4, the repeat testing must occur as soon as possible.

Table 4. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameters	Toxicity Management Guidelines
Hemoglobin	• If hemoglobin < 8 g/dL interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from baseline and an alternative etiology is known, the subject may remain on study drug at the investigator's discretion. If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its baseline value.
Absolute neutrophil count (ANC)	If confirmed < 750 cells/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its baseline value. Subjects who meet this criterion should be evaluated for an alternative etiology and closely monitored for infections. • The alternative etiology should be documented appropriately in the eCRF. If restarting study drug, documentation should include reason rechallenge is expected to be safe.
Platelet count	If confirmed < 30,000 platelets/µL by repeat testing with new sample, interrupt study drug dosing until platelet count returns to normal reference range or its baseline value.

Laboratory Parameters	Toxicity Management Guidelines

Aspartate transaminase (AST) or alanine transaminase (ALT)	• Interrupt study drug immediately if confirmed ALT or AST > 3 × upper limit of normal (ULN) by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio (INR) > 1.5.
	  • INR will only need to be measured in subjects with ALT or AST > 3 × ULN by the central lab. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug immediately if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
	• Interrupt study drug immediately if ALT or AST > 5 × ULN by repeat testing with new sample.
	• Interrupt study drug immediately if ALT or AST > 8 × ULN and contact the AbbVie TA MD.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. The investigator should contact the AbbVie Therapeutic Area MD (TA MD) to discuss the management of a subject when an alternative etiology has been determined. The alternative etiology should be documented appropriately in the eCRF; study drug should be discontinued if no alternative etiology can be found.
	For any confirmed ALT or AST elevations > 3 ULN, complete supplemental hepatic eCRF.
	• Subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at Screening who develop the following should have HBV DNA by PCR testing performed within one week:
	  • ALT > 5 × ULN OR
	  • ALT or AST > 3 × ULN if an alternative cause is not readily identified.
	A positive result for HBV DNA PCR testing in these subjects will require immediate interruption of study drug (per local guidelines) and a hepatologist consultation should occur within one week for recommendation regarding subsequent treatment.

Serum Creatinine	• If serum creatinine is > 1.5 × the baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion then interrupt study drug and re-start study drug once serum creatinine returns to ≤ 1.5 × baseline value and ≤ ULN. • If confirmed new serum creatinine ≥ 2 mg/dL interrupt study drug, and re-start study drug once serum creatinine returns to normal reference range or its baseline value. For the above serum creatinine elevation scenarios, complete supplemental renal eCRF(s).

Laboratory Parameters	Toxicity Management Guidelines
Creatine Phosphokinase (CPK)	• CPK and aldolase will be measured at every visit but results will be blinded to sites and subjects, as CPK elevation is a known class effect of JAK inhibitors and the results could be unblinding to the sites. If symptomatic myositis is suspected, the site may send a request to the AbbVie TA MD for CPK and/or aldolase results to be unblinded. Request must be approved by the AbbVie TA MD. • If confirmed CPK ≥ 4 × ULN accompanied by symptoms suggestive of myositis or rhabdomyolysis, interrupt study drug, complete supplemental CPK eCRF, and contact AbbVie TA MD.
Lymphocyte Count Decreased	• If confirmed Grade 4 (< 200/mm^3) by repeat testing with new sample, interrupt study drug dosing until lymphocyte count returns to at least Grade 2 (< 800 to 500/mm^3) or its baseline value.
White Blood Cell Count Decreased	• If confirmed Grade 4 (<1000/mm^3) by repeat testing with new sample, interrupt study drug dosing until white blood cell count returns to at least Grade 2 (< 3000 to 2000/mm^3) or its baseline value.
Urine Protein to Creatinine Ratio	• If > 1 g/day equivalent (1 mg/mg), repeat by testing with new sample, and if confirmed, a renal biopsy will be required. • If Class IV lupus nephritis is confirmed, subject must be permanently discontinued from study drug.

eCRF = electronic case report form; HBc Ab+ = hepatitis B core antibody positive; HBs Ab = hepatitis B surface antibody; HBV = hepatitis B virus; INR = international normalized ratio; JAK = Janus kinase; PCR = polymerase chain reaction; TA MD = Therapeutic Area Medical Director; ULN = upper limit of normal

For all other AEs or laboratory-related AEs, study drug will be interrupted immediately if a subject experiences a confirmed severe (Grade 3) clinical AE or SAE for which the investigator considers the relationship to the study drug to be a reasonable possibility. For confirmed Grade 4 AEs for which the investigator considers the relationship to the study drug to be a reasonable possibility and the event does not improve back to at least Grade 2, then the study drug must be discontinued.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). An unblinded interim analysis will be performed by an independent team at AbbVie after 50% of the planned subjects have completed Week 24 assessments. The study team will remain blinded until the Week 24 Primary Analysis. The Week 24 Primary Analysis will be conducted after all ongoing subjects have completed Week 24 assessments or have discontinued the study to inform next phase studies. The Final Analysis will be conducted when all subjects have completed the study.

Efficacy and safety analysis may be revised accordingly based on the IERC decision at the interim analysis.

Details will be included in the SAP.

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who have received at least 1 dose of study drug. Subjects will be grouped according to treatment as randomized. The FAS will be used for all efficacy and baseline analysis.

The Safety Analysis Set consists of all subjects who have received at least 1 dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

7.3 Statistical Analyses for Efficacy

Primary Endpoint Analysis

The primary efficacy endpoint, the achievement of SRI-4 and steroid dose ≤ 10 mg prednisone equivalent QD at Week 24, will be assessed for each active treatment group vs the placebo group. The treatment difference will be evaluated using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratification factors. ABBV-599 (elsubrutinib/upadacitinib) combination treatment groups will be compared to placebo and the monotherapy treatment groups. Additional comparisons or analyses will be conducted as appropriate. There will be no multiplicity adjustment for the multiple comparisons.

The Week 24 Primary Analysis will be performed when all subjects have completed the Week 24 assessments or have discontinued the study. The Final Analysis will be performed after all subjects have completed all study assessments including the 30-day follow-up phone call.

Non-**R**esponder **I**mputation while incorporating Multiple Imputation to handle missing data due to **C**OVID-19 (NRI-C) will be applied for primary endpoint analysis. As observed (AO) analysis will be performed as the sensitivity analysis for the primary endpoint.

Secondary and Additional Endpoint Analysis

All secondary and additional efficacy endpoints described in Section 3.3 and Section 3.4 will be analyzed as follows:

Categorical variables will be tabulated by the number and frequency. Between-treatment group comparison will be evaluated in the same way as the primary endpoint analysis.

All continuous endpoints will be evaluated through the change from Baseline. For continuous endpoints with multiple post-Baseline visits, the treatment effect will be assessed through Mixed-effect Model Repeated Measures (MMRM) with treatment, visit and treatment-by-visit interaction, main stratification factors, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. For continuous endpoints with single post-Baseline visit analysis, the

treatment effect may be assessed through analysis of covariance with baseline value, treatment, and stratification factors as covariates. In addition, the descriptive statistics for continuous variables will be provided including sample size, mean, standard deviation, median, minimum, and maximum.

For the count endpoints (e.g., number of flares), negative binomial regression model will be used to assess treatment effect with treatment, visit, and stratification factors as covariates.

The Cox Proportional Hazards model will be used to assess the treatment effect for the time-to-event endpoint, i.e., time to flare.

Missing Data Imputation Definition

Censoring: For the time-to-event endpoint, i.e., time to flare, missing data will be considered as censored at the last available time for the information.

NRI-C: The NRI-C will categorize any subject who does not have an evaluation during a pre-specified visit window as a non-responder for the visit, except for missing data due to COVID-19 infection or logistical restriction, which will be handled by Multiple Imputation. In addition, subjects who prematurely discontinue from study drug will be considered as non-responders for all subsequent visits after discontinuation. Subjects will also be classified as non-responders as described in Section 5.4.

As Observed: As observed analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the AO analysis for that visit. Regardless of premature discontinuation of study drug, all observed data will be used in the analysis. As observed analysis may be used for both categorical variables and continuous variables for sensitivity analysis.

Mixed-Effect Model Repeated Measurements: MMRM analysis will be conducted using a mixed-effect model for continuous variables. Data collected after study drug discontinuation or initiation of rescue treatment will not be included. The mixed model includes the categorical fixed effects of treatment, visit and treatment-by-visit interaction, main stratification factors, and the continuous fixed covariate of baseline measurement. An unstructured variance covariance matrix will be used. The parameter estimations are based on the assumption of data being missing at random and using the method of restricted maximum likelihood (REML).

7.4 Statistical Analyses for Safety

Safety analyses will be carried out using the Safety Analysis Set, which includes all subjects who receive at least 1 dose of study drug. Subjects will be grouped to the treatment actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, ECGs, and vital signs. Frequency tables and lists of subjects with treatment-emergent adverse events (TEAEs) by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary, by system organ class, by severity, and by relationship to the study drug as assessed by the Investigator will be provided. The changes from Baseline in vital signs, physical examination results, and clinical laboratory values will be analyzed in a descriptive manner. Shift of laboratory values from Baseline to defined time points will be tabulated. Pre-treatment AEs will be summarized separately.

