Protocol I8K-MC-JPDA (d)

A Randomized, Double-Blind, Placebo-Controlled, 2-Part Phase 2 Study to Evaluate the Safety and Efficacy of LY3337641 in Adult Subjects with Rheumatoid Arthritis: The RAjuvenate Study

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Confidential Information

LY3337641

Study I8K-MC-JPDA is a 2-part Phase 2, randomized, double-blind, placebo-controlled trial in subjects with rheumatoid arthritis. In Part A, subjects will be dosed with 5, 10, or 30 mg of LY3337641 or placebo for 4 weeks. Following a safety analysis, Part B will enroll subjects to be dosed with the planned doses of 5, 10, or 30 mg of LY3337641 or placebo for 12 weeks.

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1. Protocol Synopsis

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, 2-Part Phase 2 Study to Evaluate the Safety and Efficacy of LY3337641 in Adult Subjects with Rheumatoid Arthritis: The RAjuvenate Study

Rationale:

Study I8K-MC-JPDA (JPDA) is a 2-part Phase 2 study designed to determine whether once-daily (qd) oral administration of LY3337641, an inhibitor of Bruton's tyrosine kinase (BTK), is safe and efficacious in subjects with rheumatoid arthritis (RA). Part A will enroll subjects with at least mildly active RA to be dosed with 5, 10, or 30 mg of LY3337641 or placebo for 4 weeks. Following an interim analysis of safety data from Part A, Part B will enroll subjects with moderately to severely active RA to be dosed with the planned doses of 5, 10, or 30 mg of LY3337641 or placebo for 12 weeks. Findings from the study are intended to assess the utility of LY3337641 for the treatment of RA and related autoimmune diseases, further the understanding of the benefit/risk relationship for LY3337641, and inform the design of future studies.

Objective(s)/Endpoints:

Part A:

Objectives	Endpoints
Primary • to evaluate the safety and tolerability of LY3337641 at 5, 10, and 30 mg qd in subjects with RA	• The safety endpoints evaluated will include but are not limited to the following: o TEAEs, AESIs, SAEs o clinical laboratory tests, vital signs, physical examinations

Abbreviations: AESIs = adverse events of special interest; qd = once daily; RA = rheumatoid arthritis; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

Part B:

Objectives	Endpoints
Primary • to evaluate the efficacy, safety, and tolerability of LY3337641 at 5, 10, and 30 mg qd versus placebo at Week 12 for the treatment of subjects with moderately to severely active RA	• proportion of subjects who achieve ACR20 • The safety endpoints evaluated will include but are not limited to the following: o TEAEs, AESIs, SAEs o clinical laboratory tests, vital signs, physical examinations
Secondary • to evaluate the efficacy of LY3337641 at 5, 10, and 30 mg qd versus placebo at Week 12 on RA clinical endpoints	• proportions of subjects achieving ACR50 and ACR70 • change from baseline in the DAS28-hsCRP • proportion of subjects achieving LDA based on DAS28-hsCRP • proportion of subjects achieving clinical remission based on DAS28-hsCRP
• to characterize the PK of LY3337641 in subjects with RA	• population PK model estimate of clearance

Abbreviations: ACR = American College of Rheumatology; ACR20 = at least 20% improvement in the ACR criteria; ACR50 = at least 50% improvement in the ACR criteria; ACR70 = at least 70% improvement in the ACR criteria; AESIs = adverse events of special interest; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; hsCRP = high-sensitivity C-reactive protein; LDA = low disease activity; PK = pharmacokinetics; qd = once daily; RA = rheumatoid arthritis; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

Summary of Study Design:

Study JPDA is a multicenter, randomized, double-blind, placebo-controlled trial with 2 parts. Part A has 3 study periods in subjects with at least mildly active RA with a dosing period of 4 weeks. Part B has 3 study periods in subjects with moderately to severely active RA with a dosing period of 12 weeks.

Treatment Arms and Duration:

In Part A, the study will include 4 arms: 3 experimental arms in which LY3337641 will be dosed orally at 5, 10, or 30 mg qd and 1 placebo comparator arm. In Part B, the study will include 4 arms: 3 experimental arms in which LY3337641 will be dosed orally at the planned doses of 5, 10, or 30 mg qd and 1 placebo comparator arm. Blinding will be maintained throughout. The study periods include a screening period (Weeks −4 to 0), a dosing period (Weeks 0 to 4 in Part A and Weeks 0 to 12 in Part B), and a follow-up period (Weeks 4 to 6 in Part A and Weeks 12 to 14 in Part B).

Number of Subjects:

In Part A, approximately 32 subjects with RA will be enrolled and randomly assigned in a 1:1:1:1 ratio to 1 of the 4 arms. In Part B, approximately 244 subjects with RA will be enrolled and randomly assigned in a 1:1:1:1 ratio to 1 of the 4 arms. In Part B, the percentage of subjects who are naive to biologic disease-modifying antirheumatic drugs (DMARDs) will be limited to approximately 25% of the study population; the remaining subjects in Part B will have had previous exposure to biologic DMARDs. There will be no limits on the percentage of subjects naive to biologic DMARDs in Part A. Subjects participating in Part A will not be eligible to participate in Part B.

Statistical Analysis:

Efficacy and health outcomes analyses will be conducted on the modified intent-to-treat population, defined as all randomized subjects receiving at least 1 dose of study drug. Subjects will be grouped according to the randomized treatment. The analysis population (for applicable treatment outcome measures) will be all subjects with both a baseline and at least 1 postbaseline data measurement. Safety analyses will be conducted on the safety population, defined as all randomized subjects receiving at least 1 dose of the study drug. Subjects will be grouped according to the randomized treatment. Data from Part A will be summarized separately from data from Part B. No statistical hypothesis testing is planned for Part A. All tests of treatment effects for Part B will be conducted at the 2-sided α level of .05 unless otherwise stated. No adjustments for multiplicity will be performed.

The primary endpoint in Part B will be analyzed by a logistic regression model with ACR20 at Week 12 as the dependent variable and treatment, biologic disease-modifying antirheumatic drug (DMARD) experience (yes/no), region (Japan vs non-Japan), and baseline DAS28-hsCRP as independent variables. A comparison of each LY3337641 dose to placebo will be presented. Subjects who discontinue from the study earlier than Week 12 and subjects who complete 12 weeks of dosing but do not have sufficient data to derive the ACR20 response will be considered as failing to meet the ACR20.

2. Introduction

2.1. Background

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease and is the most common type of autoimmune arthritis. The clinical features of RA include chronic joint inflammation and swelling that typically involve the small joints of the hands and feet. Rheumatoid arthritis can result in destruction of cartilage and juxta-articular bone with resultant joint space narrowing and deformities. Chronic joint destruction can lead to functional impairment with increasing disability (Klareskog et al. 2009). The disease is associated with not only progressive joint destruction and disability but also compromised quality of life as well as cardiovascular and other comorbidities (Scott et al. 2010).

Current treatment strategies for RA include synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), which are often supported by nonsteroidal anti-inflammatory medications and/or corticosteroids (Stoll and Yasothan 2009). However, despite the multiple available agents with diverse mechanisms of action, RA is not well controlled in up to 30% of patients (Koenders and van den Berg 2015). Therefore, the need for additional treatment approaches remains.

LY3337641 (chemical name, 2-propenamide, *N*-[3-[[2-[[4-(4-methyl-1-piperazinyl)phenyl]amino]furo[3,2-*d*]pyrimidin-4-yl]oxy]phenyl]) is an orally available, irreversible inhibitor of Bruton's tyrosine kinase (BTK), a member of the TEC family of cytoplasmic tyrosine kinases. BTK is a key signaling molecule in the B-cell–receptor and Fc-receptor pathways and an essential mediator of B-cell– and myeloid-cell–dependent inflammatory arthritis (Di Paolo et al. 2011; Chakravarty et al. 2013). BTK is primarily expressed in hematopoietic cells, including B cells, monocytes, and macrophages (Burger 2014). In humans, BTK loss-of-function mutations cause nonlethal X-linked agammaglobulinemia, resulting in reduced B-cell and immunoglobulin (Ig) levels (Aalipour and Advani 2014). Potential therapeutic benefits of BTK inhibition for RA include reduced pathogenic B-cell autoantibody production and myeloid-cell proinflammatory cytokine production and inhibition of mast cell and basophil degranulation (Horwood et al. 2012).

LY3337641 demonstrates potent, irreversible BTK inhibition in BTK enzyme assays, cell-based BTK phosphorylation assays, and BTK occupancy assays.

The in vivo activity of LY3337641 was investigated in mouse and rat models of collagen-induced arthritis and mouse models of systemic lupus erythematosus. LY3337641 was effective in the mouse arthritis model, where it halted progression of clinical arthritis and significantly diminished structural damage in the joints. The high level of efficacy for clinical disease activity was reproduced in the rat arthritis model. LY3337641 was also effective in a spontaneous mouse model of systemic lupus erythematosus, where it improved skin lesions, reduced proteinuria, and improved renal histopathology scores. Taken together, these results suggest that LY3337641 may be useful for treatment of autoimmune diseases, including RA.

