abbvie

Protocol for Study M20-186

Systemic Lupus Erythematosus: A Phase 2, Long-Term Extension (LTE) Study in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus

VERSION:	4.0	DATE:	26 October 2021
SPONSOR:	AbbVie	NUMBER OF SITES:	Approximately 100
ABBVIE INVESTIGATIONAL PRODUCT:	ABBV-599 (elsubrutinib in combination with upadacitinib)	EudraCT:	2020-001690-72

FULL TITLE: A Phase 2, Long-Term Extension (LTE) Study with Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus Who Have Completed the M19-130 Phase 2 Randomized Controlled Trial (RCT)

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and Administrative Change 1

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted] MD
Immunology Clinical Development
R&D
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile:
Fax:
Email: [redacted]

EMERGENCY 24-hour Number: +1 (973) 784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix H).

abbvie

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 2, Long-Term Extension (LTE) Study with Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus Who Have Completed the M19-130 Phase 2 Randomized Controlled Trial (RCT)	
Background and Rationale:	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. Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of SLE and other autoimmune diseases. Bruton's tyrosine kinase 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. The potential clinical value of BTK inhibition has been supported by studies in preclinical models of arthritis and lupus. 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 2) efficacy in myeloid-mediated animal arthritis models, consistent with the effects of BTK inhibition on macrophage, mast cell, dendritic cell, and neutrophil activity, 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. Upadacitinib (ABT-494), an oral Janus kinase (JAK) inhibitor, 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 being investigated in separate clinical studies in other indications, which include psoriatic arthritis, active axial spondyloarthritis, ulcerative colitis, Crohn's disease, atopic dermatitis, giant cell arteritis, and polyarticular course juvenile idiopathic arthritis. The clinical hypothesis for this study is that inhibition of JAK1 pathways in combination with BTK pathways in SLE will provide greater clinical efficacy compared with inhibition of each individual pathway when

	they are added to current standard of care while maintaining an acceptable safety profile.
Objective(s) and Endpoint(s):	The primary objective is to evaluate the longer-term safety and tolerability of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in SLE subjects who have completed the M19-130 Phase 2 study. The secondary objective is to obtain longer-term efficacy data beyond Week 48 and to more fully assess the benefit/risk of each assigned treatment over time. **Efficacy Endpoints:** Efficacy endpoints for this long-term extension (LTE) study will be measured at specified study visits and include the following: <u>Secondary Endpoints:</u> 1. Achievement of SLE Responder Index (SRI)-4 2. Achievement of British Isles Lupus Assessment Group (BILAG)-Based Combined Lupus Assessment (BICLA) response 3. Steroid burden, assessed as change from M19-130 Baseline 4. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLE Disease Activity Index (SLEDAI) flare index (SFI), assessed by number and types of flare per subject <u>Additional Endpoints:</u> 1. Achievement of Lupus Low Disease Activity State (LLDAS) 2. Achievement of ≥ 4-point decrease in SLEDAI-2K compared with M19-130 Baseline 3. Achievement of 50% reduction of tender or swollen lupus joints (of those starting with total ≥ 6 affected joints) from M19-130 Baseline 4. Achievement of 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score (of those starting with CLASI ≥ 10 at M19-130 Baseline) 5. Change in SLEDAI-2K from M19-130 Baseline 6. Change in BILAG from M19-130 Baseline 7. Change in Physician's Global Assessment (PhGA) from M19-130 Baseline 8. Change in Patient Global Assessment (PtGA) from M19-130 Baseline 9. Change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue from M19-130 Baseline 10. Change in 36-Item Short Form Health Survey (SF-36) from M19-130 Baseline 11. Change in Lupus Quality of Life questionnaire (LupusQoL) from M19-130 Baseline

	12. Change in Pain Numerical Rating Scale (NRS) from M19-130 Baseline 13. Number of withdrawals from study drug due to lack of efficacy **Safety Endpoints:** The following safety evaluations will be performed for the entire study duration as measures of safety and tolerability: • Adverse event (AE) monitoring • Physical examinations • Vital sign measurements • Electrocardiograms (ECGs) • Clinical laboratory testing (hematology, chemistry, and urinalysis)
Investigator(s):	Multicenter
Study Site(s):	Approximately 100 sites including, but not limited to, Argentina, Australia, Canada, China, Colombia, France, Germany, Hungary, Italy, Japan, Mexico, Netherlands, New Zealand, Poland, South Korea, Spain, Taiwan, the United Kingdom, and the United States (including Puerto Rico).
Study Population and Number of Subjects to be Enrolled:	Adult subjects with SLE who have completed the M19-130 Phase 2 study while on study drug and have not developed any laboratory or clinical discontinuation criteria as defined in that study. Based on the planned Study M19-130 Interim Analysis, 1 or more treatment groups may be discontinued. Subjects that are part of the discontinued treatment group(s) will not be eligible for this study. It is anticipated that between 60% and 80% of subjects from Study M19-130 (195 to 260 subjects) will be enrolled in this study.
Investigational Plan:	This is a multicenter, double-blind LTE study designed to investigate the longer-term safety and efficacy of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in subjects with moderately to severely active SLE despite standard of care therapy. Subjects who participated in Study M19-130 may be offered the opportunity to consent for this study. The number of subjects participating in this study will not be greater than the number randomized into Study M19-130. Subjects discontinuing study drug prematurely in Study M19-130 are not eligible to participate in the LTE study. Prior to the planned Study M19-130 Interim Analysis, qualified subjects entering LTE Study M20-186 stayed in their original treatment group from Study M19-130 if on ABBV-599 (elsubrutinib/upadacitinib) combination or elsubrutinib or upadacitinib monotherapy. Those originally assigned to the placebo group in Study M19-130 were randomized centrally in a 1:1 ratio to the 2 ABBV-599 (elsubrutinib/upadacitinib) combination treatment groups. Prior to the planned Study M19-130 Interim Analysis, there were 4 treatment groups in this study:

	• Group 1: Elsubrutinib 60 mg once a day (QD) and upadacitinib 30 mg QD • Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD • Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD • Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD A planned unblinded interim analysis for Study M19-130 was scheduled 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 Study M19-130 Interim Analysis was performed by an independent team at AbbVie that was separate and apart from the blinded study team for Study M19-130. The M19-130 study team will remain blinded through the Study M19-130 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. Based on the benefit/risk assessment of the planned Study M19-130 Interim Analysis, subjects in 1 or more groups in LTE Study M20-186 may be discontinued. Subjects in any discontinued group(s) should return for a Premature Discontinuation (PD) visit and have a follow-up phone call 30 days after the last study drug dose. Subjects originally assigned to the placebo group in Study M19-130 will be rolled over and will be randomized to an active treatment group in LTE Study M20-186. This study includes a 56-week double-blind treatment period with study visits conducted at Weeks 48, 56, 64, 72, 80, 88, 96, and 104 (from the Baseline visit of Study M19-130), and a subsequent telephone follow-up call 30 days after the last visit to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.
Key Eligibility Criteria:	Eligible subjects will have completed Study M19-130 (i.e., the Randomized Controlled Trial [RCT] of elsubrutinib, upadacitinib, and ABBV-599 [elsubrutinib/upadacitinib] combinations or matching placebo) on study drug and will not have developed any laboratory or clinical discontinuation criteria as defined in that study. Subjects must be on stable background treatment for SLE throughout the study. Subjects must not have: any active, chronic, or recurrent viral or bacterial infection; active tuberculosis (TB); or a history of gastrointestinal (GI) perforation, diverticulitis, or a significantly

	increased risk for GI perforation per investigator assessment. Subjects must not require vaccination with any live vaccine during study participation (including at least 30 days after the last dose of study drug).
Study Drug and Duration of Treatment:	Subjects may receive elsubrutinib 60 mg QD monotherapy; upadacitinib 30 mg QD monotherapy; or 1 of 2 ABBV-599 (elsubrutinib/upadacitinib) combinations (elsubrutinib 60 mg QD and upadacitinib 30 mg QD or elsubrutinib 60 mg QD and upadacitinib 15 mg QD). Study drug will be taken orally as 3 capsules of elsubrutinib or matching placebo and 1 film-coated tablet of upadacitinib or matching placebo with or without food for 56 weeks.
Date of Protocol Synopsis:	26 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 SLE and other autoimmune diseases. Bruton's tyrosine kinase 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.[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, 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 being investigated in separate clinical studies in other indications, which include psoriatic arthritis, active axial spondyloarthritis, ulcerative colitis, Crohn's disease, atopic dermatitis, giant cell arteritis, and polyarticular course juvenile idiopathic arthritis.

Clinical Hypothesis

Inhibition of JAK1 pathways in combination with BTK pathways in SLE will provide greater clinical efficacy compared with inhibition of each individual pathway when they are added to current standard of care while maintaining an acceptable safety profile.

2.2 Benefits and Risks to Subjects

Both upadacitinib and elsubrutinib have the potential, when added to current standard of care, to offer clinically meaningful efficacy over the current standard of care for the treatment of SLE with an acceptable safety profile. The ABBV-599 (elsubrutinib/upadacitinib) combination of BTK inhibition by elsubrutinib and JAK1 inhibition by upadacitinib has the potential to provide even greater clinical efficacy compared with either monotherapy while maintaining an acceptable safety profile.

Upadacitinib is approved as a single-ingredient agent for the treatment of RA and is being developed for 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. The enhanced selectivity of upadacitinib for JAK1 may offer an improved benefit/risk profile compared with less selective JAK inhibition in patients with immune-mediated inflammatory diseases due to reduced JAK2-related effects such as inhibition of erythropoiesis and inhibition of granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling, the latter of which plays a critical role in a myelopoietic response to microbial infection. In addition, there is reduced potency of upadacitinib against JAK3 thereby minimizing the reduction in natural killer (NK) cells. Hence, the JAK2- and JAK3-sparing properties of upadacitinib may manifest as a reduced risk of anemia and infection compared with less selective JAK inhibitors such as tofacitinib (Xeljanz®) and baricitinib (Olumiant®). On the basis of this differentiated selectivity profile for the inhibition of JAK kinases, there is potential for an improved benefit/risk profile of upadacitinib compared with other JAK inhibitors currently in clinical trials.

Identified risks for upadacitinib are summarized in the upadacitinib Investigator's Brochure[8] and include: serious infections, opportunistic infections and tuberculosis (TB), and herpes zoster. Potential risks for upadacitinib include: malignancies, including lymphoma and non-melanoma skin cancer (NMSC), gastrointestinal (GI) perforations, major adverse cardiovascular events (MACE), hematologic changes (anemia, neutropenia, and lymphopenia), increased serum creatinine and renal dysfunction, hepatic events and increased hepatic transaminases, elevated creatine phosphokinase (CPK), embolic and thrombotic events (non-cardiac, non-central nervous system [CNS]), and fetal risks.

As of 15 December 2019, 171 healthy volunteers have received at least 1 dose of elsubrutinib; the most common side effect reported was headache, mild in severity.

As of 06 May 2020, from the Phase 2 RA and SLE studies, there are no identified safety risks for elsubrutinib or for ABBV-599 (elsubrutinib/upadacitinib) combination.

A detailed description of the preclinical pharmacology, metabolism, and toxicology datasets can be found in the elsubrutinib[9] and upadacitinib[8] 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.

Systemic lupus erythematosus 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.

In LTE Study M20-186, benefit/risk assessment of treatment groups for rollover may require subjects to be reassigned or discontinued based on the outcome of the unblinded interim analysis from the feeder Study M19-130 (See Section 4 Investigational Plan). Routine safety evaluations of all treatment groups will be performed. These include assessments of deaths, serious adverse events (SAEs), non-serious adverse events (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 exclusions and ongoing assessments are included in the protocol:

- Exclusion of subjects with chronic or recent infections including active TB.
- Evaluating subjects for TB [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 evaluating TB while being on immunosuppressive treatment, these national regulations will be applied, respectively.
- 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 3.4 for detailed safety endpoints and Section 6.3 for information on the Data Monitoring Committee (DMC).