All TEAEs, SAEs, AEs leading to discontinuation, and AESI will be collected during the study. A TEAE is defined as an event with onset or worsening after the first study dose of study drug and within 30 days after the last dose of study drug administration. The number and percentages of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class and preferred term. Summaries (including percentages and event per 100 patient-year) of SAEs, deaths, AEs leading to discontinuation, and AESI will be provided as well. For selected laboratory and vital signs parameters, mean change from Baseline and percentage of subjects with evaluations meeting pre-defined criteria for Potentially Clinically Important values will be summarized.

7.5 Interim Analysis

A planned unblinded interim analysis was performed when 50% of the planned subjects completed their Week 24 assessments. The objective of this analysis was to reassess the treatment regimens in Study M19-130 and the benefit/risk for rollover into LTE Study M20-186.

The interim analysis was performed by an independent team at AbbVie that is separate and apart from the blinded study team. The M19-130 study team will remain blinded through the Week 24 Primary Analysis.

An Interim Unblinding Plan (IUP) was developed separately describing the analyses to be performed and included execution logistics, an unblinded analysis team, and the data chain of custody to protect the integrity of the study.

An Internal Executive Review Committee (IERC) reviewed the interim unblinded results as specified in the IERC charter and decided which treatment group(s) should be continued in Study M19-130 and for rollover into LTE Study M20-186.

Study sites and subjects remained blinded to treatment assignment in Study M19-130 and LTE Study M20-186 throughout the studies.

7.6 Overall Type I Error Control

All tests will be performed as pairwise comparison at a 2-sided statistical significance level of $\alpha = 0.1$. No multiplicity adjustment will be applied because this is a Phase 2 study.

7.7 Sample Size Estimation

The planned sample size for this study is 325 subjects in total, with 65 subjects for each of the 5 groups, determined based on the primary endpoint, the composite of SRI-4 and steroid dose ≤ 10 mg prednisone equivalent QD at Week 24. Assuming at Week 24 the placebo response rate is 25%, a two-sided χ^2 test with $\alpha = 10\%$ will provide 78% to 91% power to detect a difference of 20% to 25% between an active treatment group and the placebo group.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

In Japan, the investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

In Japan, when important new information related to the subject's consent becomes available, the investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data

are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote data review and verification of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator (and Director of the site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator (and Director of the site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to AbbVie or their representative.

The Investigator (and Director of the site in Japan) must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol.

This study will be conducted in compliance with the protocol, GCP, and all other applicable regulatory requirements, including the archiving of essential documents.

The end-of-study is defined as the date of the last subject's last visit, or date of the last follow-up contact, whichever is later.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
Ab	Antibody
ACR	American College of Rheumatology
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
Ag	Antigen
ALT	Alanine transaminase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
anti-dsDNA	Anti-double stranded DNA
AO	As observed
AST	Aspartate transaminase
axSpA	Axial spondyloarthritis
BCG	Bacilli Calmette-Guérin
BICLA	BILAG-Based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BL	Baseline
BP	Blood pressure
BTK	Bruton's tyrosine kinase
CAC	Cardiovascular Adjudication Committee
Cardiac	Cardiovascular
CD	Crohn's disease
CIS	Carcinoma in-situ
CL/F	Apparent clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPK	Creatine Phosphokinase
CRF	Case report form
CT	Computed tomography

CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
CXR	Chest x-ray
CYP3A	Cytochrome P450 3A isoform subfamily
CYP1A2	Cytochrome P450 1A2 isoform subfamily
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	Double stranded deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCA	Giant cell arteritis
GCP	Good clinical practice
GCSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HB	Hepatitis B
HBc Ab	Hepatitis B core antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
IC_{50}	Inhibitory concentration producing 50% inhibition
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IERC	Internal Executive Review Committee

IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional review board
IRT	Interactive response technology
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3
JIA	Juvenile idiopathic arthritis
LLDAS	Lupus Low Disease Activity State
LTE	Long-term extension
LupusQoL	Lupus Quality of Life questionnaire
MACE	Major adverse cardiovascular event
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed-effect Model Repeated Measures
MTX	Methotrexate
N/A	Not applicable
NCI	National Cancer Institute
NMSC	Non-melanoma skin cancer
NRI-C	**N**on-**R**esponder **I**mputation while incorporating Multiple Imputation to handle missing data due to **C**OVID-19
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OC	Observed Case

PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Premature Discontinuation
PhGA	Physician's Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPD	Purified protein derivative (tuberculin)
PRN	As needed
PRO	Patient-reported outcome
PtGA	Patient global assessment
QD	Once a day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid arthritis
RCT	Randomized clinical trial
REML	Restricted maximum likelihood
RNA	Ribonucleic acid
ROA	Route of administration
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SF-36	36-Item Short Form Health Survey
SFI	SLEDAI Flare Index
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SJC	Swollen joint count
SLICC	Systemic Lupus Erythematosus International Collaborating Clinics
SRI	SLE Responder Index
SUSAR	Suspected unexpected serious adverse reaction
TA MD	Therapeutic Area MD
TB	Tuberculosis
TBNK	T lymphocytes, B lymphocytes, and natural killer lymphocytes

TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United States
vs	versus
V_{ss}/F	Apparent volume of distribution at steady state
WBC	White blood cells
WOCBP	Women of Childbearing Potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-130: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

Protocol Date: 25 October 2021

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Director, Clinical Pharmacokinetics	Clinical Pharmacology and Pharmacometrics
[redacted]	Therapeutic Area Head	Data and Statistical Sciences
[redacted]	Director, Statistics	Data and Statistical Sciences
[redacted]	Group Medical Director	Immunology Clinical Development
[redacted]	Therapeutic Area Medical Director	Immunology Clinical Development
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Principal Medical Writer	Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across all subject encounters. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Activities Table

	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48/ Premature Discontinuation	30-Day Follow Up Phone Call*
Visit Window (Days)			**± 3**	**± 7**												
INTERVIEWS & QUESTIONNAIRES																
Subject information and informed consent	✓															
Eligibility criteria	✓	✓														
Medical/surgical history[a]	✓	✓														
Adverse event (AE) and AE of special interest (AESI) assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Steroid therapy assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-Reported Outcome[b] • PtGA		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Patient-Reported Outcomes[b] • LupusQoL • FACIT-Fatigue • SF-36 • Pain NRS		✓	✓			✓			✓						✓	
Verification of continued contraceptive measures for WOCBP		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physician Global Assessment (PhGA)[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
TB risk assessment form	✓															
SLEDAI-2K and BILAG assessments	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CLASI assessment	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48/ Premature Discontinuation	30-Day Follow Up Phone Call*
Visit Window (Days)			**± 3**	**± 7**												
SELENA SLEDAI Flare Index assessment				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Verification of continued benefit of subject participation									✓							
LOCAL LABS & EXAMS																
Chest x-ray	✓															
12-lead ECG	✓		✓	✓	✓	✓	✓	✓	✓			✓			✓	
Height (screening only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
TJC28/SJC28	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (for WOCBP only)[e]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Skin Photographs[f]	✓								✓							
CENTRAL LABS																
HIV Testing (if not prohibited by local regulation)	✓															
HBs Ag, HBc Ab, HCV Ab[g]	✓															
Complement C3, C4 testing	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
anti-dsDNA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ANA/anti-Smith	✓															
Cotinine lab measurement	✓															
Prothrombin, Partial Thromboplastin		✓														
Lupus Anticoagulant, Anti-Beta 2 Glycoprotein 1, Anticardiolipin Antibody	✓															

	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48/ Premature Discontinuation	30-Day Follow Up Phone Call*
Visit Window (Days)			**± 3**	**± 7**												
Serum pregnancy test (WOCBP), FSH (non-WOCBP presumed post-menopausal)	✓															
QuantiFERON-TB Gold test (and/or local PPD skin test, T-SPOT.TB Test)	✓															
Clinical chemistry, Hematology (CBC), Urinalysis, Urine Protein to Creatinine ratio (UPCR)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
IgG and IgM	✓	✓		✓					✓						✓	
Blood samples for elsubrutinib and upadacitinib pharmacokinetic (PK) analysis		✓[h]		✓[h,i]		✓[i,j]		✓[h,i]	✓[h,i]						✓[i,k,l]	
Biomarkers Sample: Whole blood for BTK occupancy analysis (only select # of sites and subjects in the US)[m]		✓[n]				✓[j]			✓[h]						✓[k,l]	
Biomarker Sample: Whole blood for BTK Y223 phosphorylation assay[m]		✓[n]				✓[j]			✓[h]						✓[k,l]	
Biomarker Sample: Whole Blood (plasma, serum, DNA and RNA)[m,o]		✓[j]	✓[l]	✓[l]		✓[l]			✓[l]						✓[l]	
Biomarker Sample: Whole Blood viable PBMCs[m]		✓[j]	✓[l]	✓[l]		✓[l]			✓[l]						✓[l]	
Biomarker Sample: Whole Blood: Immunophenotyping (TBNK, B cell subsets)[m]		✓[j]		✓[l]		✓[l]			✓[l]						✓[k,l]	
Biomarker Sample: Interferon signature[m]	✓			✓					✓						✓[k]	
℞ TREATMENT																
Randomization/drug assignment		✓														
Dispense study drug[i]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48/ Premature Discontinuation	30-Day Follow Up Phone Call*
Visit Window (Days)			**± 3**	**± 7**												
Dispense subject diaries		✓														
Review and copy subject dosing diary and perform drug reconciliation[i]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