A single Phase 1 study (Study 12-HM71224-101, subsequently referred to as Study I8K-MC-JPDD [JPDD]) was conducted in healthy adult males to determine the safety, tolerability, pharmacokinetics (PK), and food effect of single and multiple doses of orally administered LY3337641. In the single-dose portion of the study, the drug was well tolerated. In the multiple-dosing portion of the study during which subjects were dosed for 14 days, the drug was generally well tolerated at dosages up to 40 mg once daily (qd) (inclusive). At dosages totaling 80 mg per day and higher, significant treatment-emergent adverse events (TEAEs) (ie, TEAEs leading to discontinuation or deemed significant by the investigator) were reported. The majority of these events involved skin-related manifestations, the most common being rash. Some cases were associated with systemic signs and symptoms, such as fever, arthritis, and laboratory abnormalities. The highest dosage in Study I8K-MC-JPDA (JPDA) is 30 mg qd, which is below the doses at which skin rashes or significant TEAEs were reported in Study JPDD. On the basis of projected BTK occupancy using the Phase 1 data, the 5- to 30-mg qd dosages are predicted to result in mean BTK occupancy of approximately 70% to 90% (Section 4.4). LY3337641 was rapidly absorbed after oral administration, and plasma elimination was rapid; the geometric mean half-life was 4.6 to 6.6 hours. Administering LY3337641 with food did not affect the extent of oral absorption but resulted in a slight delay in absorption and a slightly lower maximal observed plasma concentration (C_{max}) in humans.

The results from nonclinical studies with LY3337641 and the Phase 1 safety profile support further clinical development of the drug substance for treatment of autoimmune diseases, including RA.

2.2. Study Rationale

Study JPDA is a 2-part Phase 2 study designed to determine whether oral qd dosing of LY3337641 is safe and efficacious in subjects with RA. Findings from the study will be used to assess the safety, efficacy, and tolerability of LY3337641 in this study population, further characterize the PK properties, and explore the pharmacodynamic (PD) effects of BTK inhibition. Such findings will afford a greater understanding of the benefit/risk relationship for LY3337641 and inform the design of future studies.

3. Objectives and Endpoints

Table JPDA.1 shows the objectives and endpoints for Part A of the study. Table JPDA.2 shows the objectives and endpoints for Part B of the study.

Table JPDA.1. Objectives and Endpoints for Part A

Objectives	Endpoints
Primary • to evaluate the safety and tolerability of LY3337641 at 5, 10, and 30 mg qd in subjects with RA	• The safety endpoints evaluated will include but are not limited to the following: o TEAEs, AESIs, SAEs o clinical laboratory tests, vital signs, physical examinations
Exploratory • to explore the effects of treatment with LY3337641 at 5, 10, and 30 mg qd on RA clinical endpoints over the course of the study	• proportions of subjects achieving ACR20 • hybrid ACR • change from baseline in DAS28-hsCRP • change from baseline in the individual components of the ACR core set
• to explore the effect of treatment with LY3337641 at 5, 10, and 30 mg qd on morning joint stiffness duration	• change from baseline in morning joint stiffness duration
• to characterize the dose-response and exposure-response relationships of LY3337641 for efficacy measures and PD effects	• model parameters (eg, slope) for the dose-response and exposure-response relationships for efficacy measures and PD effects
• to identify the plasma metabolites of LY3337641	• qualitative identification of the circulating metabolites of LY3337641 after oral administration

Abbreviations: ACR = American College of Rheumatology; ACR20 = at least 20% improvement in the ACR criteria; AESIs = adverse events of special interest; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; hsCRP = high-sensitivity C-reactive protein; PD = pharmacodynamic; qd = once daily; RA = rheumatoid arthritis; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events.

Table JPDA.2. Objectives and Endpoints for Part B

Objectives	Endpoints
Primary • to evaluate the efficacy, safety, and tolerability of LY3337641 at 5, 10, and 30 mg qd versus placebo at Week 12 for the treatment of subjects with moderately to severely active RA	• proportion of subjects who achieve ACR20 • The safety endpoints evaluated will include but are not limited to the following: o TEAEs, AESIs, SAEs o clinical laboratory tests, vital signs, physical examinations
Secondary • to evaluate the efficacy of LY3337641 at 5, 10, and 30 mg qd versus placebo at Week 12 on RA clinical endpoints	• proportions of subjects achieving ACR50 and ACR70 • change from baseline in the DAS28-hsCRP • proportion of subjects achieving LDA based on DAS28-hsCRP • proportion of subjects achieving clinical remission based on DAS28-hsCRP
• to characterize the PK of LY3337641 in subjects with RA	• population PK model estimate of clearance
Tertiary/Exploratory • to evaluate the efficacy of treatment with LY3337641 at 5, 10, and 30 mg qd versus placebo on RA clinical endpoints over the course of the study	• proportions of subjects achieving ACR20, ACR50, ACR70, and ACR90 • ACR-N, hybrid ACR • change from baseline in DAS28-hsCRP • proportion of subjects achieving clinical remission based on DAS28-hsCRP • proportion of subjects achieving LDA based on DAS28-hsCRP • change from baseline in the individual components of the ACR core set
• to assess the effect of treatment with LY3337641 at 5, 10, and 30 mg qd versus placebo on other patient-reported outcomes over the course of the study	• change from baseline in morning joint stiffness duration • change from baseline in patient's assessment of sexual function (VAS) • change from baseline in SF-36 Physical Component Score and Mental Component Score • change from baseline in FACIT-F score
• to evaluate the effect of treatment with LY3337641 at 5, 10, and 30 mg qd versus placebo on PD measures and biomarkers over the course of the study	• percentage of BTK occupancy • change from baseline in phosphorylated BTK • change from baseline in T-cell and B-cell subsets
• to characterize the dose-response and exposure-response relationships of LY3337641 for efficacy measures and PD effects	• model parameters (eg, slope) for the dose-response and exposure-response relationships for efficacy measures and PD effects

Objectives	Endpoints
• to evaluate the effect of treatment with LY3337641 on autoantibody formation at Week 12 in subjects whose test results are positive for these antibodies at baseline and to characterize the relationship between baseline status and clinical response	• change from baseline in rheumatoid factor • change from baseline in ACPA • association (if any) between baseline status for these antibodies (positive or negative) and clinical response

Abbreviations: ACPA = anti-citrullinated peptide antibodies; ACR = American College of Rheumatology; ACR20 = at least 20% improvement in the ACR criteria; ACR50 = at least 50% improvement in the ACR criteria; ACR70 = at least 70% improvement in the ACR criteria; ACR90 = at least 90% improvement in the ACR criteria; ACR-N = continuous measure of percentage of improvement from baseline in the ACR criteria; AESI = adverse event of special interest; BTK = Bruton's tyrosine kinase; DAS28 = Disease Activity Score modified to include the 28 diarthrodial joint count; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; hsCRP = high-sensitivity C-reactive protein; LDA = low disease activity; PD = pharmacodynamic; PK = pharmacokinetics; qd = once daily; RA = rheumatoid arthritis; SAE = serious adverse event; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; TEAE = treatment-emergent adverse event; VAS = visual analog scale.