For further details, please see findings from completed studies, including safety data in the elsubrutinib[9] and upadacitinib[8] 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. Further guidance regarding COVID-19 infection is provided in Section 6.2.

3 OBJECTIVES AND ENDPOINTS

Objectives and Hypothesis

Primary

The primary objective is to evaluate the longer-term safety and tolerability of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in SLE subjects who have completed the M19-130 Phase 2 study.

There is no planned hypothesis to be tested for this long-term extension (LTE) study.

Secondary

The secondary objective is to obtain longer-term efficacy data beyond Week 48 and to more fully assess the benefit/risk of each assigned treatment over time.

3.1 Primary Endpoint

There is no primary efficacy endpoint since this is the extension to the feeder Study M19-130.

3.2 Secondary Endpoints

Secondary efficacy endpoints for this study, measured at specified study visits, include the following:

1. Achievement of SLE Responder Index (SRI)-4
2. Achievement of British Isles Lupus Assessment Group (BILAG)-Based Combined Lupus Assessment (BICLA) response
3. Steroid burden, assessed as change from M19-130 Baseline
4. Number of mild, moderate, or severe flares per patient-year (respectively and overall) by Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLE Disease Activity Index (SLEDAI) flare index (SFI), assessed by number and types of flare per subject

3.3 Additional Efficacy Endpoints

Additional efficacy endpoints for this study, measured at specified study visits, include the following:

1. Achievement of Lupus Low Disease Activity State (LLDAS)
2. Achievement of ≥ 4-point decrease in SLEDAI-2K compared with M19-130 Baseline
3. Achievement of 50% reduction of tender or swollen lupus joints (of those starting with total ≥ 6 affected joints) from M19-130 Baseline
4. Achievement of 50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score (of those starting with CLASI ≥ 10 at M19-130 Baseline)
5. Change in SLEDAI-2K from M19-130 Baseline

6. Change in BILAG from M19-130 Baseline
7. Change in Physician's Global Assessment (PhGA) from M19-130 Baseline
8. Change in Patient Global Assessment (PtGA) from M19-130 Baseline
9. Change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue from M19-130 Baseline
10. Change in 36-Item Short Form Health Survey (SF-36) from M19-130 Baseline
11. Change in Lupus Quality of Life questionnaire (LupusQoL) from M19-130 Baseline
12. Change in Pain Numerical Rating Scale (NRS) from M19-130 Baseline
13. Number of withdrawals from study drug due to lack of efficacy

For more information on the description of efficacy measures, refer to Appendix E.

3.4 Safety Endpoints

The following safety evaluations will be performed for the entire study duration as measures of safety and tolerability:

- AE monitoring
- Physical examinations
- Vital sign measurements
- ECGs
- Clinical laboratory testing (hematology, chemistry, and urinalysis)

Serious adverse events 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 (see Section 6.1 for more details).

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 GI perforations, adjudicated cardiovascular events (e.g., MACE), anemia, neutropenia, lymphopenia, renal dysfunction, hepatic disorders, and adjudicated embolic and thrombotic events (non-cardiac, non-CNS) including venous thromboembolic events defined as pulmonary embolism and deep vein thrombosis (see Section 6.1 for more details).

Specific toxicity management measures will be utilized, as described in Section 6.2, for serious infections, serious GI events, cardiovascular events (MACE), malignancy, 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.

Additional safety monitoring measures include an independent Cardiovascular Adjudication Committee (CAC) (see Section 6.1) and an internal DMC (see Section 6.3).

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, double-blind LTE Phase 2 study to investigate the longer-term safety and efficacy of elsubrutinib and upadacitinib given alone or as the ABBV-599 (elsubrutinib/upadacitinib) combination in subjects with moderately to severely active SLE. The study population will consist of approximately 195 to 260 individuals with moderately to severely active SLE despite standard of care therapy.

Subjects who participated in Study M19-130 may be offered the opportunity to consent for this study. The number of subjects participating in this study will not be greater than the number randomized into Study M19-130. Subjects discontinuing study drug prematurely in Study M19-130 are not eligible to participate in the LTE study.

In Study M19-130, subjects were randomized in a 1:1:1:1:1 ratio to one of 5 treatment groups:

- Elsubrutinib 60 mg once a day (QD) and upadacitinib 30 mg QD (projected n = 65)
- Elsubrutinib 60 mg QD and upadacitinib 15 mg QD (projected n = 65)
- Elsubrutinib 60 mg QD and upadacitinib placebo QD (projected n = 65)
- Elsubrutinib placebo QD and upadacitinib 30 mg QD (projected n = 65)
- Elsubrutinib placebo QD and upadacitinib placebo QD (projected n = 65)

Prior to the planned Study M19-130 Interim Analysis, qualified subjects entering into LTE Study M20-186 stayed in their original treatment group from Study M19-130 if on an ABBV-599 (elsubrutinib/upadacitinib) combination, elsubrutinib 60 mg monotherapy, or upadacitinib 30 mg monotherapy. Those originally assigned to the placebo group in Study M19-130 were randomized centrally in a 1:1 ratio to the 2 ABBV-599 (elsubrutinib/upadacitinib) combination treatment groups.

Prior to the planned Study M19-130 Interim Analysis, there were 4 treatment groups in this LTE study:

- Group 1: Elsubrutinib 60 mg QD and upadacitinib 30 mg QD
- Group 2: Elsubrutinib 60 mg QD and upadacitinib 15 mg QD
- Group 3: Elsubrutinib 60 mg QD and upadacitinib placebo QD
- Group 4: Elsubrutinib placebo QD and upadacitinib 30 mg QD

A planned unblinded interim analysis for Study M19-130 was scheduled 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 Study M19-130 Interim Analysis was performed by an independent team at AbbVie that was separate and apart from the blinded study team for Study M19-130. The M19-130 study team will remain blinded through the Study M19-130 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.