ANA = antinuclear antibody; anti-dsDNA = anti-double stranded DNA; BILAG = British Isles Lupus Assessment Group; BTK = Bruton's tyrosine kinase; CBC = complete blood count; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; FACIT = Functional Assessment of Chronic Illness Therapy; FSH = follicle stimulating hormone; HBc Ab = hepatitis B core antibody; HBs Ag = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IgM = immunoglobulin M; LupusQoL = Lupus Quality of Life questionnaire; Pain NRS = pain numerical rating scale; PBMC = peripheral blood mononuclear cell; PPD = purified protein derivative (tuberculin); PtGA = patient global assessment; RNA = ribonucleic acid; SF-36 = 36-Item Short Form Health Survey; SELENA = Safety of Estrogens in Lupus Erythematosus National Assessment; SJC = swollen joint count; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; TB = tuberculosis; TBNK = T lymphocytes, B lymphocytes, and natural killer lymphocytes; TJC = tender joint count; US = United States; WOCBP = women of childbearing potential

* The 30-day follow up call will be calculated from the last study drug administration date/last visit for all subjects not entering the long-term extension LTE Study M20-186.

a. A complete medical history and prior/concomitant therapy will be taken at Screening and will be updated at the Baseline Visit.

b. The patient-reported outcome instrument should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings. The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

c. This is a clinician-reported outcome that is completed on the tablet.

d. A complete physical examination will be performed during Screening and Study Day 1. Physical examinations at other visits can be symptom-directed.

e. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

f. Any subject who has a positive skin score at screening (i.e., Principal Investigator [PI] believes they have a Lupus rash) needs photos for adjudication; photos will only be collected for subjects presenting with a possible Lupus rash during Screening and at Week 24 for those who have a confirmed (by adjudicator) Lupus rash at screening.

g. Subjects will be tested for the presence of the hepatitis B and C virus (HBV and HCV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable for any subject with positive anti-HCV Ab) will be exclusionary. For subjects who are negative for HBsAg but positive for core antibody (HBc Ab), HBV DNA polymerase chain reaction (PCR) will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

h. Post-dose collection.

i. Not required if subject discontinues study drug but remains in the study.

j. Pre-dose collection.

k. To be completed at Premature Discontinuation only.

l. Collection at any time during visit.

m. Will not be collected in China.

n. Pre-dose and post-dose collection.

o. Blood samples collected and analyzed from all subjects unless precluded by local regulations or restrictions.

APPENDIX E. DESCRIPTION OF EFFICACY MEASURES

Measure	Definition	Scale
Systemic Lupus Erythematosus Responder Index (SRI)[13]	Composite responder index based on improvement in disease activity (number following SRI indicates numerical improvement in SLEDAI-2K score) without worsening of the overall condition (no worsening in PhGA, < 0.3 point increase) or the development of significant disease activity in new organ systems (no new BILAG A or > 1 new BILAG B).	Not Applicable
British Isles Lupus Assessment Group Based Combined Lupus Assessment (BICLA)[14]	Composite responder index based on improvement in organ systems (improvement in all initial A and B scores, no more than one new BILAG B score) without worsening of the overall condition (no worsening in PhGA, < 0.3 point increase) and no worsening of SLEDAI-2K score.	Not Applicable
Lupus Low Disease Activity State (LLDAS)[15]	A state of low disease activity based on SLEDAI score (SLEDAI-2K score ≤ 4 excluding SLEDAI-2K activity in major organ systems), absence of SLE disease activity in major organ systems and new disease activity, Physician's Global Assessment (PhGA ≤ 1), and concomitant medication usage (steroid dose ≤ 7.5 mg QD and toleration of immunosuppressive drugs at standard maintenance doses).	Not Applicable
Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)[16]	Global SLE disease activity index that focuses on high-impact disease manifestations across 9 organ systems. It includes 24 clinical and laboratory variables with manifestations weighted by the affected organ system.	Scores range from 0 to 105, with higher scores indicating more severe disease
British Isles Lupus Assessment Group (BILAG) 2004[17]	Global SLE disease activity index designed on the basis of the physician's intention to treat, focusing on changes in disease manifestations. The instrument assesses 97 clinical signs, symptoms, and laboratory parameters across 9 organ systems.	Letter score assigned to each organ system with following indications: A = severe, B = moderate, C = mild, D = inactive with prior history, and E = inactive with no history

Measure	Definition	Scale
Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)[18]	Index used to assess cutaneous manifestations of SLE summarizing the activity of the disease.	Scores range from 0 to 70, with higher scores indicating more severity
SELENA SLEDAI Flare Index (SFI)[19]	An index defining SLE flares using changes in the SLEDAI score, definitions of worsening signs and symptoms, treatment changes, and Physician's Global Assessment of Disease Activity.	Mild/moderate or severe flare
Physician's Global Assessment of Disease Activity[19]	Physician's assessment of patient's overall disease activity due to SLE, as compared with all possible patients with SLE. The benchmarks of the visual analog scale are 0, 1, 2, and 3 on the line corresponding to no, mild, moderate, and severe SLE disease activity, respectively.	Visual-analog scale ranging from 0 to 3, with higher values indicating more severe disease

APPENDIX F. LOCAL REQUIREMENTS

Clarification for Japan Contraception Recommendations

Women of Childbearing Potential (WOCBP) must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug. They must commit to one of the following **highly effective** methods of birth control with:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal,* transdermal,* injectable*) associated with the inhibition of ovulation, initiated at least 30 days prior to Study Day 1.
- Progestogen-only hormonal contraception (oral,** injectable,* implantable*) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation (in Japan, only bilateral tubal occlusion).
- Vasectomized partner, provided the vasectomized partner has received medical confirmation of surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Practice true abstinence (if acceptable per local requirements): Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal] is not acceptable).

* Not approved in Japan.
** Not applicable in Japan due to the approval only for emergency contraception.

APPENDIX G. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	15 April 2019
Version 2.0	02 July 2019
Version 3.0	25 July 2019
Version 4.0	12 December 2019
Version 4.1 (China Only)	21 April 2020
Administrative Change 1	13 November 2019
Administrative Change 2	20 February 2020
Administrative Change 3	07 April 2020
Version 5.0	04 June 2020
Version 5.1 (China Only)	15 July 2020
Version 6.0	15 October 2020
Version 6.1 (China Only)	10 November 2020

PROTOCOL

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

1. ***Rationale:*** *To clarify the adjustment of treatment groups in Study M19-130 as a result of the completed 50% interim analysis at Week 24.*
    - Section 1 Synopsis and Section 4.1 Overall Study Design and Plan
        - Added Study M19-130 to the objective to reassess treatment regimens and details regarding the IERC review.
    - Section 3.5 Safety
        - Removed mention of additional multi-disciplinary Safety review team and added details to Section 7.5.
    - Section 5.5 Withdrawal of Subjects and Discontinuation of Study
        - Clarified that the Sponsor may "partially" terminate the study, meaning 1 or more treatment groups may be terminated.

- Section 7.5 Interim Analysis
  - Added Study M19-130 to the objective to reassess treatment regimens and also added details regarding IERC that was identified and reviewed which treatment group(s) should be continued in Study M19-130 and for rollover into LTE Study M20-186.

2. ***Rationale:*** *If the study is partially terminated (i.e., only certain groups are discontinued), details for follow-up of subjects were provided.*
   - Section 5.5 Withdrawal of Subjects and Discontinuation of Study
     - Added if the study is partially terminated, a subject will be asked to return for a PD visit and to perform a 30-day follow-up phone call after the last dose of study drug.

OPERATIONS MANUAL

3. **Rationale:** To clarify that not all subjects will be eligible for roll over.
   - Section 5.2 Treatment After End of Study
     - Added clarification that only "eligible" subjects will be permitted to rollover from the initial randomized portion of the study.
4. ***Rationale****: To clarify, the Study Team does not have access to HIV results, but AbbVie field personnel ("monitors") do have access to site laboratory results, including HIV testing.*
   - Section 3.13 Clinical Laboratory Tests
     - Removed from the HIV section the statement "Abbvie will not receive results from the testing and will not be made aware of any positive results."

In addition to these modifications, minor typographical edits and corrections were made throughout the protocol and operations manual for consistency, and other revisions were made for clarity and readability (e.g., addition of abbreviations).