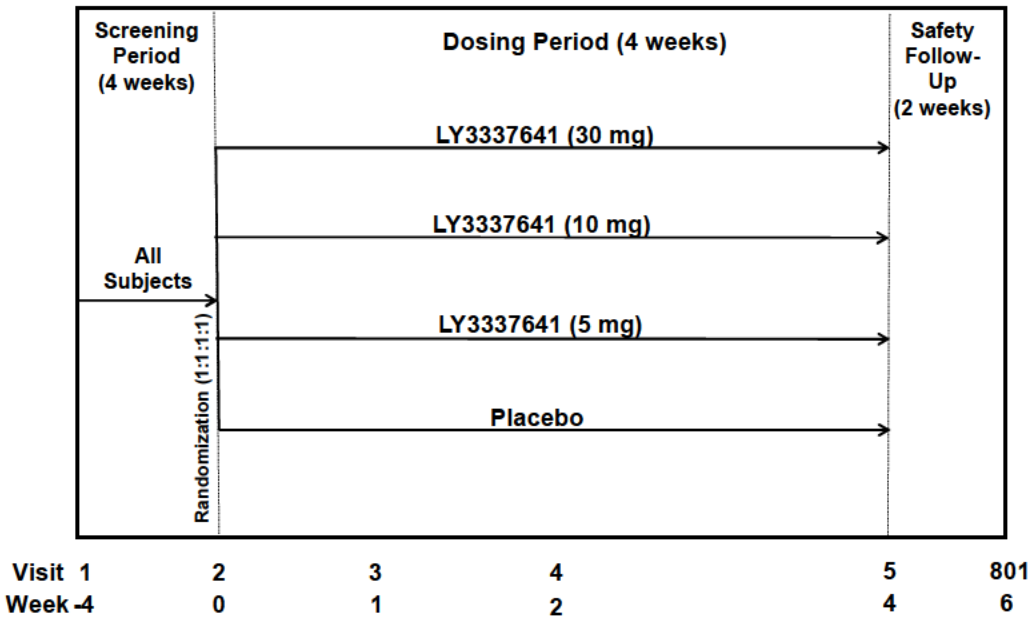
4. Study Design

4.1. Overview of Study Design

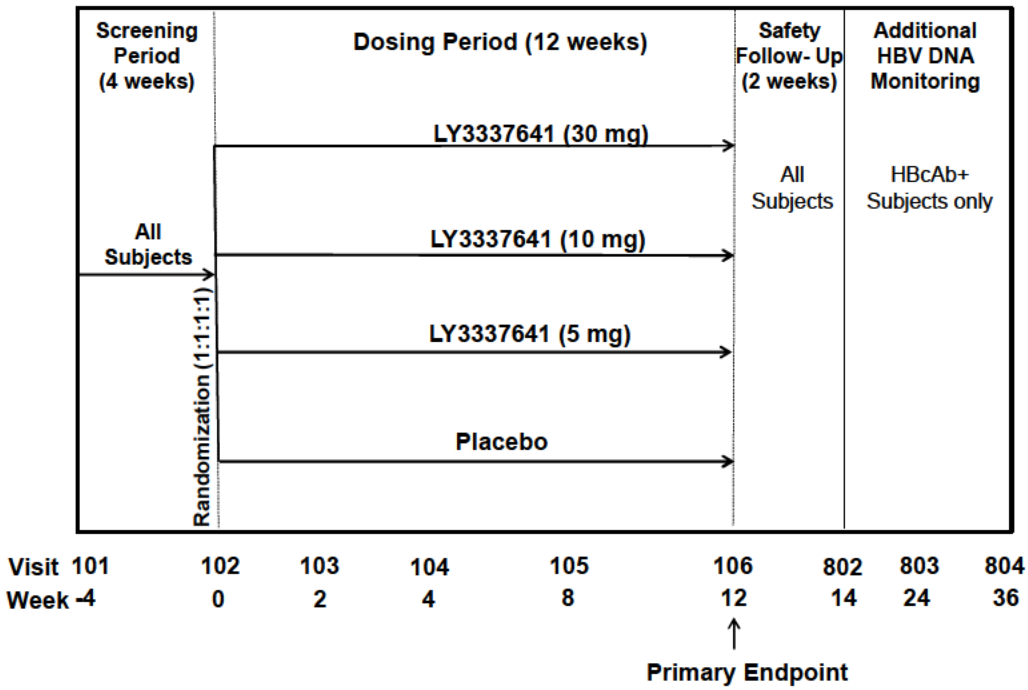
Study JPDA is a multicenter, randomized, double-blind, placebo-controlled, 2-part Phase 2 trial in adult subjects with RA. Part A will enroll subjects with at least mildly active RA. Part B will enroll subjects with moderately to severely active RA who have had an inadequate response, loss of response, or intolerance to at least 1 synthetic or biologic DMARD treatment for RA. In Part B only, the percentage of subjects who are naive to biologic DMARDs will be limited to approximately 25% of the study population.

In Part A, after a screening period of up to 28 days, subjects will be randomly assigned in a 1:1:1:1 ratio to receive oral dosages of LY3337641 at 5, 10, or 30 mg qd or placebo for 4 weeks. At Week 6, there will be a safety follow-up visit for Part A. An internal Assessment Committee will conduct an unblinded interim analysis of safety data at least 2 weeks after all subjects have had their last dose, and will provide a recommendation to the study team whether or not to proceed to Part B. If a decision to proceed with the study is made, Part B will start enrolling new subjects who did not participate in Part A (see details in Section 8.4.7). In Part B, after a screening period of up to 28 days, subjects will be randomly assigned in a 1:1:1:1 ratio to receive the planned oral dosages of LY3337641 of 5, 10, or 30 mg qd or placebo for 12 weeks. The primary efficacy endpoint of the study will be assessed at the Week 12 visit in Part B. At Week 14, there will be a safety follow-up visit for Part B (see Figure JPDA.1).

Part A



Part B



Note: There will be an interim unblinded safety analysis by the Assessment Committee at least 2 weeks after all subjects have had their last dose in Part A. If a decision to proceed with the study is made, Part B will start enrolling new subjects. Part A subjects cannot participate in Part B.

Figure JPDA.1. Illustration of the study design for Clinical Protocol I8K-MC-JPDA.

4.2. End of Trial Definition

The end of the trial is the date of the last visit or last scheduled procedure shown in the Schedule of Activities for the last subject.

4.3. Scientific Rationale for Study Design

Study JPDA is the first clinical trial evaluating the safety and efficacy of LY3337641 in subjects with RA. The trial is conducted in 2 parts. Part A will enroll subjects with at least mildly active RA to be dosed for 4 weeks. Findings from Part A will provide additional understanding of the safety and tolerability of LY3337641 in subjects with RA prior to testing a longer-term dosing period in Part B. Three active dose levels of LY3337641 will allow an evaluation of safety and tolerability across a broad dose range. An unblinded interim analysis of safety data will take place at least 2 weeks after all subjects have had their last dose. All interim analyses for the study (both Parts A and B) will be reviewed by an Assessment Committee comprised of members who are external to the JPDA study team to minimize operational and statistical bias.

If the decision is made to proceed with Part B after reviewing the Assessment Committee recommendation, Part B will initiate with enrollment. As the primary objective of Part B is to test the efficacy of LY3337641, in addition to safety and tolerability, a moderately to severely active RA patient population was deemed most appropriate to understand the effect of LY3337641 on clinical disease activity. As this is the initial study evaluating the efficacy of LY3337641 in RA, subjects in Part B must have demonstrated an inadequate response, loss of response, or intolerance to a synthetic or biologic DMARD therapy to participate in the study. Three active doses of LY3337641 are planned for Part B to assess efficacy across a broad dose range. The American College of Rheumatology (ACR) 20% response rate (ACR20) is the proportion of patients who achieve at least a 20% improvement in a core set of measures that include patient-reported assessments, physician assessments, and an acute-phase reactant. It is widely used in RA clinical trials, continues to be an accepted measure to demonstrate reduction in RA disease activity (FDA 2013), and is an appropriate primary outcome measure for an early phase proof-of-concept study. A double-blind placebo-controlled design limits bias for both patient and investigator assessments.

In addition to the ongoing safety monitoring of subjects by the study team, the Assessment Committee will review unblinded safety data at planned intervals during the study, as well as unplanned requests based on emerging data, to ensure subject safety.

4.4. Justification for Dose

The LY3337641 dosage range of 5 to 30 mg qd administered orally is based on nonclinical toxicology data, clinical safety data from the Phase 1 study, as well as the effective BTK occupancies projected on the basis of both the Phase 1 clinical data and the nonclinical results. The maximum dose of 30 mg qd provides >1-fold exposure multiple (margin of safety) based on area under the curve (AUC) in 2 species (rat and monkey) at the NOAEL in the 13-week nonclinical toxicology studies (see Section 5.2.1 of the Investigator's Brochure [IB]). This dose is also below the highest dosage tested in the Phase 1 study (40 mg qd) at which there were no

skin rashes or significant TEAEs (that is, TEAEs leading to discontinuation or deemed significant by the investigator).

In a rat collagen-induced arthritis model, BTK occupancy of approximately 80% was sufficient to achieve efficacy. On the basis of Phase 1 BTK occupancy data in humans, 30 mg qd is expected to achieve BTK occupancy of approximately 90%. The 5- and 10-mg qd dosages are projected to achieve BTK occupancy of approximately 70% and 80%, respectively. Thus, this study will test dosages that were well tolerated in the Phase 1 study and are projected to achieve BTK occupancies that are expected to be efficacious.

4.5. Benefit/Risk Assessment

There are currently no human data regarding the efficacy of LY3337641 in RA. Nonclinical data and safety data in Phase 1 support further development of LY3337641 in RA at the proposed doses.

The safety profile for LY3337641 has been informed by the results from nonclinical toxicology and safety pharmacology studies and the Phase 1 clinical study (JPDD). The primary toxicity observed in animal studies was gastrointestinal tract injury. Pancreatic and immune system effects were also observed (see Section 5.2.1 of the IB). In humans, the drug was generally well tolerated at dosages up to 40 mg per day. At total daily dosages of 80 mg and higher in the multiple dose portion of the study, significant TEAEs were reported in some subjects. The majority involved skin manifestations, the most common being skin rash. Associated signs and symptoms ranged from pruritus to systemic features such as fever and elevated levels of acute phase reactants. The highest dosage in Study JPDA is 30 mg qd, which is below the doses at which skin rashes or significant TEAEs were reported in Study JPDD. However, adverse events (AEs) of skin rash will be monitored over the course of the study by the medical monitor using blinded data. In addition, skin rash will be monitored by an Assessment Committee using unblinded data. The Assessment Committee members will be independent from the Lilly study team (Section 8.4.7).

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3337641 can be found in the IB.

5. Study Population

Part A will include subjects with at least mildly active RA. Part B will include subjects with moderately to severely active RA who have had an inadequate response, loss of response, or intolerance to at least 1 DMARD therapy (synthetic and/or biologic). In Part B only, the percentage of subjects who are naive to biologic DMARDs will be limited to approximately 25% of the study population; the remaining subjects in Part B will have had previous exposure to biologic DMARDs. Subjects participating in Part A will not be eligible to participate in Part B.

Subjects must give written informed consent (approved by Lilly or its designee and the ethical review board [ERB] governing the site) before being allowed to participate in the study and before any screening assessments are performed.