Based on the benefit/risk assessment of the planned Study M19-130 Interim Analysis, subjects in 1 or more groups of LTE Study M20-186 may be discontinued. Subjects in any discontinued group(s) should return for a Premature Discontinuation (PD) visit and have a follow-up phone call 30 days after the last study drug dose.

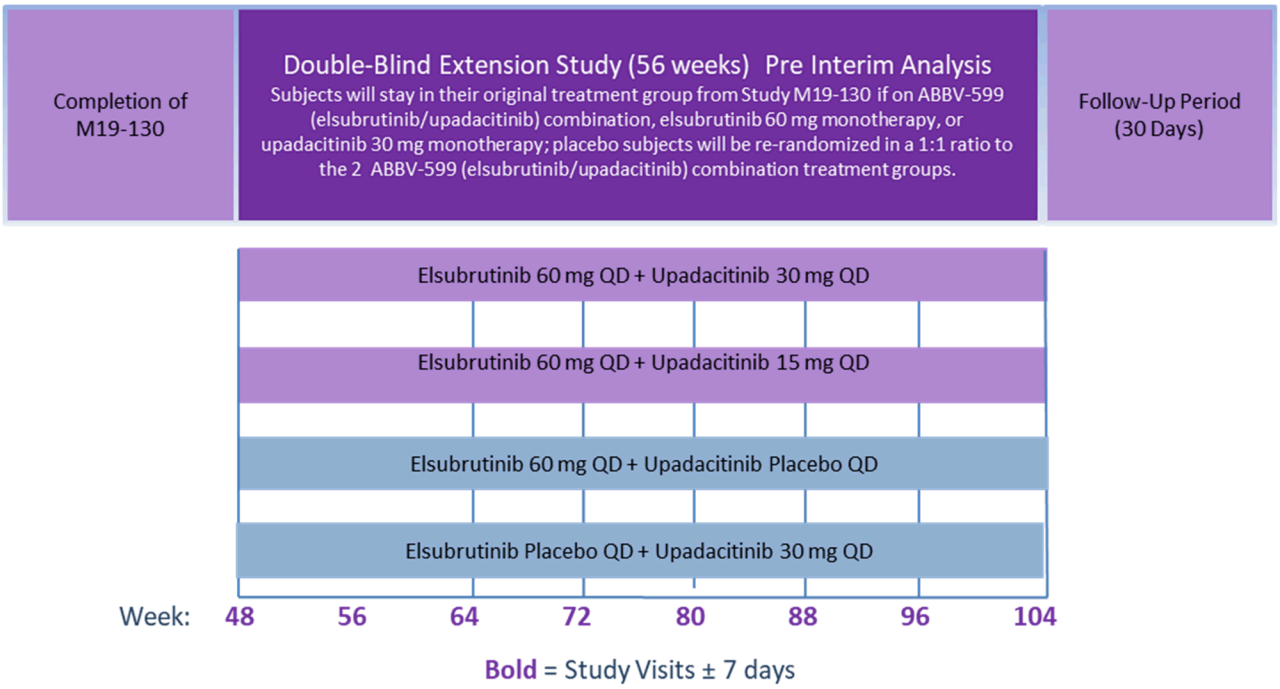
Subjects originally assigned to the placebo group in Study M19-130 will be rolled over and will be randomized to an active treatment group in LTE Study M20-186.

This study includes a 56-week double-blind treatment period with study visits conducted at Weeks 48, 56, 64, 72, 80, 88, 96, and 104 (from the Baseline visit of Study M19-130), and a subsequent telephone follow-up call 30 days after the last visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. The plan is to extend the trial if data support the safety and efficacy endpoints during the 56-week LTE study duration.

An interim analysis for LTE Study M20-186 may be performed to aid data interpretation and to facilitate interactions with regulatory authorities.

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

Figure 1. Study Schematic



QD = once daily

4.2 Discussion of Study Design

Choice of Control Group

There will not be any placebo control in LTE Study M20-186. Subjects in LTE Study M20-186 will roll over from Study M19-130. The objective of this LTE study is to evaluate longer-term safety and tolerability of elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination in SLE, and thus the primary comparison will be relative to the safety profile observed in each treatment group during the initial randomized study.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All safety and efficacy measurements in this study are standard for assessing disease activity in subjects with SLE being treated with immunosuppressive therapies. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

After the planned Study M19-130 Interim Analysis, this rollover LTE study will enroll subjects who have successfully completed 48 weeks of treatment in Study M19-130 on placebo or a treatment group that is still active. Only those subjects who have met all of the specified eligibility criteria will have an option to

enter the LTE study to receive continued therapy, provided the subject is willing and the investigator believes that continuing therapy is appropriate.

Selection of Doses in the Study

The dose selection in Study M19-130 was based on analysis of pharmacokinetic, pharmacodynamic, safety, and efficacy (upadacitinib only) data from Phase 1 studies in healthy volunteers for elsubrutinib, Phase 2 and Phase 3 studies for upadacitinib in RA, as well as a published study of baricitinib in SLE.[8-10]

The 60 mg dose of elsubrutinib is intended to target exposures at or greater than those needed to achieve maximal peripheral BTK occupancy. Following QD 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 and 30 mg QD (testing both dose levels in the ABBV-599 [elsubrutinib/upadacitinib] combination and only the higher dose in the upadacitinib monotherapy treatment group). These doses are based on the well-tolerated safety profile of upadacitinib in Phase 3 RA studies as well as extrapolation of data from a recently published Phase 2 study of baricitinib in SLE.[10] In that study, the baricitinib 2 mg QD dosing regimen demonstrated negligible efficacy while the 4 mg QD regimen provided evidence of therapeutic benefit; indicating that higher doses of baricitinib may be needed to demonstrate efficacy in SLE compared with RA.[10] Furthermore, comparison of in vitro cellular inhibition of Type I IFN signaling 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 higher inhibitory efficacy (e.g., time above IC_{50}) compared with the baricitinib 2 mg QD dosing regimens; whereas the upadacitinib 30 mg QD regimen is predicted to provide similar or higher inhibitory efficacy compared with the baricitinib 4 mg QD dosing regimen.