APPENDIX H. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-130

Systemic Lupus Erythematosus: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-599 (elsubrutinib in combination with upadacitinib)

FULL TITLE: A Phase 2 Study to Investigate the Safety and Efficacy of Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599 Combination) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] MD Therapeutic Area Medical Director AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: Mobile: [redacted] Fax: Email: [redacted]
Safety Concerns	Immunology Safety Team [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 (847) 938-8737 Email: GPRD_SafetyManagement_Immunology@abbvie.com
SAE Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations	[redacted] AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Fax: Email:

Certified Clinical Laboratories	For sites in North America: Labcorp Drug Development 8211 Scicor Drive Indianapolis, IN 46214	Phone: +1 (866) 762-6209 Fax: + 1 (317) 616-2362
	For Sites in Europe: Labcorp Drug Development 7 rue Marcinhes 1217 Geneva Meyrin Switzerland	Phone (local calls): +41 58 822 7000 Fax: +41 58 822 6999
	For sites in Asia-Pacific: Labcorp Drug Development 1 International Business Park The Synergy, #04-14 Singapore 609917	Phone: 65-6560-8793 Fax: 65-6565-5901
	Labcorp Drug Development Central Laboratory Services, Inc. 1st Floor, No.6 Building, 151 Li Bing Road, Zhangjiang Hi-Tech Park, Shanghai 201203 P.R. of China	Phone: +86 21 5137 1111 Fax: +86 21 51371301
	CB Lab c/o BML General Laboratory 1361-1 Matoba/Kawagoe-shi Saitama 350-1101, Japan Japan Toll free: 0120-123-905	Phone: +81-3-6837-9536 Fax: +81-3-6220-3667 For country-specific lab contact information, please refer to Labcorp Lab Manual.
Pharmacokinetic Lab	Attn: AbbVie Sample Receiving [redacted] c/o: Delivery Services 1150 S. Northpoint Blvd. Waukegan, IL 60085	Phone: +1 (847) 937-0889 Fax: +1 (847) 938-9898
Exploratory Sample Lab	Cambridge Biomedical Inc. Maloy Mangada Project 214A 1320 Soldiers Field Road Boston, MA 02135	Phone: +1 (617) 456-0870 Fax: +1 (617) 456-0701
Interferon Signature	DxTerity Diagnostics Attn: Olga Derbeneva 19500 S. Rancho Way Suite 112 Compton, CA 90220	Phone: 310-537-7857

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2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING:

INTERVIEW	• Subject information and informed consent • Eligibility criteria • Medical and surgical history[a] • Adverse event (AE) and AE of special interest (AESI) assessment	• Prior and concomitant therapy[a] • Steroid therapy assessment • Tuberculosis (TB) risk assessment form
EXAM	Investigator Assessments: • Physician Global Assessment (PhGA)[b] • Systemic lupus erythematosus (SLE) Disease Activity Index (SLEDAI)-2K assessment • British Isles Lupus Activity Group (BILAG) assessment • Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) assessment	• Chest x-ray (CXR) • 12-lead electrocardiogram (ECG) • Height • Weight • Vital signs • Physical exam[c] • Tender joint count (TJC)28/swollen join count (SJC)28 • Skin photographs[d]
CENTRAL LAB	• Human immunodeficiency virus (HIV) testing (if not prohibited by local law) • Hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab), hepatitis C virus antibody (HCV Ab)[e] • Complement C3 and C4 testing • Anti-double stranded DNA (anti-dsDNA) test • Antinuclear antibody (ANA) test/anti-Smith antibody test	• Cotinine lab measurement • Lupus anticoagulant, anti-beta 2 glycoprotein 1, anticardiolipin antibodies • Serum pregnancy test (WOCBP), follicle-stimulating hormone (FSH; non-WOCBP presumed post-menopausal) • QuantiFERON-TB Gold test (and/or local purified protein derivative [PPD] skin test, T-SPOT.TB test) • Clinical chemistry, hematology (complete blood count [CBC]), urinalysis, urine protein to creatinine ratio (UPCR) • Immunoglobulin G (IgG) and immunoglobulin M (IgM)
SPECIALTY LAB	• Biomarker Sample: Interferon Signature[f]	

BASELINE:

INTERVIEW	• Eligibility criteria • Medical/surgical history[a] • AE and AESI assessment	• Prior and concomitant therapy[a] • Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• Patient Global Assessment (PtGA) • Lupus Quality of Life questionnaire (LupusQoL)	• Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue • SF-36 Health Survey (SF-36) • Pain Numerical Rating Scale (NRS)
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment	• Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Prothrombin, partial thromboplastin • Clinical chemistry, hematology (CBC), urinalysis, UPCR • IgG and IgM • Blood samples for elsubrutinib and upadacitinib pharmacokinetic (PK) analysis[i]	• Biomarker Sample: whole blood for Bruton's tyrosine kinase (BTK) occupancy analysis (<u>only select number of sites and subjects in the US</u>)[f,j] • Biomarker Sample: whole blood for BTK Y223 phosphorylation assay[f,j] • Biomarker Sample: whole blood (plasma, serum DNA, and RNA)[f,k,l] • Biomarker Sample: whole blood viable peripheral blood mononuclear cells (PBMCs)[f,l] • Biomarker Sample: whole blood: immunophenotyping (T lymphocytes, B lymphocytes, and natural killer lymphocytes [TBNK], B cell subsets)[f,l]
TREATMENT	• Randomization/drug assignment	• Dispense subject dosing diary • Dispense study drug

WEEK 2:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA • LupusQoL	• FACIT-Fatigue • SF-36 • Pain NRS
EXAM	Investigator Assessments: • PhGA[b]	• 12-lead ECG • Weight • Vital signs • Physical exam[c]
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR	• Biomarker Sample: whole blood (plasma, serum DNA, and RNA)[f,k,m] • Biomarker Sample: whole blood viable PBMCs[f,m]
TREATMENT	• Review and copy subject dosing diary and perform drug reconciliation[n]	

WEEK 4:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA	
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR • IgG and IgM	• Blood samples for elsubrutinib and upadacitinib PK analysis[i,n] • Biomarker Sample: whole blood (plasma, serum, DNA and RNA)[f,k,m] • Biomarker Sample: whole blood viable PBMCs[f,m] • Biomarker Sample: whole blood: immunophenotyping (TBNK, B cell subsets)[f,m] • Biomarker Sample: Interferon signature[f]
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 8:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA	
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA	• Clinical chemistry, hematology (CBC), urinalysis, UPCR
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 12:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA • LupusQoL	• FACIT-Fatigue • SF-36 • Pain NRS
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR • Blood samples for elsubrutinib and upadacitinib PK analysis[l,n]	• Biomarker samples: whole blood for BTK occupancy analysis (only select number of sites and subjects in the US)[f,l] • Biomarker Sample: whole blood for BTK Y223 phosphorylation assay[f,l] • Biomarker Sample: whole blood (plasma, serum, DNA and RNA)[f,k,m] • Biomarker Sample: whole blood viable PBMCs[f,m] • Biomarker Sample: whole blood: Immunophenotyping (TBNK, B cell subsets)[f,m]
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 16:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA	
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA	• Clinical chemistry, hematology (CBC), urinalysis, UPCR
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 20:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA	
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR	• Blood samples for elsubrutinib and upadacitinib PK analysis[i,n]
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 24:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy • Verification of continued benefit of subject participation	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA • LupusQoL	• FACIT-Fatigue • SF-36 • Pain NRS
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28 • Skin photographs[d]
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR • IgG and IgM • Blood samples for elsubrutinib and upadacitinib PK analysis[i,n]	• Biomarker samples: whole blood for BTK occupancy analysis (only select number of sites and subjects in the US)[f,i] • Biomarker Sample: whole blood for BTK Y223 phosphorylation assay[f,i] • Biomarker Sample: whole blood (plasma, serum, DNA and RNA)[f,k,m] • Biomarker Sample: whole blood viable PBMCs[f,m] • Biomarker Sample: whole blood: Immunophenotyping (TBNK, B cell subsets)[f,m] • Biomarker Sample: Interferon signature[f]
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 28, Week 32, Week 36, Week 40, Week 44

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA	
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• Weight • Vital signs • Physical exam[c] • TJC28/SJC28 • 12-lead ECG (Week 36 only)
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA	• Clinical chemistry, hematology (CBC), urinalysis, UPCR
TREATMENT	• Dispense study drug[n]	• Review and copy subject dosing diary and perform drug reconciliation[n]

WEEK 48/Premature Discontinuation:

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment • Verification of continued contraceptive measures for WOCBP
PRO[g]	• PtGA • LupusQoL	• FACIT-Fatigue • SF-36 • Pain NRS
EXAM	Investigator Assessments: • PhGA[b] • SLEDAI-2K assessment • BILAG assessment • CLASI assessment • SELENA SLEDAI Flare Index Assessment	• 12-lead ECG • Weight • Vital signs • Physical exam[c] • TJC28/SJC28
LOCAL LAB	• Urine pregnancy test (WOCBP only)[h]	
CENTRAL LAB	• Complement C3 and C4 testing • anti-dsDNA • Clinical chemistry, hematology (CBC), urinalysis, UPCR • IgG and IgM • Blood samples for elsubrutinib and upadacitinib PK analysis[m,n,o]	• Biomarker samples: whole blood for BTK occupancy analysis (only select number of sites and subjects in the US)[f,m,o] • Biomarker Sample: whole blood for BTK Y223 phosphorylation assay[f,m,o] • Biomarker Sample: whole blood (plasma, serum, DNA and RNA)[f,k,m] • Biomarker Sample: whole blood viable PBMCs[f,m] • Biomarker Sample: whole blood: Immunophenotyping (TBNK, B cell subsets)[f,m,o] • Biomarker Sample: Interferon signature[f,o]
TREATMENT	• Review and copy subject dosing diary and perform drug reconciliation[n]	

Footnotes for Protocol Activities:

a. A complete medical history and prior/concomitant therapy will be taken at Screening and will be updated at the Baseline Visit.

b. This is a clinician-reported outcome on the tablet.

c. A complete physical examination will be performed during Screening and Study Day 1. Physical examinations at other visits can be symptom-directed.

d. Any subject who has a positive skin score at screening (i.e., Principal Investigator [PI] believes they have a Lupus rash) needs photos for adjudication; photos will only be collected for subjects presenting with a possible Lupus rash during Screening and at Week 24 for those who have a confirmed (by adjudicator) Lupus rash at screening.

e. Subjects will be tested for the presence of the hepatitis B and C virus (HBV and HCV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) or hepatitis C (HCV RNA detectable for any subject with positive anti-HCV Ab) will be exclusionary. For subjects who are negative for HBsAg but positive for core antibody (HBc Ab), HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

f. Will not be collected in China.

g. The patient-reported outcome (PRO) instrument should be completed prior to drug administration on Day 1 and prior to any discussion of adverse events or any review of laboratory findings. The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

h. Urine pregnancy test will be performed locally as indicated in the table for all females of childbearing potential. The urine pregnancy test must be negative to receive study drug. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

i. Post-dose collection.

j. Pre-dose and post-dose collection.

k. Blood samples collected and analyzed from all subjects unless precluded by local regulations or restrictions.

l. Pre-dose collection.

m. Collection at any time during the visit.

n. Not required if subject discontinues study drug but remains in the study.

o. To be completed at Premature Discontinuation (PD) only.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

30-Day Follow Up Phone Call:*

INTERVIEW	• AE and AESI assessment • Prior and concomitant therapy	• Steroid therapy assessment

* The 30-day follow up call will be calculated from the last study drug administration date/last visit for all subjects not entering the long-term extension (LTE) Study M20-186.

3 STUDY PROCEDURES

Screening Period

Within 42 days prior to the Baseline visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in the Activity Schedule in Protocol Appendix D. With the exception of the QuantiFERON TB-Gold and purified protein derivative (PPD) tests (requirements outlined in Section 3.13), otherwise exclusionary laboratory values can be re-tested once during the screening period. If the re-tested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since previous result was never obtained.

Re-Screening

Subjects who initially screen-fail for the study are permitted to be re-screened once following reconsent. For additional re-screening, AbbVie Therapeutic Area Medical Director (TA MD)/Scientific Director approval is required. All screening procedures, with the exceptions noted below, will be repeated during re-screening. The subject must meet all of the eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time that a subject must wait to re-screen for the study, except for the SARS-CoV-2 infection criteria.

Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only re-screen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least 14 days since first molecular test (e.g., PCR) result have passed in asymptomatic subjects or 14 days since onset of signs/symptoms, defined as resolution of fever without use of antipyretics and improvement in symptoms.

If the subject had an initial screening evaluation including the following assessments, the below tests will not be required to be repeated for re-screening, provided the conditions noted in Protocol Section 5.1 (Eligibility Criteria) are met, there are no changes in the subject's medical history that warrant re-testing, and no more than 90 days have passed:

- Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) serology
- Interferon (IFN)-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In-Tube test or equivalent) and/or a PPD test (or both if required per local guidelines)
- Interferon signature, antinuclear antibody (ANA) test/anti-Smith Antibody (Ab)
- Immunoglobulin G (IgG), immunoglobulin M (IgM)
- Cotinine measurement
- Chest x-ray (CXR)
- Electrocardiogram (ECG)

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

3.2 Medical History and Prior/Concomitant Medications

A complete list of prior/concomitant medications and medical history including demographics, history of tobacco (e.g., smoking and/or vaporizing or other routes of administration or nicotine substitutes), alcohol, and drug use will be taken at Screening. The subject's prior/concomitant medications and medical history, including history of herpes zoster vaccination (and the name of the specific vaccine) will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment. Concomitant medications will be reviewed at each study visit listed in Section 2.1.

3.3 Adverse Event Assessment and Adverse Events of Special Interest

Please refer to Section 4 for adverse events (AEs) and Section 6 of the protocol for adverse events of special interest (AESI).

3.4 Skin Photographs

Subjects with rash at Screening, considered by the investigator to be due to systemic lupus erythematosus (SLE), should have photographs taken at Screening for adjudication. For those subjects who have confirmed (by adjudication) Lupus rash at screening, photographs will also be taken at Week 24. Subject must voluntarily provide consent, approved by an institutional review board/independent ethics committee (IRB/IEC), after the nature of the skin photographs has been explained and the subject has had an opportunity to ask questions. If the subject presents with a rash requiring adjudication at Screening, the subject must consent to skin photographs or they will not be allowed to participate in the study. Subjects who agree to skin photographs are consenting to photographs at Screening and at Week 24 (for those who have confirmed Lupus rash by adjudication).

3.5 Patient-Reported Outcomes

Subjects will complete the self-administered patient-reported outcome (PRO) instruments (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The PRO instrument should be completed prior to drug administration on Day 1 and prior to any discussion of AEs or any review of laboratory findings. The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

LupusQoL

The Lupus Quality of Life questionnaire (LupusQoL) is a disease-specific health-related quality of life (HRQoL) PRO instrument. It has 8 domains including physical health, emotional health, body image, pain, planning, fatigue, intimate relationships, and burden on others. Item responses are based on a 5-point Likert scale ranging from 0 = "All the time" to 4 = "Never." These 8 domains are measured via 34 items and are scored separately. Scores range from 0 (worst HRQoL) to 100 (best HRQoL).

Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) system is a collection of quality of life (QoL) questionnaires targeted to the management of cancer and other chronic illnesses. The FACIT-Fatigue questionnaire was developed to assess fatigue associated with anemia. It consists of 13 fatigue-related questions. The responses to the 13 items on the FACIT-Fatigue questionnaire are each measured on a 5-point Likert scale. The responses to the answers are the following: (i) not at all: 0 points; (ii) a little bit: 1 point; (iii) somewhat: 2 points; (iv) quite a bit: 3 points; (v) very much: 4 points. Items are summed, and reverse scored when appropriate, to provide a total score ranging from 0 to 52, where higher scores represent better QoL.

SF-36

The SF-36v2 is a general health-related quality of life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises 36 total items (questions) targeting a subject's functional health and well-being in 8 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Scoring is totaled into a Physical Component Summary and a Mental Component Summary. Higher SF-36v2 scores indicate a better state of health.

Patient Global Assessment of Disease Activity (PtGA)

The PtGA is a single-item assessment in which subjects are asked to rate the overall effect that lupus has on them at the time the assessment is completed. The PtGA is a visual analog scale with scores ranging from 0 to 100 and high scores indicating greater disease activity.

Pain Numerical Rating Scale (NRS)

The pain NRS is a single-item questionnaire in which subjects are asked to rate the overall pain level. The pain NRS scores range from 0 to 10, with higher scores indicating a higher level of pain.

3.6 Pharmacokinetic Sampling

Starting 3 days prior to each clinical site visit, subjects are advised to take the study drug dose at the time that matches their scheduled visit time at the clinical site. Following the clinical visit, subjects may continue taking study drug dose according to their regular schedule.

On the day of the study visit, subjects will take their dose of study drug at the clinical site and 1 blood sample for pharmacokinetic (PK) assessments should be collected within specified time intervals at each visit below as follows:

- At Baseline, between 0.5 and 2 hours following dosing;
- At Week 4, between 2 and 6 hours following dosing;
- At Week 12, pre-dose;
- At Week 20, between 0.5 and 2 hours following dosing; and
- At Week 24, between 2 and 6 hours following dosing;
- Premature Discontinuation (PD), at any time during the visit.

3.7 Biomarker Research Sampling

Blood samples will be collected for biomarker research. Refer to Section 2.1 for the schedule of biomarker research sample collections. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will use and store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on elsubrutinib (ABBV-105), upadacitinib (ABT-494), ABBV-599 (elsubrutinib/upadacitinib) combination (or drugs of this class), or SLE and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Whole blood for Bruton's tyrosine kinase (BTK) Y223 phosphorylation assay will be collected twice at Baseline, pre-dose and post-dose collection. This biomarker will also have Week 12, Week 24, and PD visits collection. The collection window at Baseline (post-dose only), Week 12 (pre-dose), Week 24 (post-dose), and at PD visits should be the same as collection of blood samples for PK assessment.