Study investigator(s) will review the subject's records and/or history and screening test results/measurements to determine if the subject meets all inclusion and no exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the subject is randomly assigned to study drug.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria:

[1] are male or female between the ages of 18 and 65 years (inclusive) at the time of initial screening and are able and willing to provide written informed consent as a legal adult according to local regulations

[2] female subjects of childbearing potential: test negative for pregnancy at screening and agree not to breastfeed from the start of screening until 2 weeks after the last dose of study drug

[3] female subjects: agree to use a reliable method of birth control (eg, intrauterine contraceptive devices, hormonal contraceptives, or complete abstinence from sexual intercourse with men) from the start of screening until 28 days after the last dose of study drug or be classified as female subjects of nonchildbearing potential, defined as meeting at least 1 of the following criteria:

- are postmenopausal with spontaneous amenorrhea for at least 12 months and have a follicle-stimulating hormone level >40 mIU/mL (>40 IU/L) at screening
- have undergone bilateral tubal ligation, bilateral oophorectomy, and/or hysterectomy at least 6 weeks prior to screening
- have another medical cause of female infertility that has been discussed with and accepted in writing by the sponsor

[4] male subjects: agree to use a reliable method of birth control from the start of screening until 2 weeks after the last dose of study drug (eg, barrier contraceptives, such as latex condoms, or complete abstinence from sexual intercourse with women) or have undergone vasectomy at least 6 weeks prior to screening with documentation of sperm-free ejaculate

[5] have a diagnosis of RA based on the 2010 ACR/European League against Rheumatism criteria (Aletaha et al. 2010) for at least 6 months prior to screening.

[6] have at least 1 of the following:

- positive test results for rheumatoid factor or anti-citrullinated peptide antibodies (ACPA) at screening

  OR

- previous radiographs documenting bony erosions in hands or feet consistent with RA

[7] have active RA, defined as meeting all of the following criteria at screening:

Part A: ≥3 swollen joints (based on 66-joint counts)

Part B:

- ≥6 swollen joints (based on 66-joint counts)
- ≥6 tender joints (based on 68-joint counts)
- high-sensitivity C-reactive protein (hsCRP) levels greater than the upper limit of normal (ULN) OR positive test results for ACPA

[8] **Part B only:** have had inadequate response, loss of response, or intolerance to at least 1 synthetic or biologic DMARD treatment for RA, regardless of treatment duration

[9] have venous access sufficient to allow blood sampling per protocol

[10] are reliable, willing, and able to follow study procedures (in the opinion of the investigator) and will be available for the duration of the study

5.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria:

[11] have previously completed or withdrawn from <u>any part</u> of this study (does not apply to subjects who are allowed to rescreen prior to randomization)

[12] have received any of the following synthetic immunosuppressive therapies under the defined conditions:

- methotrexate (MTX), hydroxychloroquine, sulfasalazine, or leflunomide at an UNSTABLE PRESCRIBED DOSE (defined as a change in prescription) within 28 days prior to baseline or planned dose change (including initiation or

discontinuation) during the study. The following therapies <u>are permitted</u> during the study:

- parenteral MTX up to 20 mg/week OR oral MTX up to 25 mg/week (subjects on MTX should receive supplementation with folic acid according to local standard of care)
- hydroxychloroquine up to 400 mg/day
- oral sulfasalazine up to 3000 mg/day
- leflunomide up to 20 mg/day

- concomitant treatment with MTX plus leflunomide within 28 days prior to baseline or planned concomitant treatment with both during the study
- gold salts, kinase inhibitors (such as tofacitinib), cyclophosphamide, mycophenolic acid, azathioprine, cyclosporine, sirolimus, or tacrolimus within 28 days prior to screening or planned treatment during the study
- **Part B only**: any prior treatment with a product directly targeting BTK (marketed or investigational)

[13] have received any of the following biologic immunosuppressive therapies under the defined conditions or plan any such treatments during the study (other biologic agents may be allowed after discussion with the sponsor and upon agreement in writing):

- etanercept, adalimumab, or anakinra within 14 days prior to baseline
- infliximab, certolizumab pegol, golimumab, abatacept, or tocilizumab within 4 weeks prior to baseline
- belimumab, natalizumab, or vedolizumab within 6 months prior to baseline
- **Part A only:** B-cell–depleting agents (such as rituximab) or other cell-depleting biologics (eg, anti-CD3 antibody) within 12 months prior to screening
- **Part B only:** B-cell–depleting agents (such as rituximab) or other cell-depleting biologics (eg, anti-CD3 antibody) at any time prior to screening

[14] have received any of the following other types of therapies under the defined conditions:

- parenteral corticosteroids within 28 days prior to baseline or planned treatment during the study. (A single intra-articular corticosteroid injection is permitted within 28 days prior to baseline if no more than 40 mg triamcinolone [or equivalent] is administered and no further injections are planned during the study. The treated joint should be excluded from any joint-specific evaluations during the study.)
- prescription for oral prednisone (or equivalent) >10 mg/day or UNSTABLE PRESCRIBED DOSE within 28 days prior to baseline
- a chronic narcotic drug at an UNSTABLE PRESCRIBED DOSE within 28 days prior to baseline or planned increase/new prescription during the study
- gemfibrozil (a strong cytochrome P450 2C8 inhibitor) or alfentanil, dihydroergotamine, dofetilide, ergotamine, fentanyl, pimozide, or quinidine

(sensitive narrow therapeutic index cytochrome P450 3A substrates) within 28 days prior to baseline or planned treatment during the study

[15] have any clinically significant hematological or chemistry abnormalities at screening, including

- hemoglobin level <8.5 g/dL (<85 g/L)
- total platelet count $<100 \times 10^9$/L ($<100 \times 10^3$/μL or <100 Gi/L)
- total white blood cell count $<3.0 \times 10^9$/L ($<3.0 \times 10^3$/μL or <3.0 Gi/L)
- aspartate aminotransferase (AST) level >2.5 × ULN
- alanine aminotransferase (ALT) level >2.5 × ULN
- creatinine level ≥1.5 mg/dL (≥129 μmol/L)
- amylase >1.5 x ULN
- lipase >1.5 x ULN

A single repeat analysis is allowed according to investigator judgment prior to making a final determination of eligibility. The repeat laboratory test does not require a reconsent because the result does not constitute a screening failure until the clinically significant, out-of-range value is confirmed.

[16] have known hypogammaglobulinemia or a screening serum IgG level <565 mg/dL (<5.65 g/L)

A single repeat analysis is allowed according to investigator judgment prior to making a final determination of eligibility. The repeat laboratory test does not require a reconsent because the result does not constitute a screening failure until the clinically significant out-of-range value is confirmed.

[17] have evidence of or test positive for hepatitis C virus (HCV) at screening (defined as a positive test result for hepatitis C antibody [anti-HCVAb] plus a positive confirmatory test result for HCV [eg, HCV RNA])

Subjects whose results are anti-HCVAb positive and HCV RNA negative can be enrolled in the study, according to investigator judgment.

[18] have evidence of or test positive for hepatitis B virus (HBV) at screening, defined as (1) testing positive for hepatitis B surface antigen OR (2) testing positive for anti–hepatitis B core antibody (HBcAb) AND positive for HBV DNA

Subjects whose results are HBcAb positive and HBV DNA negative may be enrolled in the study, according to investigator judgment. Subjects whose results are HBcAb positive and HBV DNA negative at screening will be monitored for HBV during the study as detailed in Section 8.4.7.1.

[19] have evidence of or test positive for human immunodeficiency virus at screening

[20] have symptomatic herpes zoster within 6 months prior to screening that constitutes a clinically significant risk to the subject (according to investigator judgment)

[21] have active tuberculosis (TB) determined on the basis of a positive medical history, physical examination, or chest radiography (per local standard of care) or have exclusionary TB test results, which include either of the following:

- a positive tuberculin skin test (TST) result (defined as a skin induration >5 mm at 48 to 72 hours after the test date, regardless of Bacillus Calmette-Guérin vaccination history) or
- a positive (or persistently indeterminate/invalid/borderline) interferon γ release test (eg, QuantiFERON®-TB Gold or T-Spot®.*TB*)

The choice to perform either a TST or an interferon γ release test will be made by the investigator according to local licensing and standard of care. If the QuantiFERON-TB Gold is indeterminate or the T-Spot.TB is invalid or borderline, one retest is allowed according to investigator judgment. If the repeat test is also indeterminate, the subject will be excluded. The interferon γ release test can be used only in countries where it is licensed, and the use of this test is dependent on previous treatment(s).

Subjects with known latent TB should not undergo a TST or interferon γ release test and must have documentation of receiving at least 4 weeks of appropriate, ongoing latent TB therapy, according to local standard of care, prior to screening. Such patients must continue/complete appropriate latent TB therapy during the course of the study in order to remain eligible.

[22] are at high risk of infection or have recent evidence of clinically significant infection, based on findings that include the following:

- fever of 100.5ºF (38ºC) or above at screening or baseline that is not due to the underlying autoimmune disease (eg, RA)
- history of serious opportunistic or chronic/recurring infection(s) within 6 months prior to screening (such as infections requiring IV antibiotics, hospitalization, or prolonged treatment) or deemed by the investigator to be immune compromised, such that participation in the study would pose an unacceptable risk to the subject
- have a predisposed high risk of infection or risk of serious complications from infection, such as a history of infected joint or heart valve prosthesis (with prosthesis still in situ), an indwelling urinary catheter, etc.