Doses selected for continuation in the LTE study may be modified or discontinued at any time based on the outcome of the planned Study M19-130 Interim Analysis and at AbbVie's discretion.

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 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.
- 2. Subjects are willing and able to comply with procedures required in this protocol.

Demographic and Laboratory Assessments

- 3. Subjects have completed Study M19-130 on study drug and have not developed any laboratory or clinical discontinuation criteria as defined in that study.

  Relevant Study M19-130 eligibility requirements applicable to LTE Study M20-186 are as follows:

  a. Must be on stable background treatment 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.

  b. 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.

  c. Must not have active TB.

  d. Must not have a history of any malignancy except for successfully treated NMSC or localized carcinoma in-situ (CIS) of the cervix.

  e. Must not currently have clinically significant (per investigator's judgment) drug or alcohol abuse.

  f. 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.

  g. 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.

  h. Must not be a recipient of an organ transplant.

  i. 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.

j. 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.

k. Must not have any clinically relevant or significant ECG abnormalities at LTE Baseline/M19-130 Week 48, 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.

l. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test at LTE Baseline/M19-130 Week 48 prior to the first dose of study drug.

m. 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

n. 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.

o. Subjects must not require vaccination with any live vaccine during study participation including at least 30 days after the last dose of study drug (see Section 5.3 for additional information on vaccines).

- 4. Latent TB for which the subject refuses to or cannot take prophylaxis.

Subject History

- 5. No history of clinically significant medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.

Concomitant Medications

- 6. Subject must not have been treated with any investigational drug (except those used in Study M19-130) 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 any study (except in the preceding Study M19-130) or planning to enroll in another interventional clinical study while participating in this study.

5.2 Contraception Recommendations

Contraception Requirements for Females

Systemic lupus erythematosus 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:

- Females, 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 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.
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
    - 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 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] are 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.
- 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 labeling. 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

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)
- Intravenous immunoglobulin (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
- 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 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 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 Prior and 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/week with concomitant folic acid ≥5 mg/week
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 per day, decrease no faster than 5 mg QD per week

Rescue Concomitant Medications/Therapy	**Comments/Notes**
Corticosteroids (prednisone-equivalent)	Continued reduction of corticosteroids is an important goal of therapy, as medically indicated, throughout this long-term study.

Subjects 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.

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 for toxicity management criteria.

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. Introduction of the following in addition to study drug 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 steroids (≥ 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 decides to withdraw from study drug or the study, or the Sponsor decides to discontinue 1 or more treatment groups after the planned Study M19-130 Interim Analysis.
- Inclusion or exclusion criterion 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 Study M19-130 Baseline.
  - Subject's QTcF increases from Baseline ≥ 60 msec, the investigator will evaluate, confirm the value, and treatment should be stopped.
- Subject develops active TB at any time during the study.
- Subject with latent TB who is non-compliant with or refuses to initiate TB prophylaxis.
- 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, if possible:

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

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 electronic case report form (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 should be treated in accordance with the investigator's best clinical judgment.

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 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 treatment 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. 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 may 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.

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

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.

5.7 Study Drug

Based on the Sponsor's discretion, doses of the investigational study drug (s) selected for continuation in the LTE study may be reassigned or discontinued at any time based on the outcome assessment of the planned Study M19-130 Interim Analysis.

Investigational study drug(s) should be taken at approximately the same time each day (Table 2). Subjects will be instructed to take study drugs orally, which includes only 1 capsule of elsubrutinib or matching placebo from each of the 3 dispensed bottles per day, with or without food, and only 1 tablet of upadacitinib or matching 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 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 bottles (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. Investigational Study Drug(s)

	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)	Not applicable	Not applicable
Mode/Route of Administration	Oral	Oral	Oral	Oral
Dosage Form	Capsule	Film-coated tablet	Capsule	Film-coated tablet
Dose and units	20 mg	15 mg, 30 mg	Not applicable	Not applicable
Frequency of administration	Daily	Daily	Daily	Daily
Storage Conditions	Room temperature (15°–25°C)	Room temperature (15°–25°C)	Room temperature (15°–25°C)	Room temperature (15°–25°C)

Note: Potential doses of the investigational study drug(s) for rollover may be reassigned or discontinued based on the outcome of the planned Study M19-130 Interim Analysis benefit/risk assessment or planned Study M19-130 Week 24 Primary Analysis.

5.8 Randomization/Drug Assignment

AbbVie reassessed the treatment assignments in the LTE Study M20-186 based on data from the planned Study M19-130 Interim Analysis. Based on the outcome of the planned Study M19-130 Interim Analysis, subjects in LTE Study M20-186 may be prematurely discontinued due to lack of efficacy observed in individual treatment groups at the Sponsor's discretion.

All subjects were assigned a unique identification number by the IRT at the Screening visit for Study M19-130. Prior to the planned Interim Analysis for Study M19-130, subjects entering LTE Study M20-186 who were originally assigned to the blinded ABBV-599 (elsubrutinib/upadacitinib) combination groups or the elsubrutinib or upadacitinib monotherapy groups in Study M19-130 were to continue on their current treatment for the duration of the study. After the planned Study M19-130 Interim Analysis, subjects who were originally assigned to placebo will be randomized to an active treatment group.

The investigator, study site personnel, and the subject will remain blinded to each subject's treatment assignment throughout Study M19-130 and LTE Study M20-186. AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Management Team) will remain blinded to study treatment through Week 24 of Study M19-130; the study team will become unblinded to study treatment in both studies after the Primary Analysis at Week 24 of Study M19-130 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.