At select study sites, whole blood for BTK occupancy will be collected twice at Baseline, pre-dose and post-dose collection. This biomarker will also have Week 12, Week 24, and at PD visits collection (in a subset of sites/subjects). The collection window at Baseline (post-dose only), Week 12 (pre-dose), Week 24 (post-dose), and at PD visits should be the same as collection of blood samples for PK assessment.

Whole blood for immunophenotyping (T lymphocytes, B lymphocytes, and natural killer lymphocytes [TBNK], B cell subsets) will be collected pre-dose at Baseline, and at any time during the visit at Week 4, Week 12, Week 24, and PD.

Whole blood for plasma, serum, viable peripheral blood mononuclear cells (PBMCs), DNA, and RNA, will be collected pre-dose at Baseline, and at any time during the visit at Week 2, Week 4, Week 12, Week 24, Week 48, or at PD.

Interferon signature will be collected at Screening, Week 4, Week 24, and at PD.

3.8 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the designated study visits as specified in Section 2.1. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

ECGs with QT interval corrected for heart rate using Fridericia's correction formula (QTcF) should be reported (or calculated) and documented in the source documents and later transcribed on to the appropriate electronic case report form (eCRF) if QTcF prolongation is observed.

A valid QTcF cannot be calculated in subjects who have a pacemaker or supraventricular or ventricular conduction abnormalities. In cases of QTcF prolongation, the baseline QTcF will need to be entered into the appropriate eCRF for comparison as well. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF. Each signed original ECG will be monitored by the responsible site monitor and kept with a subject's source documents onsite.

Subjects can have a repeat ECG at any time during the study as warranted based on the opinion of the investigator.

3.9 Height and Weight

Height will be measured at Screening only. Body weight will be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing.

3.10 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure (BP), pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure, pulse rate, and respiratory rate should be measured after the subject has been sitting for at least 3 minutes and prior to drawing lab samples.

3.11 Physical Examination and Assessments

A physical examination will be performed at the designated study visits as specified in Section 2.1. The complete physical examination performed on Study Day 1 will serve as the baseline physical examination for the entire study. Physical examinations at subsequent study visits can be symptom-directed. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

Chest x-ray (CXR)

A CXR (posterior-anterior and lateral views) is required for all subjects at Screening to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) or computed tomography (CT) scan of the chest within 90 days of Screening, provided all source documentation is available at the site, as outlined below and provided nothing has changed in the subject's medical history to warrant a repeat test. A radiologist or pulmonologist must perform and document an assessment of the CXR at Screening (If allowed per local regulation, a qualified physician can perform and document an assessment of the CXR at Screening.). The Principal Investigator (PI) will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the PI or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR or prior chest CT scan demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the PI should contact the AbbVie TA MD before enrolling the subject.

Subjects can have a repeat CXR at any time during the study as warranted based on the opinion of the investigator.

TB risk assessment

Done at Screening only (see Section 3.13 for more information about TB testing and Appendix B).

Physician Global Assessment of Disease Activity (PhGA)

The physician will rate global assessment of the subject's current disease activity, ranging from 0 to 3 independent of the subject's self-assessment using the visual analogue scale, which consists of a horizontal 3-inch line anchored at either end by opposite adjectives reflecting the spectrum/severity of the parameters assessed at visits specified in Section 2.1.

Swollen and Tender Joint Count Assessment

An assessment of 28 joints will be done by directed physical examination at visits specified in Section 2.1. Joint swelling will be classified as present ("1"), absent ("0"), replaced ("9"), or no assessment ("NA"). Joint tenderness will additionally be classified as present ("1"), absent ("0"), replaced ("9"), or "NA."

Any injected joints will be considered as "not assessed" ("NA") for 3 months from the time of the intra-articular injection.

If possible, the swollen joint count (SJC) and tender joint count (TJC) should be performed by an independent and blinded joint assessor who should not perform any other study-related procedures.

In order to minimize variability, the same independent joint assessor should evaluate the subject at each visit for the duration of the trial as much as possible. A back-up independent joint assessor should be identified. The independent joint assessors should be a qualified medical professional (e.g., nurse, physician's assistant, physician). Any other joint assessor must be trained and competent in performing such assessments. It is the responsibility of the investigator to ensure that all assessors are qualified and trained to perform joint assessments. If the independent assessor is not available, the preidentified back-up assessor should perform such assessments.

SLE Disease Activity Index (SLEDAI)-2K assessment

The SLEDAI-2K is a global index that evaluates disease activity over the previous 30 days and includes 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular, and hematological. The SLEDAI-2K scores all active (not merely emerging) rash, alopecia, oral ulcers, and proteinuria, and collects disease aspects as present or absent. Thus, it may not reflect partial improvement.

British Isles Lupus Activity Group (BILAG) assessment 2004

The British Isles Lupus Assessment Group (BILAG) 2004 evaluates specific manifestations over the previous four weeks in a total of 8 organs systems, 9 in the revised Index: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal (GI), ophthalmic, renal, and hematological. Activity in each organ system is scored as: A = severe disease; B = moderate activity; C = mild disease; D = previous involvement, currently inactive; E = no previous activity. The BILAG also is used to evaluate the occurrence of flares in patients with SLE. A severe flare is defined as a score of A, new appearance and a moderate flare is defined with a score of B, and a reoccurrence is defined with a score of D or E.

The BILAG-Based Combined Lupus Assessment (BICLA)

The BILAG-Based Combined Lupus Assessment (BICLA) is a composite index used in clinical trials. This differs from the SLE Responder Index (SRI) in that the BILAG-2004 index is the driver of efficacy. BICLA requires patients to meet response criteria across the BILAG-2004 index, SLEDAI-2K, and PhGA. To be classified as a BICLA responder, patients must meet the following criteria: BILAG-2004 index improvement in all A and B scores, no more than one new BILAG B score, no worsening of the total SLEDAI-2K score from Baseline, no significant deterioration (not > 10% worsening) in the 100 mm visual

analogue PhGA and no treatment failure. The BICLA also identifies deterioration in clinical features and excludes treatment failures.

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) assessment

The CLASI is a simple, single-page tool that separately quantifies disease activity and damage. Each part of the body is listed separately, from the scalp to the feet, in addition to sections focusing on mucous membrane involvement and alopecia. Scores for each area are assigned based on the most severe lesion within the area of interest. Of note, affected body parts are weighted equally regardless of surface area and number of lesions present. The selection of these equally weighted segments was designed to reflect the impact of more common areas of SLE skin involvement. Unlike the SLEDAI and BILAG, interim disease between visits is not accounted for, only the condition on the day of the examination.

SELENA SLEDAI Flare Index assessment

The SELENA SLEDAI Flare Index (SFI), developed by the SELENA trials, is a composite outcome of SELENA; distinguishing mild/moderate, and severe flares; integrating specific descriptors, medication changes, the Physician Global Assessment of Disease Activity (PhGA), and changes in the total SLEDAI score.[1]

3.12 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 2.1. The first dose of study drug will be administered after all other Baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the subject dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Elsubrutinib capsules, upadacitinib tablets, and matching placebo capsules and tablets should be dosed together at approximately the same time each day and taken with or without food.

3.13 Clinical Laboratory Tests

The blood samples for serum chemistry tests should be collected following a minimum 8-hour fast prior to study drug intake (with the exception of the Screening visit, which may be nonfasting). Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study drug with food. Subjects whose visits occur after the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Study Day 1 visit, a fasting blood sample should be collected prior to the first dose of study drug. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or nonfasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from study drug or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE.

If renal and hematological laboratory results required for physician indices are not available (e.g., specimen hemolyzed, specimen lost in transit, specimen received beyond stability, etc.), re-draw should occur within 7 days of notification from Labcorp Drug Development that results are unavailable.