[23] have had lymphoma, leukemia, or any malignancy within the previous 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of recurrence or metastatic disease

[24] have a concomitant autoimmune or connective tissue disease at screening that is deemed active enough to interfere with the subject's safety or with evaluation of RA disease activity, in the opinion of the investigator

[25] have a bleeding disorder, anti-phospholipid antibody syndrome or other hypercoagulable disorder, are on chronic anticoagulation therapy such as warfarin or heparin, or are on an antiplatelet agent such as clopidogrel or ticlopidine (a stable regimen of aspirin is permitted)

[26] have a history of acute or chronic pancreatitis of any etiology, or severely uncontrolled hypertriglyceridemia, in the opinion of the investigator

[27] have had any surgical procedure (except for minor surgery requiring only local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening or have any planned surgical procedure scheduled to occur during the study

[28] have a history of clinically significant multiple or severe drug allergies or a history of severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[29] have clinically significant or uncontrolled cardiovascular disease (eg, hypertension, angina, or congestive heart failure); endocrine disorder (eg, diabetes, thyroid dysfunction); or respiratory, hepatic, renal, gastrointestinal, hematologic, or neuropsychiatric disorder, including recent history of suicide attempt

[30] have any other clinically significant condition, abnormality, or finding that may compromise the subject's safety or confound data analysis, according to investigator judgment

[31] have received a live (attenuated) vaccine within 28 days prior to baseline or plan to receive one during the study

[32] are currently enrolled in any other clinical trial involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study or have received any of the following IPs under the defined conditions:

- any nonbiologic IP within 5 half-lives prior to baseline
- any leukocyte-depleting agent (eg, anti-CD22 or anti-CD3) at any time
- any non–cell depleting biologic IP within 90 days or 5 drug half-lives (whichever is longer) prior to screening

[33] have donated more than 500 mL of blood within 28 days of screening or plan to donate blood during the study

[34] have a history of significant alcohol or drug abuse or are currently a heavy smoker, in the opinion of the investigator

[35] are investigator site personnel directly affiliated with this study and/or their immediate families (defined as a spouse, parent, child, or sibling, whether biological or legally adopted)

[36] are Lilly employees or are employees of third-party organizations involved in the study

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened ONE time in selected situations upon written approval from the sponsor (eg, if they failed to meet minimum disease activity criteria defined in Inclusion Criterion [7] at initial screening, required more time for appropriate drug washout periods, tested positive for latent TB and subsequently completed at least 4 weeks of appropriate prophylactic treatment, or had a fever (Exclusion Criterion [22]) that resolved, did not require IV antibiotics or hospitalization, and did not pose a risk to the subject for participation in the study, according to investigator judgment). Subjects who failed screening in Part A may be rescreened for either Part A or Part B; however, only ONE rescreen is permitted regardless of which part the subject is rescreening for.

Subjects who fail screening because of administrative reasons (eg, fall out of the screening window because of scheduling reasons) may be rescreened ONE time (in addition to the above) upon written approval from the sponsor.

If rescreening is performed, the individual must sign a new informed consent form (ICF) for each rescreening and will be assigned a new identification number. Subjects in rescreening who have previously completed screening chest radiography and/or TB tests according to the protocol do not need to repeat these procedures if they were performed within 90 days before their rescreening date of consent but may do so at the discretion of the investigator.

5.4. Lifestyle and/or Dietary Requirements

Strenuous exercise should be avoided for at least 24 hours before study visits.

Subjects should continue their usual dietary intake during the study.

6. Treatment

6.1. Treatments Administered

This study involves a comparison of each LY3337641 dosing regimen (5, 10, and 30 mg administered orally qd) with placebo. The study drug is supplied as tablets containing 5 and 20 mg of LY3337641 with matching placebo tablets. A single dose in Part A will include 4 tablets in various combinations depending on the assigned regimen. Table JPDA.3 shows the combinations of tablets used for the 4 dosing regimens. A single dose in Part B will include 4 tablets in various combinations depending on the assigned regimen. Table JPDA.4 shows the combinations of tablets used for the 4 dosing regimens. More information on the tablets and blinded regimens can be found in Section 6.4.

Table JPDA.3. Dosing Regimens – Part A

Regimen[a]	20-mg Tablets	5-mg Tablets
LY 30 mg	1 × 20-mg LY tablet 1 × 20-mg matching placebo tablet	2 × 5-mg LY tablets
LY 10 mg	2 × 20-mg matching placebo tablets	2 × 5-mg LY tablets
LY 5 mg	2 × 20-mg matching placebo tablets	1 × 5-mg LY tablet plus 1 × 5-mg matching placebo tablet
Placebo Comparator	2 × 20-mg matching placebo tablets	2 × 5-mg matching placebo tablets

Abbreviation: LY = LY3337641.

[a] Each dose consists of 4 tablets taken orally once daily (qd). The 5- and 20-mg placebo tablets match the respective 5- and 20-mg LY tablets.

Table JPDA.4. Dosing Regimens – Part B

Regimen[a]	20-mg Tablets	5-mg Tablets
LY 30 mg	1 × 20-mg LY tablet	2 × 5-mg LY tablets 1 × 5-mg matching placebo tablet
LY 10 mg	1 × 20-mg matching placebo tablet	2 × 5-mg LY tablets 1 × 5-mg matching placebo tablet
LY 5 mg	1 × 20-mg matching placebo tablet	1 × 5-mg LY tablet 2 × 5-mg matching placebo tablet
Placebo Comparator	1 × 20-mg matching placebo tablet	3 × 5-mg matching placebo tablets

Abbreviation: LY = LY3337641.

[a] Each dose consists of 4 tablets taken orally once daily (qd). The 5- and 20-mg placebo tablets match the respective 5- and 20-mg LY tablets. Four (4) tablets are required to provide for intermediate doses in the event of dose modification as defined in Section 6.6.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the study drug to the subject
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection

- returning all unused medication to Lilly, or its designee, at the end of the study, unless the sponsor and sites have agreed that all unused medication is to be destroyed by the site, as allowed by local law

6.2. Method of Treatment Assignment

For Part A, subjects who meet all criteria for enrollment will be randomly assigned in a 1:1:1:1 ratio to 1 of the 4 study arms at Visit 2 in a double-blind fashion. For Part B, subjects who meet all criteria for enrollment will be randomly assigned in a 1:1:1:1 ratio to 1 of the 4 study arms at Visit 102 in a double-blind fashion. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign packages containing double-blind study drug to each subject. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the package label into the IWRS.

To achieve between-group comparability in Part B, randomization will be stratified by biologic DMARD experience (yes/no), region (Japan vs non-Japan), and disease severity (Disease Activity Score modified to include the 28 diarthrodial joint count [DAS28]-hsCRP ≤5.1 vs >5.1). The screening value for hsCRP will be used to calculate DAS28-hsCRP (Section 8.1.2.2) for randomization.

6.2.1. Selection and Timing of Doses

Subjects will be randomly assigned to the dosing regimens as described in Section 6.2, and the assigned study drug will be administered as described in Section 6.1. Subjects will be instructed to take doses at approximately the same time each day. Study drug may be taken with or without food. The time of dose administration before a scheduled PK sampling should be recorded by the site at the clinic visit.

6.3. Blinding

This is a double-blind study; investigators, subjects, and study site personnel will be blinded to assigned dosing regimens throughout the study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete (Section 8.4.7).

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All transactions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, the site personnel performing assessments, or a subject is unblinded, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain written approval from Lilly or its designee for the subject to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first

consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly medical monitor prior to unblinding a subject's treatment assignment. If a subject's treatment assignment is unblinded, Lilly or its designee must be notified immediately.

6.4. Packaging and Labeling

The study drug will be supplied by the sponsor in accordance with current good manufacturing practices. The material will be labeled with a unique identifier for drug accountability. Clinical trial materials will be labeled according to the country's regulatory requirements.

The study drug will be supplied as tablets containing 5 and 20 mg of LY3337641 with matching placebo tablets. The LY3337641 5-mg tablets and corresponding 5-mg matched placebo are identical in appearance, and the LY3337641 20-mg tablets and corresponding 20-mg matched placebo are identical in appearance. However, the 5- and 20-mg tablets are not identical in appearance. To maintain blinding in Part A, individual doses will include 4 tablets: 2 from the 5-mg LY3337641/5-mg matched placebo set and 2 from the 20-mg LY3337641/20-mg matched placebo set, corresponding to the specific dose (see Table JPDA.3 for a listing of the various combinations for each of the 3 doses and placebo). For Part B, individual doses will include 4 tablets: 3 from either the 5-mg LY3337641/5-mg matched placebo set and 1 of the 20-mg LY3337641/20-mg matched placebo (see Table JPDA.4 for a listing of the various combinations for each of the 3 doses and placebo). Thus, there should be no distinguishable differences between doses. Subjects will be given a sufficient number of tablets to supply the required doses and maintain blinding for the duration of the visit interval (Schedule of Activities, Appendix 2).

6.5. Preparation/Handling/Storage

The study drug should be stored within the temperature range specified on the product label. The study drug should not be removed from the original packaging until the time that each dose is taken. All clinical trial materials will be stored, inventoried, and reconciled according to applicable regulations.

6.6. Dose Modification

Dose adjustments for individual subjects are not planned for this study.

However, during the course of the study, the dose for a study arm may be lowered for safety reasons. The Assessment Committee may review unblinded safety data throughout the study (Section 8.4.7) to assess the incidence and nature of significant AEs (including adverse events of special interest [AESIs, Section 8.2.2]).