The IRT will provide access to unblinded subject treatment assignment from Study M19-130 or LTE Study M20-186 in the case of a medical emergency.

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 IEC/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.

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 24 hours 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 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 if 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 SFI) 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 AE 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. 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 (Table 3) are reported, 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 an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 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.

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 routinely 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 Principal Investigator will provide documentation of all SAEs to the Director of the investigative site and to the Sponsor.

Cardiovascular Adjudication Committee

An independent CAC will adjudicate all blinded cardiovascular and cerebrovascular events, embolic/thrombotic events, and deaths, as defined in the CAC charter.

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 the 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 in LTE Study M20-186 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 an 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 review of safety issues by an internal independent 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, absolute neutrophil count (ANC), platelet count, alanine transaminase (ALT) or aspartate transaminase (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 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 should 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 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 AbbVie 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). 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 the 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 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an INR > 1.5.
	  • INR will only need to be measured in subjects with ALT or AST > 3 × ULN by the central laboratory. 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 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+ status (irrespective of HBs Ab status) and negative HBV DNA at Study M19-130 Screening who develop the following should have HBV DNA by PCR testing performed within 1 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 1 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 the 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 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 > 2 g/day equivalent (2 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.

DNA = Deoxyribonucleic acid; 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.

6.3 Data Monitoring Committee

An internal safety DMC composed of persons independent of the RCT Study M19-130 and LTE Study M20-186 teams and with relevant expertise in their field will review unblinded safety data. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this LTE 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 for LTE Study M20-186 is available and describes the roles and responsibilities of the DMC members, frequency of data reviews, planned interim analyses, relevant safety data to be assessed, and expectations for blinded communications for LTE Study M20-186.

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). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all subjects received at least 1 dose of study drug in LTE Study M20-186. The FAS will be used for efficacy and baseline analyses. Subjects will be grouped according to treatment sequence as randomized for Studies M19-130 and M20-186.

The Safety Analysis Set includes all subjects who received at least 1 dose of study drug in LTE Study M20-186. Subjects will be grouped according to treatment sequence actually received. The Safety Analysis Set will be used for safety analyses.

7.3 Statistical Analyses for Efficacy

Analysis of secondary efficacy endpoints will be conducted on the FAS based on treatment sequence as randomized for Study M19-130 and continued/reassigned to rollover into LTE Study M20-186. The analysis will be based on As Observed (AO) data, and no imputation will be conducted. The treatment groups will be described as follows whenever applicable indicating treatments from Study M19-130 to LTE Study M20-186:

- Group 1: Elsubrutinib 60 mg / upadacitinib 30 mg to elsubrutinib 60 mg / upadacitinib 30 mg
- Group 2: Elsubrutinib 60 mg / upadacitinib 15 mg to elsubrutinib 60 mg / upadacitinib 15 mg
- Group 3: Elsubrutinib 60 mg to elsubrutinib 60 mg
- Group 4: Upadacitinib 30 mg to upadacitinib 30 mg
- Group 5a: Placebo to elsubrutinib 60 mg / upadacitinib 30 mg
- Group 5b: Placebo to elsubrutinib 60 mg / upadacitinib 15 mg

The Baseline for all secondary efficacy analyses in this study will be the Baseline in Study M19-130.

There is no primary efficacy endpoint and no formal statistical tests will be applied. Only descriptive statistics will be used for all efficacy endpoints. Descriptive statistics will be provided for each treatment group for all visits. These include the number of observations; mean with 95% confidence interval, standard deviation, median, minimum, and maximum for continuous endpoints (or the change from baseline measurements); and frequencies and percentages with 95% confidence interval for binary endpoints.

No missing data imputation will be applied. All efficacy analyses will be based on AO analysis, and thus a subject who does not have an evaluation at the analysis time point will not be included. Missing value/visit information due to COVID-19 will be collected and reported.

Details on other efficacy analyses will be provided in the SAP.

7.4 Statistical Analyses for Safety

All safety analyses will be performed on the Safety Analysis Set.

All treatment-emergent adverse events (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 Medical Dictionary for Drug Regulatory Activities (MedDRA®) System Organ Class (SOC) and preferred term (PT). Summaries (including percentages and events per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation, and AESI will be provided as well. For selected laboratory and vital sign parameters, mean change from Baseline and the percentage of subjects with evaluations meeting pre-defined criteria for Potentially Clinically Important values will be summarized.

7.5 Interim Analysis

An interim analysis may be performed as needed in order to provide long-term safety data to inform the benefit-risk assessment of elsubrutinib, upadacitinib, and ABBV-599 (elsubrutinib/upadacitinib) combination. All endpoints will be summarized using descriptive statistics, and summaries will be displayed both overall and split by treatment groups indicating treatments from Study M19-130 to LTE Study M20-186. The detailed interim analysis plan will be provided in the SAP.

7.6 Overall Type I Error Control

Not applicable for this study.

7.7 Sample Size Determination

The sample size will be determined by the number of available subjects who were randomized into Study M19-130 and are eligible for the current study. All eligible subjects who completed Study M19-130 will be enrolled in this study if the subject signs and dates the informed consent. It is anticipated that between 60% and 80% of subjects from Study M19-130 (195 to 260 subjects) will be enrolled in this LTE study.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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.

12 REFERENCES

1. Kil LP, de Bruijn MJ, van Nimwegen M, et al. Btk levels set the threshold for B-cell activation and negative selection of autoreactive B cells in mice. Blood. 2012;119(16):3744-56.

2. Flemming A. Target discovery: Blocking BTK in B-cell disorders. Nat Rev Drug Discov. 2010;9(9):681.

3. Chang BY, Huang MM, Francesco M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 ameliorates autoimmune arthritis by inhibition of multiple effector cells. Arthritis Res Ther. 2011;13(4):R115.

4. Di Paolo JA, Huang T, Balazs M, et al. Specific Btk inhibition suppresses B cell- and myeloid cell-mediated arthritis. Nat Chem Biol. 2011;7(1):41-50.