Clinical Laboratory Tests[a]		
HEMATOLOGY	**CLINICAL CHEMISTRY**	**URINALYSIS**
Hematocrit Hemoglobin Red Blood Cell (RBC) count/ Erythrocytes White Blood Cell (WBC) count/ Leukocytes Platelet count/Thrombocytes Prothrombin Partial thromboplastin **Differential Automatic (absolute count):** Neutrophils Eosinophils Basophils Monocytes Lymphocytes **Manual Differential (ONLY IF Automated Differential is abnormal):** Neutrophils, bands (stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes	**Electrolytes** Calcium Sodium Potassium Chloride Bicarbonate **Substrates** Glucose Blood urea nitrogen Creatinine (Glomerular Filtration Rate [GFR]) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Albumin Cholesterol, total Low-density lipoprotein cholesterol High-density lipoprotein cholesterol Triglycerides Follicle-stimulating hormone (FSH)[b] Cotinine **Enzymes** Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase Creatine phosphokinase (CPK)[c] Aldolase[c]	**Dipstick Urinalysis** Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocytes Urine WBC/Leukocytes Urine pH Urine creatinine **Urine-Sediment** (microscopic examination, **only if** urine analysis abnormal) Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sediment Crystals, Unspecified Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leukocytes **Urine** Urine Protein to Creatinine Ratio

INFECTION SCREENING	PREGNANCY TESTING	PHARMACOKINETIC/ PHARMACODYNAMIC
HBs Ag (qualitative) HBs Ab (qualitative) Anti-HBc total (qualitative) HBV DNA (quantitative) HCV Ab (qualitative) HCV RNA (quantitative) HIV-1 and HIV-2 Ab (qualitative) QuantiFERON®-TB and/or PPD Beta-D-glucan (for Japan subjects only)	Urine pregnancy test (local) Serum pregnancy test	Plasma elsubrutinib and upadacitinib concentration
	CENTRAL LAB[a]	**SPECIALTY LAB**
	B cell subsets and TBNK cells ANA Anti-Smith Anti-dsDNA Complement C3, C4 IgG and IgM Anticardiolipin antibody Anti-beta 2 glycoprotein 1 antibody Lupus anticoagulant	Blood sample for BTK occupancy analyses (only select number of sites and subjects in the US) Blood sample for BTK Y223 IFN signature

Ab = antibody; ANA = antinuclear antibody test; COVID-19 = coronavirus disease 2019; BTK = Bruton's tyrosine kinase; dsDNA = double-stranded deoxyribonucleic acid; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; HBV = hepatis B virus; HBc = Hepatitis B core (antibody); HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; IgG = immunoglobulin G; IgM = immunoglobulin M; JAK = Janus kinase; PPD = purified protein derivative; TA MD = Therapeutic Area Medical Director; TB = tuberculosis; TBNK = T lymphocytes, B lymphocytes, and natural killer lymphocytes; US = United States

a. Tests may also be performed by a certified local lab if sending samples to the central lab is not possible due to COVID-19-related restrictions.

b. Performed only at Screening.

c. CPK and aldolase will be measured at every visit but results will be blinded to sites and subjects, as CPK elevation is a known class effect of JAK inhibitors and the results could be unblinding to the sites. If symptomatic myositis is suspected, the site may send a request to the AbbVie TA MD for CPK and/or aldolase results to be unblinded. Request must be approved by the AbbVie TA MD.

Pregnancy Testing (Serum and Urine)

Pregnancy testing should not be performed for women who are not of childbearing potential, as described above.

A quantitative serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at Baseline.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;

- Still borderline, ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Urine pregnancy tests will be performed at all scheduled visits. An at-home pregnancy test is required if a scheduled study visit is missed. The results of at-home testing must be communicated to the site. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the Baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the Baseline or post-Baseline urine pregnancy test is positive, dosing with study drug must be withheld, and a serum pregnancy test is required (as stated above).
- Unless a woman is suspected to have become pregnant, additional pregnancy testing beyond the monthly testing during the clinical trial is not required.

At each visit, the study staff should review the pregnancy avoidance recommendations with each female of childbearing potential and document this discussion in the subject's source records.

Clinical Chemistry

A minimum 8-hour fast is recommended for blood samples to be drawn for chemistry. If a subject is not able to fast when necessary due to unforeseen circumstances, the nonfasting status will be recorded in study source documentation.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

TB Testing/TB Prophylaxis

The TB screening tests provide diagnostic test results to be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the investigator to determine if a subject has previous, active, or latent TB. Expert consultation for the evaluation and/or management of TB may be considered per investigator discretion.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment form (see Appendix B) and tested for TB infection by QuantiFERON-TB Gold test. The PPD skin test should be utilized only when a QuantiFERON-TB Gold test is not possible for any reason (unless both tests are required per local guidelines). IGRA equivalent test may be used as available and if compliant with local TB guidelines. The site staff will complete the TB risk assessment form and enter the data into an appropriate eCRF.

If a subject had a negative QuantiFERON-TB Gold (and/or PPD) test (or IGRA equivalent such as T-SPOT.TB test) within 90 days prior to Screening and source documentation is available, the test does

not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test. These cases may be discussed with the AbbVie TA MD. The results of the TB test(s) will be retained at the site as the original source documentation.

Subjects with a negative TB test and CXR not suggestive of active TB or prior TB exposure may be enrolled.

Subjects with a positive TB test must be assessed for evidence of active TB or latent TB, including signs and symptoms and CXR. Subjects with no signs or symptoms and a CXR not suggestive of active TB may be enrolled if the subject has documentation of a full course of prophylaxis (at least 6 months of treatment with isoniazid per investigator discretion based on local guidelines) or treatment for TB. Subjects with a prior history of latent TB who have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment. If documentation of a full course prophylaxis or treatment for TB is not available, the subject should be excluded from the study and be referred to a physician for evaluation and treatment.

Subjects with evidence of active TB must not be enrolled.

Any newly positive TB screen after the subject has started the study should be reported as an AE of latent TB or active TB (as applicable), and subject must be discontinued from the study drug.

TB Testing

- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Test (or equivalent) and/or PPD are not required to repeat either test at Screening and should be considered positive.
- For regions that require both PPD and QuantiFERON-TB Gold testing, both will be performed. If either PPD or QuantiFERON-TB Gold tests are positive, the TB test is considered positive.
- The PPD Skin Test (also known as a TB Skin Test or Mantoux Test) should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless both tests are required per local guidelines).
- If the QuantiFERON-TB Gold Test is NOT possible (or if both the QuantiFERON-TB Gold Test and the PPD are required per local guidelines), the PPD will be performed. The PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration, and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative." Subjects who have had an ulcerating reaction to the PPD in the past should not be re-exposed, and the PPD should be considered positive.
- If the QuantiFERON-TB Gold test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the subject is considered to be negative.

- Interpretation of a positive TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus test by the central laboratory is positive and the investigator considers the subject at low risk for TB (i.e., no risk factors identified using the Part I and Part II questions of the TB risk assessment questionnaire at Screening) and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- If different national regulations exist for screening for latent TB while being on immunosuppressive treatment, these national regulations will be applied, respectively.

Hepatitis Screen

All subjects will be tested for the presence of HBV and HCV at Screening.

Hepatitis B Virus:

Subjects will be tested for the presence of HBV at Screening using the following tests:

- Hepatitis B surface antigen (HBs Ag)
- Hepatitis B core antibody (HBc Ab/anti-HBc)
- Hepatitis B surface antibody (HBs Ab/anti-HBs)

A positive result for HBs Ag will be exclusionary.

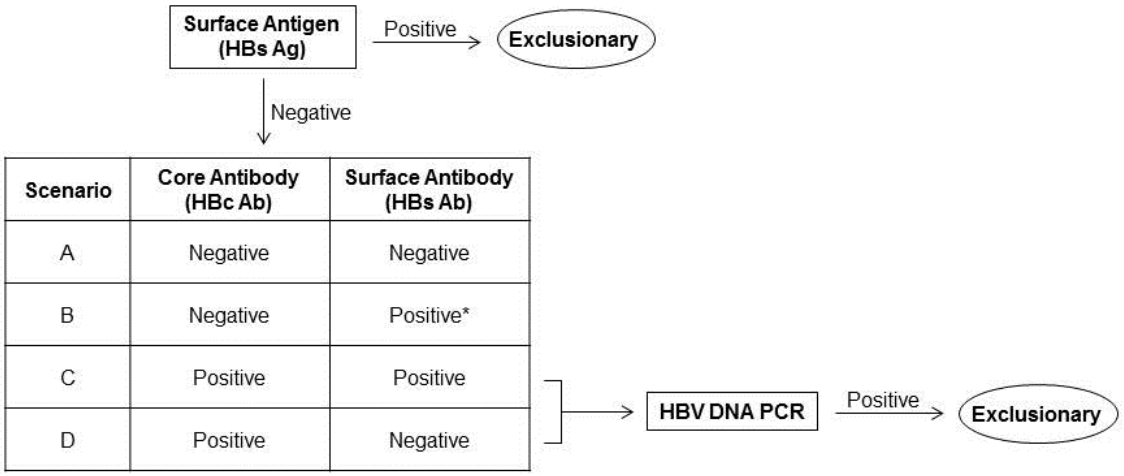
A negative result for HBs Ag will trigger automatic reflex testing for core antibodies (HBc Ab) and surface antibodies (HBs Ab).

- A negative test result for HBc Ab does not require HBV DNA PCR qualitative testing, and the subject may be enrolled (Figure 1, Scenarios A and B).
- For a subject who has had an HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected. The HBV DNA PCR qualitative testing is not required, and the subject may be enrolled (Figure 1, Scenario B).*
- A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 1, Scenarios C and D).
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.
- Where mandated by local requirements: A positive result for HBs Ab requires HBV DNA PCR testing.
  - A result that exceeds detection sensitivity by central laboratory will be considered a positive result for HBV DNA and will be exclusionary.
  - A subject with a negative result for HBV DNA may be enrolled.