On the basis of emerging safety information, the Assessment Committee will determine whether any LY3337641 dose level(s) should be reduced in order to maintain continued subject safety. Reduction of LY3337641 dose level(s) in this study will not require a protocol amendment, but all sites will be notified in writing. For example, if subjects in a 30-mg arm report any AEs that prompt the Assessment Committee to endorse a dose reduction for all subjects in that arm, the committee may select a lower dose reassignment, based on the nature and clinical course of the

reported AE. In this example, if a 10-mg dose reassignment is selected, all active subjects in the 30-mg arm will exchange their study drug supply for new study drug in a blinded fashion and continue dosing at the reduced dose; any new subjects randomly assigned to the 30-mg dose arm will receive only the reduced dose during their study participation. Subjects in the 5-mg, 10-mg, or placebo arm will continue at their current doses but will also participate in the study drug exchange in order to maintain the study blind for all subjects; this exchange will be carried out for all subjects using the IWRS.

If the Assessment Committee determines that it is appropriate to reduce the dose below 5 mg qd, the dose and/or frequency of administration for ALL subjects on LY3337641 (whether randomly assigned to a 30-, 10-, or 5-mg arm) will be reduced. As above, all active subjects in the study (including those receiving placebo tablets) will participate in the study drug exchange in order to maintain the study blind.

If the Assessment Committee decides to reduce any study arm dose of LY3337641, a return to the original dose will not be permitted in any part of the study. However, doses may be adjusted to levels that are intermediate to the dose levels planned, as long as they are lower than doses that have been discontinued for safety reasons.

Replacement of subjects: If the study drug dose is reduced and results in an insufficient number of subjects (per dose) completing either Part A or B to allow assessment of the primary endpoint, the sponsor might choose to replace study subjects by increasing enrollment. If this occurs, all sites will be notified in writing.

6.7. Treatment Compliance

Subject compliance with study medication will be assessed at each visit. Compliance will be assessed by counting returned tablets of study drug. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A subject will be considered significantly noncompliant if he or she misses more than 20% of the prescribed doses during the study. Similarly, a subject will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Subjects found to be noncompliant with the study drug should be assessed to determine the reason for noncompliance and educated and/or managed as deemed appropriate by the investigator to improve compliance, or they should be discontinued from the study.

6.8. Concomitant Therapy

Allowed and excluded medications and procedures will be provided in the Listing of Excluded and Restricted Medications tool.

Subjects on concurrent, protocol-permitted RA treatments should remain on stable doses during the course of the study.

Subjects taking other concomitant medications should be on stable doses at baseline and should remain at stable doses throughout the study to the extent possible, unless changes are needed for

treatment of an AE. The introduction of any other new prescription or over-the-counter drugs is to be avoided during the study unless required to treat an AE. Any medication used during the course of the study must be documented.

6.9. Treatment after Study Completion

Study drug is experimental and will be provided to study subjects only according to the protocol; it will not be made available to subjects after they have completed or discontinued from the study unless the subject qualifies to continue study drug in another protocol.

7. Discontinuation Criteria

7.1. Discontinuation from Study Treatment

7.1.1. Interruption of Study Drug

According to investigator judgment, study drug doses may be temporarily interrupted in subjects who develop skin rash, an AESI. See Section 8.4.6 for details on the assessment and management of subjects developing a rash.

7.1.2. Permanent Discontinuation from Study Drug

Discontinuation of the study drug for abnormal liver test results **should be considered** by the investigator (in consultation with the Lilly designated medical monitor) when a subject meets any of the following conditions:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN and either total bilirubin level >2 × ULN or international normalized ratio >1.5
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

In addition, immediate and permanent discontinuation of study drug should be considered for all subjects after the development of a rash (an AESI) deemed clinically significant by the investigator. See Section 8.4.6 for details on the assessment and management of subjects developing a rash.

The reason for and date of discontinuation from study drug will be collected for all randomized subjects. Subjects who discontinue study drug should also be discontinued from the study according to Section 7.1.4. All subjects who discontinue study drug early will have end-of-therapy procedures performed as shown for the early discontinuation visit (EDV) in the Schedule of Activities (Appendix 2).

7.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor's medical monitor and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled subject to continue in the study with or without treatment with study drug.

7.1.4. Permanent Discontinuation from the Study

Possible reasons that may lead to permanent discontinuation include

- enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the subject should be discontinued from the study drug or study
    - the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of RA but is contraindicated in this study (in such cases, discontinuation from the study occurs prior to introduction of the new agent)
- subject decision
    - the subject requests to be withdrawn from the study

The reason for and date of discontinuation from study will be collected for all randomized subjects. All subjects who have received study drug and discontinue the study early will have end-of-study procedures performed as shown for the EDV in the Schedule of Activities (Appendix 2). Subjects who are randomized but discontinue the study prior to receiving a single dose of study drug will not have an EDV or a safety follow-up visit.

7.1.5. Subjects Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and cannot be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or are otherwise unavailable for follow-up by the site.

8. Study Assessments and Procedures

Study procedures and their timing (including tolerance limits for timing) are summarized in the Schedule of Activities (Appendix 2).

A list of the laboratory tests that will be performed for this study is provided in Appendix 3.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy assessment is the proportion of subjects in Part B who achieve an ACR20 response.

To achieve the ACR20 response, a subject must have at least 20% improvement from baseline in the following ACR core set components:

- tender joint count (TJC; 68-joint count)
- swollen joint count (SJC; 66-joint count)
- at least 3 of the following 5 assessments:
  (1) Physician's Global Assessment of Disease Activity (visual analog scale [VAS])
  (2) Patient's Global Assessment of Disease Activity (VAS)
  (3) Patient's Global Assessment of Arthritis Pain (VAS)
  (4) Patient's assessment of physical function as measured by the Health Assessment Questionnaire–Disability Index (HAQ-DI)
  (5) acute phase reactant as measured by hsCRP

While the primary efficacy assessment is calculated based on data from Part B, the ACR core set components will still be collected as exploratory endpoints in Part A.

8.1.1.1. Joint Assessments

For the joint count evaluations, a joint assessor, who should be a rheumatologist or skilled arthritis assessor, will be responsible for completing the joint counts. To ensure consistent joint evaluation throughout the trial, evaluations of an individual subject should be performed by the same joint assessor for all study visits. The joint assessor should not have access to or discuss with the subject the patient-reported assessments, Physician's Global Assessment of Disease Activity, and safety assessments.

Missing, replaced, ankylosed, or arthrodesed joints will be identified at the screening visit and will be excluded from evaluation during the trial. The locations (or a listing) of previous surgical procedures should be documented in the subject's source documents/eCRF pages for the joint and in the AE eCRF for any surgical procedures that may occur during the study.

8.1.1.1.1. Tender Joint Count

The number of tender and painful joints will be determined by examination of 68 joints (34 joints on each side of the subject's body). The 68 joints to be assessed and classified as tender or not tender are 2 temporomandibular joints, 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 hip joints, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be assessed for tenderness by pressure and joint manipulation on physical examination. The subject will be asked for pain sensations on these manipulations and watched for spontaneous pain reactions. Any positive response on pressure, movement, or both will then be translated into a single tender-versus-nontender dichotomy.

8.1.1.1.2. Swollen Joint Count

The number of swollen joints will be determined by examination of 66 joints (33 joints on each side of the subject's body). The 66 joints to be assessed and classified as swollen or not swollen are 2 temporomandibular joints, 2 sternoclavicular joints, 2 acromioclavicular joints, 2 shoulder joints, 2 elbow joints, 2 wrist joints, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints of the hands, 8 distal interphalangeal joints of the hands, 2 knee joints, 2 ankle joints, 2 tarsus, 10 metatarsophalangeal joints of the feet, 2 great toes (first proximal interphalangeal joint of the feet), and 8 proximal interphalangeal joints of the feet.

Joints will be classified as either swollen or not swollen. Swelling is defined as palpable fluctuating synovitis of the joint. Swelling secondary to osteoarthrosis will be assessed as not swollen, unless there is unmistakable fluctuation.

8.1.1.2. Physician's Global Assessment of Disease Activity (VAS)

The investigator will be asked to give an overall assessment of the severity of the subject's current RA disease activity using a 100-mm horizontal VAS, where the left end represents no disease activity and the right end represents extremely active disease.

Results will be expressed in millimeters measured between the left end of the scale and the crossing point of the vertical line; *this procedure is applicable for all VAS measures used in the trial.*

8.1.1.3. Patient's Global Assessment of Disease Activity (VAS)

Subjects will be asked to give an overall assessment of the severity of their current RA disease activity using a 100-mm horizontal VAS where the left end represents no disease activity ("very well") and the right end represents extremely active disease ("very poor"). This assessment should be completed before the study visit examinations.

8.1.1.4. Patient's Global Assessment of Arthritis Pain (VAS)

Subjects will be asked to assess their current level of arthritis pain by using a 100-mm horizontal VAS where the left end represents no pain and the right end represents the worst possible pain. This assessment should be completed before the study visit examinations.