5. Hutcheson J, Vanarsa K, Bashmakov A, et al. Modulating proximal cell signaling by targeting Btk ameliorates humoral autoimmunity and end-organ disease in murine lupus. Arthritis Res Ther. 2012;14(6):R243.

6. Mina-Osorio P, LaStant J, Keirstead N, et al. Suppression of glomerulonephritis in lupus-prone NZB x NZW mice by RN486, a selective inhibitor of Bruton's tyrosine kinase. Arthritis Rheum. 2013;65(9):2380-91.

7. Rankin AL, Seth N, Keegan S, et al. Selective inhibition of BTK prevents murine lupus and antibody-mediated glomerulonephritis. J Immunol. 2013;191(9):4540-50.

8. AbbVie. Upadacitinib Investigator's Brochure Edition 11. 18 August 2020.

9. AbbVie. ABBV-105 Investigator's Brochure Edition 4. 03 February 2020.

10. Wallace DJ, Furie RA, Tanaka Y, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2018;392(10143):222-31.

11. Furie RA, Petri MA, Wallace DJ, et al. Novel evidence-based systemic lupus erythematosus responder index. Arthritis Rheum. 2009;61(9):1143-51.

12. Wallace DJ, Strand V, Furie R, et al. Evaluation of treatment success in systemic lupus erythematosus clinical trials: development of the British Isles Lupus Assessment Group-based Composite Lupus Assessment Endpoint. Presented at: ACR 2011: Poster 2265. Arthritis Rheum. 2011;63:S885-6.

13. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2016;75(9):1615-21.

14. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-91.

15. Yee CS, Farewell V, Isenberg DA, et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum. 2007;56(12):4113-9.

16. Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005;125(5):889-94.

17. 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
Ab	Antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
ANC	Absolute neutrophil count
anti-dsDNA	anti-double stranded DNA
AO	As observed
AST	Aspartate transaminase
BCG	Bacilli Calmette-Guérin
BICLA	BILAG-Based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BTK	Bruton's tyrosine kinase
CAC	Cardiovascular Adjudication Committee
CBC	Complete blood count
Cardiac (eCRF)	Cardiovascular (electronic Case Report Form)
CIS	Carcinoma in-situ
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
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
DSUR	Development Safety Update Report
EC	Ethics Committee

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMR	Electronic medical records
EU	European Union
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCSF	Granulocyte-colony stimulating factor
GFR	Glomerular filtration rate
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HBc Ab/Ab+	Hepatitis B core antibody/antibody positive
HBs Ab	Hepatitis B surface antibody
HBV	Hepatitis B virus
HRQoL	Health-related quality of life
IC_{50}	Inhibitory concentration producing 50% inhibition
ICH	International Council for Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IERC	Internal Executive Review 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
IU	International unit
IUD	Intrauterine device

IUP	Interim Unblinding Plan
IUS	Intrauterine hormone-releasing system
IVIG	Intravenous immunoglobulin
JAK	Janus kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK3	Janus kinase 3
LLDAS	Lupus Low Disease Activity State
LTE	Long-term extension
LupusQoL	Lupus Quality of Life questionnaire
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MTX	Methotrexate
NA	No assessment
NCI	National Cancer Institute
NK	Natural killer
NMSC	Non-melanoma skin cancer
NRS	Numerical Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PD	Premature discontinuation
PhGA	Physician's Global Assessment
PHI	Protected health information
PII	Personally identifiable information
PMN	Polymorphonuclear white blood cells
PPD	Purified protein derivative (tuberculin)
PRN	As needed
PRO	Patient-reported outcome
PT	Preferred term
PtGA	Patient Global Assessment
QD	Once a day
QoL	Quality of life
QTc	QT interval corrected for heart rate

QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid arthritis
RBC	Red blood cell
RCT	Randomized controlled trial
RSI	Reference Safety Information
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
SF-36v2	36-Item Short Form Health Survey version 2
SFI	SLEDAI Flare Index
SLE	Systemic Lupus Erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SJC	Swollen joint count
SOC	System Organ Class
SRI	SLE Responder Index
SUSAR	Suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
UK	United Kingdom
ULN	Upper limit of normal
UPCR	Urine protein to creatinine ratio
US	United States
WBC	White blood cell
WOCBP	Women of childbearing potential

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-186: A Phase 2, Long-Term Extension (LTE) Study with Elsubrutinib and Upadacitinib Given Alone or in Combination (ABBV-599) in Subjects with Moderately to Severely Active Systemic Lupus Erythematosus Who Have Completed the M19-130 Phase 2 Randomized Controlled Trial (RCT)

Protocol Date: 26 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]		Pharmaceutical Development, Immunology
		Pharmaceutical Development, Immunology
		Clinical Study Leadership
		Data and Statistical Sciences
		Data and Statistical Sciences
		Medical Writing (Protocol Author)