- For subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening, HBV DNA PCR test should be performed every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–.

- At any time during the study for subjects with HBc Ab+ (irrespective of HBs Ab status) and negative HBV DNA at Screening, a positive result for HBV DNA PCR testing accompanied by the following will require immediate interruption of study drug (per local guidelines) and a hepatologist consultation should occur within one week for recommendation regarding subsequent treatment:
  - Alanine transaminase (ALT) > 5 × upper limit of normal (ULN) OR
  - ALT/Aspartate transaminase (AST) > 3 × ULN and either a total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5 OR
  - ALT/AST > 3 × ULN along with clinical signs of possible hepatitis.

Figure 1. Interpretation and Management of HBV Serologic Test Results



HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction

* A positive test result for HBs Ab is expected for subjects who have had an HBV vaccination. For subjects without a history of HBV vaccination (and for subjects in Japan and China or where mandated by local requirements), a positive result for HBs Ab/anti-HBs requires HBV DNA PCR testing.

Hepatitis C Virus

Blood samples for HCV serology will be obtained at the Screening visit. A positive HCV Ab will trigger an HCV RNA test. A subject will not be eligible for study participation if test results indicate active hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

HIV

Subjects with HIV infection (positive HIV test) are excluded from study participation. HIV testing will be performed at Screening, unless prohibited by local regulations. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health, and subject should receive or be referred for clinical care promptly.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations, or changes in shipping logistics in light of the coronavirus disease 2019 (COVID-19) pandemic prevent the subject from having blood drawn and analyzed for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued for 1 month provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.

3.14 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

3.15 Unscheduled Visits

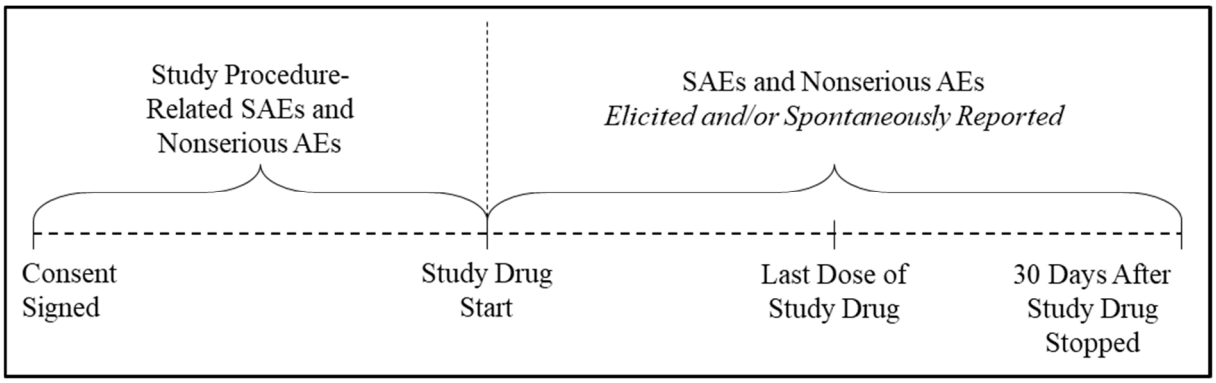
An Unscheduled Visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3.13, or for other tests, at the investigator's discretion.

Visits for dispensing new study drug in case of temperature excursion, loss or damage are not considered an Unscheduled Visit. In addition, visits to only retest a lab will not be considered an Unscheduled Visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs which could be related to study procedures (e.g., infection at blood draw site, done during Screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (TEAEs; i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA system organ class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with TEAEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA PT will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of a serious adverse event (SAE), whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the Electronic data capture system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

abbvie

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064
Office: +1 847-938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

For any subject safety concerns, please contact the contact listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

In Japan, the PI will provide documentation of all SAEs to the Director of the investigative site and to the Sponsor.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19-related missed visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines; Appendix A of the Investigator Brochure for elsubrutinib and for upadacitinib will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a drug safety update report reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.2 Treatment After End of Study

For active subjects randomized to elsubrutinib, upadacitinib, or ABBV-599 (elsubrutinib/upadacitinib) combination, subjects will continue on study treatment throughout the study for a period of up to 48 weeks, or until premature discontinuation of study drug. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject. A long-term extension (LTE) study (Study M20-186) is planned to be conducted under a separate protocol at sites where it is permitted by the local Competent Authority and Ethics Committee. Eligible subject rollover from the initial randomized portion of the study will occur at Week 48.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (elsubrutinib, upadacitinib, and/or matching placebo) will be dispensed in the form of a capsule (elsubrutinib or matching placebo), or film-coated tablet (upadacitinib or matching placebo) at

the visits listed in Section 2.1. Subjects will be instructed to take study drugs at the same time every day.

Study drug will be provided by AbbVie as elsubrutinib 20 mg capsules, upadacitinib 15 mg and 30 mg film-coated tablets, and matching placebo capsules and film-coated tablets.

Study drug will be taken orally as 3 capsules of elsubrutinib and/or matching placebo and 1 film-coated tablet of upadacitinib and/or matching placebo once daily with or without food.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the PD visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

For study drug interruption, the following rules apply:

1. If the subject undergoes elective surgery, the study drug should be interrupted 1 week prior to the planned surgery.
2. Up to Week 24, allow study drug interruption up to 10 consecutive days for AEs, emergency surgery, and abnormal labs. After Week 24, allow study drug interruption up to 30 consecutive days for AEs, emergency surgery, and abnormal labs. Elective surgery will not be allowed during the first 24 weeks of the study. If subject misses or is anticipated to miss > 10 days of study drug during the first 24 weeks of the study or > 30 days of study drug after Week 24, it will be considered a protocol deviation and reported as described in the protocol.
3. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the surgeon has examined the surgical site and determined that it has healed and there is no sign of infection.

At the end of the Treatment Period or at the PD visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

All study drugs will be supplied in bottles.

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Study drug must be stored at controlled room temperature (15° to 25°C/59° to 77°F). Elsubrutinib and placebo must be protected from freezing.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 2, 48-week, multi-center, randomized, double-blind, placebo-controlled study. All eligible subjects will receive the study drug for 48 weeks.

At the Screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

Three capsules of elsubrutinib or matching placebo and 1 tablet of upadacitinib or matching placebo tablet will be dosed together once daily. All subjects should take all doses of study drug around the same time each day, with or without food.

7 References

1. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus. 1999;8(8):685-91.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
NA	No assessment
Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
ANA	Antinuclear antibody
Anti-dsDNA	Anti-double stranded DNA
AST	Aspartate transaminase
BICLA	BILAG-Based Combined Lupus Assessment
BILAG	British Isles Lupus Activity Group
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CXR	Chest x-ray
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
FSH	Follicle-stimulating hormone
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IEC	Independent ethics committee

IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
LTE	Long-term extension
LupusQoL	Lupus Quality of Life questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Premature Discontinuation
PhGA	Physician Global Assessment
PI	Principal Investigator
PK	Pharmacokinetic
PMN	Polymorphonuclear white blood cells
PPD	Purified protein derivative
PRO	Patient-reported outcome
PT	Preferred term
PtGA	Patient Global Assessment
QoL	Quality of life
QTcF	QTc using Fridericia's correction formula
RBC	Red blood cells
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAE	Serious adverse event
SF-36	SF-36 Health Survey
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction

TB	Tuberculosis
TBNK	T lymphocytes, B lymphocytes, and natural killer lymphocytes
TJC	Tender joint count
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United States
WBC	White blood cells
WOCBP	Women of childbearing potential

APPENDIX B. SCREENING TB RISK ASSESSMENT QUESTIONNAIRE (SAMPLE FORM)

For Screening TB risk assessment, ask Part I and Part II questions.

For Annual TB risk assessment, only ask the Part I questions.

Part 1

1. Has an immediate family member or other close contact been newly diagnosed with or treated for active or latent tuberculosis during the last 3 months?
2. Within the past year, have you, or an immediate family member, had any of the following problems lasting for 3 weeks or longer which remained unexplained:
   - Chronic Cough
   - Production of Sputum
   - Blood-Streaked Sputum
   - Weight Loss
   - Fever
   - Fatigue/Tiredness
   - Night Sweats
   - Shortness of Breath

   (Reference: https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm)

Part II

3. Have you ever been diagnosed or treated for active or latent tuberculosis?
4. Have you lived in or had prolonged travels to any of the following TB endemic regions?

Angola	China	India	Mozambique	Papua New Guinea	Thailand
Bangladesh	Congo	Indonesia	Myanmar	Philippines	UR Tanzania
Brazil	DPR Korea	Kenya	Namibia	Russian Federation	Viet Nam
Cambodia	DR Congo	Lesotho	Nigeria	Sierra Leone	Zambia
Central African Republic	Ethiopia	Liberia	Pakistan	South Africa	Zimbabwe

   (Reference: World Health Organization Global Tuberculosis Report 2018. Available from: https://www.who.int/tb/publications/global_report/en/)

5. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?