8.1.1.5. Patient's Assessment of Physical Function (HAQ-DI)

The HAQ-DI is a patient-reported questionnaire that is commonly used in RA to measure disease-associated disability (assessment of physical function). It consists of 24 questions referring to 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other daily activities (Fries et al. 1980, 1982; Ramey et al. 1996). The disability section of the questionnaire scores the patient's self-perception of the degree of difficulty (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do) covering the 8 domains mentioned above. The reported use of special aids or devices and/or the need for assistance of another person to perform these activities is also assessed. The scores for each of the functional domains will be averaged to calculate the functional disability index. This assessment should be completed before the study visit examinations.

8.1.1.6. High-Sensitivity C-Reactive Protein

The ACR core set measure of acute phase reactant will be hsCRP (measured at the central laboratory from blood samples obtained at specified study visits [Schedule of Activities, Appendix 2]).

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Additional ACR Response Levels: ACR50 and ACR70

The ACR50 and ACR70 responses are calculated as improvements of at least 50% and 70%, respectively, in the ACR core set using an algorithm similar to that used for ACR20.

8.1.2.2. Disease Activity Score: DAS28-hsCRP

The DAS28-hsCRP is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: TJC, SJC, hsCRP (mg/L), and the Patient's Global Assessment of Disease Activity (Vander Cruyssen et al. 2005).

$$DAS28 - hsCRP = 0.56\left(\sqrt{TJC28}\right) + 0.28\left(\sqrt{SJC28}\right) + 0.36[ln(CRP + 1)] + 0.014(VAS) + 0.96$$

For DAS28-hsCRP, the 28 joints to be examined and assessed as tender or not tender (TJC) and swollen or not swollen (SJC) are 14 joints on each side of the subject's body: the 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal joints, 2 interphalangeal joints of the thumb, 8 proximal interphalangeal joints, and 2 knees (Smolen et al. 1995).

Clinical remission is defined as DAS28-hsCRP <2.6, and low disease activity (LDA) as DAS28-hsCRP ≤3.2.

8.1.3. Appropriateness of Assessments

All of the clinical and safety assessments made in this study are standard, widely used, and generally recognized as reliable, accurate, and relevant.

8.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study drug or the study, or that caused the subject to discontinue the study drug before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in this study because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via the eCRF the occurrence and nature of each subject's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record via the eCRF any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or study drug, via the eCRF.

The investigator decides whether he or she interprets the observed AEs as reasonably possibly related to RA, study drug, study procedure, or other concomitant treatment or pathology. To assess the relationship of the AEs, the following is defined:

> reasonably possibly related: reasonable and temporal possibility that there is a cause and effect relationship between the study drug and/or study procedure and the AE

The investigator answers yes/no when making this assessment.

Adverse events will be graded for severity as mild, moderate, or severe, except for rashes (AESIs), which will be graded according to the Common Terminology Criteria for Adverse Events.

Planned nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's study drug is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via the eCRF, clarifying if possible the circumstances leading to any dose interruptions or discontinuations of treatment.

8.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs occurring after a subject signs the ICF are recorded in the eCRF, SAE reporting begins after the subject has both signed the ICF and received study drug. However, if an SAE occurs after a subject signs the ICF but prior to receiving study drug, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study drug) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the subject's summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study drug or study participation, the investigator must promptly notify Lilly.

8.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study drug or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.2.2. Adverse Events of Special Interest

Skin rash is considered an AESI. If a subject develops a rash during the study, the subject should notify the site immediately in order to conduct an unscheduled visit. The visit should be

scheduled as soon as possible to enable evaluation of the rash while it is still present. See Section 8.4.6 for instructions on rash assessment and management.

8.2.3. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

Subjects will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

8.3. Treatment of Overdose

In case of suspected overdose, subjects should be closely monitored for electrocardiogram (ECG) changes; clinical laboratory abnormalities (hematology and serum chemistry); and adverse skin reactions and any associated localized, generalized, and/or systemic symptoms, which may include skin irritation, rash, skin exfoliation, pruritus, urticaria, fever, edema, or joint pain/swelling. Investigators should remain vigilant for unknown effects related to LY3337641 overdose.

There is no known antidote for overdose of LY3337641.

8.4. Safety Assessments

8.4.1. Physical Examination

Complete physical examinations and symptom-directed physical examinations will be conducted as specified in the Schedule of Activities (Appendix 2) and as clinically indicated. A complete physical examination should include evaluation of the following regions/systems:

- general appearance
- skin
- head, ears, eyes, nose, throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal
- genitourinary (only as clinically indicated)
- extremities (tender/swollen joint counts to be documented separately)
- neurologic

On visit days where a complete physical examination is not required, as detailed in the Schedule of Activities (Appendix 2), the investigator may conduct a symptom-directed physical examination as clinically indicated.

8.4.2. Vital Signs

Blood pressure and heart rate will be measured as specified in the Schedule of Activities (Appendix 2) and as clinically indicated. These should be measured after at least 5 minutes of sitting.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If the subject feels unable to stand, sitting or supine vital signs should be recorded.

Additional vital signs may be measured during each study visit if warranted, as determined by the investigator.

Body temperature will be measured as specified in the Schedule of Activities (Appendix 2) and as clinically indicated.

Any clinically significant findings that occur after the subject receives the first dose of study drug should be reported to Lilly or its designee as an AE via the eCRF.

8.4.3. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Appendix 2).

Subjects should lie supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. If possible, ECGs should be recorded prior to drawing blood and measuring blood pressure and pulse.

Electrocardiograms may be obtained at additional times when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be locally interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria and for immediate subject management, should any clinically relevant findings be identified. The investigator (or qualified designee) must document the review of the ECG. All recorded ECGs should be stored at the site and made available to the sponsor as requested.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the study drug should be reported to Lilly or its designee as an AE via the eCRF.

8.4.4. Chest Radiography and Tuberculosis Testing

Posteroanterior and lateral chest radiography will be performed at screening for all subjects unless these have been obtained within 90 days prior to initial screening and the radiographs or report is available for investigator review. Variations on the chest radiography view requirements will only be permitted if the country/local guidelines of care for standard TB screening differ from these protocol specifications.

All subjects will undergo a TB test at screening (TST or interferon γ release test). Refer to Exclusion Criterion [21] for details regarding TB testing.

See Section 5.3 for subjects who are rescreening for this study and have undergone radiography and/or TB testing as part of their initial screening.

8.4.5. Laboratory Tests

For each subject, the laboratory tests detailed in Appendix 3 should be conducted according to the Schedule of Activities (Appendix 2).

Any clinically significant findings that occur after the subject receives the first dose of study drug should be reported to Lilly or its designee as an AE via the eCRF.

8.4.6. Assessment and Management of Subjects Developing a Rash

Subjects who develop a skin rash should be evaluated as soon as possible. Investigators will be prompted to categorize and diagnose the rash (per clinical judgment), assess relatedness to study drug, and grade severity according to Common Terminology Criteria for Adverse Events. This information will be entered into a form incorporated into the eCRF. Additional information related to the rash evaluation will also be entered into this form and will include a history of infections and allergies; and recent exposure to prescription or over-the-counter medications, skin products, detergents, or other potential skin irritants. A review of systems will be completed to assess for systemic symptoms and concurrent illnesses. A targeted physical examination should be performed, including an evaluation of the rash distribution and type, vital signs and temperature, and other organ systems, as clinically indicated. In addition, photographs and laboratory measurements should be obtained as clinically indicated, according to investigator judgment. The subject should be evaluated to determine whether there are any signs or symptoms suggesting a severe, potentially life-threatening condition.

If a subject develops a rash that is assessed as not related to study drug, is transient, or is not clinically significant in the opinion of the investigator, the study drug may be continued without interruption. In some cases, the investigator may instead choose to interrupt the study drug and restart it at a later date. The dates for stopping and restarting the study drug should be captured.

Immediate and permanent discontinuation of study drug should be considered for all subjects with clinically significant rash. For rashes deemed clinically significant, punch biopsy(ies) of the rash should also be performed. In addition, a venous blood sample should be collected for PK analysis at the time of evaluation with documentation of the date and time of administration of the most recent dose of study drug.

Subjects should be followed up until resolution of the rash, to the extent possible.

The site should manage any rash that occurs during the study according to the judgment of the investigator. Interventions may include supportive care, pharmacotherapy, laboratory evaluation, additional skin biopsies, and consultation with a dermatologist, as clinically indicated. Data from these additional interventions should be provided to the sponsor as part of the AE reporting after being deidentified and summarized by the investigative site.

8.4.7. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly medical monitor or designee will, as is appropriate, consult with the functionally independent Global Patient Safety medical physician or clinical scientist and periodically review the following in a blinded fashion:

- trends in safety data
- laboratory analytes
- AEs (including AESIs)

If a study subject experiences elevated ALT ≥3 × ULN or elevated total bilirubin level ≥2 × ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure subject safety and comply with regulatory guidance, the investigator is to consult with the Lilly medical monitor regarding collection of specific recommended clinical information and follow-up laboratory tests (Appendix 4).

In addition to the safety reviews performed by the blinded Study JPDA team mentioned above, the Assessment Committee will review the safety data in an unblinded fashion during the study and will determine whether dose reductions to any study arm should be made, and whether enrollment of Part B may proceed after review of Part A data. The Assessment Committee reviewing the safety data will include, at a minimum, a Lilly medical physician, a statistician, and a representative from Global Patient Safety; it will not include any Lilly study team members.