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

Activity	LTE Baseline/ Week 48*	Week 56	Week 64	Week 72	Week 80	Week 88	Week 96	Week 104/ Premature Discontinuation	30-Day Follow Up Phone Call**
Visit Window	**± 7 days**								
INTERVIEWS & QUESTIONNAIRES									
Subject information and informed consent	✓								
Eligibility criteria	✓								
Medical/surgical history	✓								
Token information (optional, US subjects only)[a]	✓								
Adverse event (AE) and AE of special interest (AESI) assessment		✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓
Steroid therapy assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-Reported Outcomes[b] • PtGA • LupusQoL • FACIT-Fatigue • SF-36 • Pain NRS	✓			✓			✓		
Verification of continued contraceptive measures for WOCBP	✓	✓	✓	✓	✓	✓	✓	✓	
TB risk assessment form	✓						✓		
Verification of continued benefit of subject participation	✓								
LOCAL LABS & EXAMS									
Chest x-ray[c]	✓						✓		
12-lead ECG	✓		✓		✓		✓		
Height (LTE Baseline only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	LTE Baseline/ Week 48*	Week 56	Week 64	Week 72	Week 80	Week 88	Week 96	Week 104/ Premature Discontinuation	30-Day Follow Up Phone Call**
Visit Window	± 7 days								
Physical examination[d]	✓	✓	✓	✓	✓	✓	✓	✓	
TJC28/SJC28	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (for WOCBP only)[e]	✓	✓	✓	✓	✓	✓	✓	✓	
Dispense urine pregnancy tests for monthly home testing[e]	✓	✓	✓	✓	✓	✓	✓		
Physician Global Assessment (PhGA)[f]	✓	✓	✓	✓	✓	✓	✓	✓	
SLEDAI-2K assessment	✓	✓	✓	✓	✓	✓	✓	✓	
BILAG assessment	✓	✓	✓	✓	✓	✓	✓	✓	
CLASI assessment	✓	✓	✓	✓	✓	✓	✓	✓	
SELENA SLEDAI flare index (SFI) assessment	✓	✓	✓	✓	✓	✓	✓	✓	
CENTRAL LABS									
Complement C3, C4 testing	✓	✓	✓	✓	✓	✓	✓	✓	
anti-dsDNA	✓	✓	✓	✓	✓	✓	✓	✓	
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	✓						✓		
TREATMENT									
Drug assignment	✓								
Dispense study drug[g]	✓	✓	✓	✓	✓	✓	✓		
Dispense subject diaries	✓								
Review and copy subject dosing diary and perform drug reconciliation[g]	✓	✓	✓	✓	✓	✓	✓	✓	

anti-dsDNA = anti-double stranded DNA; BILAG = British Isles Lupus Assessment Group; 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; IgG = Immunoglobulin G; IgM = Immunoglobulin M; LTE = Long-term extension; LupusQoL = Lupus Quality of Life questionnaire; NRS = Numerical Rating Scale; PPD = Purified protein derivative; PtGA = Patient Global Assessment; 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; TJC = Tender joint count; US = United States; WOCBP = Women of childbearing potential

* Tests/study activities are only to be performed if not done as part of Study M19-130.

** The 30-day follow up call will be calculated from the last study drug administration date/last visit.

a. Subjects in US who are already enrolled in the LTE study can be tokenized beyond the LTE Baseline/M19-130 Week 48 visit once they consent to be tokenized.

b. The patient-reported outcome instruments should be completed prior to drug administration at LTE Baseline/M19-130 Week 48 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.

c. A chest x-ray (CXR) will be obtained annually for subjects with TB risk factors as identified by the TB risk assessment form or for subjects with a newly positive PPD or QuantiFERON-TB Gold test.

d. A complete physical examination will be performed during the LTE Baseline/M19-130 Week 48 visit. Physical examinations at other visits can be symptom-directed.

e. A urine pregnancy test will be performed locally for all females of childbearing potential prior to the first dose of study drug in LTE Study M20-186 and at a minimum of monthly intervals (either at study visits or at home between scheduled study visits). The results of the monthly at-home tests must be communicated to the site. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

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

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

APPENDIX E. DESCRIPTION OF EFFICACY MEASURES

Measure	Definition	Scale
Systemic Lupus Erythematosus Responder Index (SRI)[11]	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 Physician's Global Assessment [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)[12]	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)[13]	A state of low disease activity based on SLEDAI score (SLEDAI-2K score ≤ 4 excluding SLEDAI-2K activity in major organ systems), absence of systemic lupus erythematosus (SLE) disease activity in major organ systems and new disease activity, 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)[14]	Global SLEDAI 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[15]	Global SLEDAI 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)[16]	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)[17]	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[17]	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.
- Progestogen-only hormonal contraception (oral,** injectable,* implantable*) associated with inhibition of ovulation.
- 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

Protocol	Date
Version 1.0	14 May 2020
Version 2.0	21 July 2020
Version 3.0	28 October 2020
Version 3.1 (China Only)	15 January 2021

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

PROTOCOL

1. ***Rationale**: After the planned Study M19-130 Interim Analysis assessment was completed, AbbVie selected treatment groups to move forward in LTE Study M20-186 based upon efficacy results. These changes were necessary to reflect the possible treatment groups that may be active in LTE Study M20-186 after the planned Study M19-130 Interim Analysis.*

   - Section 1 Synopsis and Section 4.1 Overall Study Design and Plan
     - Updated secondary objective and investigational plan to reflect changes that were made as a result of the planned Study M19-130 Interim Analysis. Clarity was provided regarding reassignment of subjects in the placebo groups of Study M19-130. Also, in Section 4.1 the Study Schematic was updated to reflect "Pre Interim Analysis."
   - Section 3 Objectives and Endpoints
     - Updated secondary objective to provide clarity regarding changes that were made as a result of the planned Study M19-130 Interim Analysis.
   - Section 4.2 Discussion of Study Design
     - Clarified that subjects will need to successfully complete 48 weeks of Study M19-130 on placebo or a group that is currently active after the planned Study M19-130 Interim Analysis and meet all eligibility criteria to be considered eligible to enroll into LTE Study M20-186
   - Section 5.7 Study Drug
     - At the Sponsor's discretion, doses of study drug(s) selected for continuation in LTE Study M20-186 may be reassigned or discontinued at any time based on the outcome assessment of the Study M19-130 Interim Analysis.
   - Section 5.8 Randomization/Drug Assignment
     - Based on the outcome of the planned Interim Analysis for Study M19-130, subjects in LTE Study M20-186 may be prematurely discontinued at the Sponsor's discretion.
   - Section 7.5 Interim Analysis
     - Added clarification regarding how endpoints will be displayed if an interim analysis for LTE Study M20-186 is performed.

2. ***Rationale:*** *If the study is partially terminated, 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 in a terminated group 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****: Alignment with protocol-required screening*
    - Section 3.11 Clinical Laboratory Tests
        - Added HBV DNA (quantitative) to infection screening in Table 1 Clinical Laboratory Tests.

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).