8.4.7.1. Hepatitis B Monitoring

Subjects whose results are HBcAb positive at screening, regardless of hepatitis B surface antibody (HBsAb) status, will have an HBV DNA test performed by the central laboratory. Subjects whose results are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Subjects whose results are HBV DNA negative (undetectable) may be enrolled into the study, according to investigator judgment, with HBV DNA monitoring approximately every 4 weeks during treatment as detailed in the Schedule of Activities (Appendix 2). Subjects participating in Part B who are positive for HBcAb will continue to have HBV DNA monitoring every 3 months (for 6 months) after the last dose of study drug. Once

subjects test positive for HBV DNA, they should be managed as clinically indicated and discontinued from the study (HBV monitoring is no longer required within the study at that point).

Subjects whose results are HBcAb negative and HBsAb positive will not require testing for HBV DNA because they are likely to have been vaccinated for HBV and have a very low risk of reactivation. These subjects will be followed up by routine liver tests as part of the monitoring process.

If the result of the HBV DNA testing is positive at any time after screening, the subject must discontinue the study drug and should receive appropriate follow-up medical care, including consideration for antiviral therapy. A specialist physician in the care of patients with hepatitis (for example, infectious disease physician or hepatologist) should be consulted. The timing of discontinuation from the study drug and any other immunosuppressant therapy should be based on the recommendations of the consulting specialist physician in conjunction with the investigator and medical guidelines/standard of care.

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of LY3337641. At the baseline visit (Visit 2 in Part A and Visit 102 in Part B), the first dose of study drug will be administered, and subjects will remain at the site and have the PK sample drawn between 30 minutes and 2 hours postdose. At subsequent visits, the PK sample will be drawn at any time during the visit; it is not required that the dose be administered during the visit.

A maximum of 2 PK samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. For example, if an SAE or a clinically significant rash is observed by the investigator and a PK sample is not scheduled for that visit, a sample may be drawn at that time.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. It is essential that the actual times of dosing and sampling are recorded accurately.

Drug concentration information that may unblind the study will not be reported to investigative sites or personnel who are blinded to study data.

Plasma samples will be analyzed for LY3337641 at a laboratory approved by the sponsor using validated liquid chromatography-tandem mass spectrometry methodology. Analysis of samples collected from placebo-treated subjects is not planned.

Plasma PK samples may be analyzed for exploratory metabolite identification, as deemed appropriate by the sponsor. The results of such exploratory metabolism work may only be included in the clinical study report (CSR) if deemed appropriate by the sponsor or may be reported in a separate exploratory metabolism report.

Bioanalytical samples collected to measure LY3337641 concentration will be retained for a maximum of 1 year following the last subject visit for the study.

8.6. Pharmacodynamics

At the visits and times specified in the Schedule of Activities (Appendix 2), venous blood samples will be collected for the analysis of PD endpoints. Pharmacodynamic endpoints that are planned to be measured include total Ig, IgG, IgM, and IgA (Part B only). Additionally, BTK occupancy and phosphorylated BTK will be assessed and samples will be drawn only at sites that meet assay requirements.

Bioanalytical samples collected to measure PD endpoints will be identified by the subject number (coded) and retained for a maximum of 1 year following last subject visit for the study at a facility selected by the sponsor.

8.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Appendix 2) where local regulations and ERBs allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3337641 and to investigate genetic variants thought to play a role in RA. Assessment of variable response may include evaluation of AEs or differences in efficacy. These studies may include but are not limited to genetic variants thought to play a role in RA and genes that play a role in leukocyte (B-cell receptor, Fc receptor, or T-cell receptor) signaling pathways to evaluate their association with observed response to LY3337641.

All pharmacogenetic samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum of 15 years after the last subject visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described here.

8.8. Biomarkers

Serum, plasma, and whole blood samples for nongenetic biomarker research will be collected at the times specified in the Schedule of Activities (Appendix 2) where local regulations and ERBs allow.

Samples will be used for research on the drug target, disease process, pathways associated with RA, mechanism of action of LY3337641, and/or research method or in validating diagnostic tools or assay(s) related to RA. Proteomic, gene-expression, genomic, epigenetic, or metabolomic analyses may be performed on these samples.

All biomarker samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigator site personnel. Samples will be destroyed according to a process consistent with local regulations.

Samples will be retained for a maximum 15 years after the last subject visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

8.9. Health Outcomes

Health outcomes measures should be administered according to the Schedule of Activities (Appendix 2) in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

The health outcomes measures to be assessed in this study are described in the following subsections (refer to Section 8.1.1 for health outcomes measures included in the ACR20 efficacy assessment).

- Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (only in Part B)
- Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (only in Part B)
- morning joint stiffness duration
- patient's assessment of sexual function (VAS) (only in Part B).

Any measures that are subject self-assessments should be completed *before* the study visit examinations.

8.9.1. SF-36

The SF-36v2 Acute measure (SF-36) is a subjective, generic, health-related quality of life instrument that is patient-reported and consists of 36 questions covering 8 health domains: physical functioning, bodily pain, role limitations due to physical problems, role limitations due to emotional problems, general health perceptions, mental health, social function, and vitality. Each domain is scored by summing the individual items and transforming the scores into a 0 to 100 scale with higher scores indicating better health status or functioning. In addition, 2 summary scores, the PCS (physical component score) and the MCS (mental component score),

will be evaluated based on the 8 SF-36v2 Acute domains (Brazier et al. 1992; Ware and Sherbourne 1992).

8.9.2. FACIT-F

The FACIT-F scale (Cella and Webster 1997) is a brief, 13-item, symptom-specific questionnaire that specifically assesses the self-reported severity of fatigue and its impact upon daily activities and functioning. The FACIT-F uses 0 ("not at all") to 4 ("very much") numeric rating scales to assess fatigue and its impact in the past 7 days. Scores range from 0 to 52 with higher scores indicating less fatigue.

8.9.3. Morning Joint Stiffness Duration

Subjects will be asked by site personnel to assess their duration of morning joint stiffness on the day prior to the visit. Responses will be recorded in minutes.

8.9.4. Patient's Assessment of Sexual Function (VAS)

Subjects will be asked to assess the extent of the effect that RA has had on their sexual activity over the past week by using a 100-mm horizontal VAS where the left end represents "no effect on my sexual activity" and the right end represents "completely stopped my sexual activity."

9. Statistical Considerations and Data Analysis

9.1. Determination of Sample Size

Approximately 32 at least mildly active RA subjects will be enrolled and randomly assigned in a 1:1:1:1 ratio to 1 of the 3 doses of LY3337641 (5, 10, or 30 mg) or placebo in Part A. This sample size is customary for evaluating safety and PK and/or PD parameters, and is not powered on the basis of statistical hypothesis testing.

Approximately 244 moderately to severely active RA subjects will be enrolled and randomly assigned in a 1:1:1:1 ratio to 1 of the 3 doses of LY3337641 (5, 10, or 30 mg) or placebo in Part B. All subjects who discontinue the treatment early (before Week 12) will be considered as failing the primary endpoint in Part B. The sample size of 61 subjects per arm will provide at least 80% power at the 2-sided .05 significance level to detect a difference of 25% in the primary endpoint (ACR20 response rate at Week 12) between each LY3337641 dose and placebo, assuming a 30% placebo response rate.

If the Assessment Committee determines that a dose adjustment is needed (Section 6.6), the total study sample size may be adjusted.

9.2. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

In general, continuous variables will be summarized including number of observations; mean; standard deviation; and minimum, median, and maximum values. Categorical variables will be presented as counts and percentages. Data from Part A will be summarized separately from data from Part B. No statistical hypothesis testing is planned for Part A. All tests of treatment effects in Part B will be conducted at the 2-sided α level of .05, unless otherwise stated. No adjustments for multiplicity will be performed.

Complete details of the planned analyses will be documented in the statistical analysis plan (SAP). Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.2.1. Analysis Population

Unless otherwise specified, efficacy and health outcomes analyses will be conducted on the modified intent-to-treat population, defined as all randomized subjects receiving at least 1 dose of study drug. The analysis population (for applicable treatment outcome measures) will be all subjects with both a baseline and at least 1 postbaseline data measurement. Subjects will be grouped according to the randomized treatment. In addition, the primary analysis of Part B will be repeated using the per-protocol set, defined as all subjects randomly assigned to the study drug and using the study drug for 12 weeks.

Safety analyses will be conducted on the safety population, defined as all randomized subjects receiving at least 1 dose of the study drug. Subjects will be grouped according to the randomized treatment.

9.2.2. Baseline Definition

The baseline will be defined as the last available value before the first administration of study drug for both efficacy and safety analyses, including unscheduled measurements for both parts separately. In most cases, this will be the measure recorded on Study Day 1 (Visit 2 in Part A, Visit 102 in Part B). Change from baseline values will be calculated as the postbaseline value minus the baseline value for each scheduled postbaseline time point. If the baseline value is missing (ie, no screening values, no Day 1 value, and no unscheduled measurements), the change from baseline will be missing as well.

9.2.3. Missing Data Imputation

The methods for imputation of missing data will be outlined in the SAP.

9.3. Treatment Group Comparability

9.3.1. Subject Disposition

A detailed description of subject disposition will be provided. Details will be outlined in the SAP.

9.3.2. Subject Characteristics

The subject's sex, weight, height, and other demographic characteristics will be recorded. Details will be outlined in the SAP.

9.3.3. Concomitant Therapy

Details will be outlined in the SAP.

9.3.4. Treatment Compliance

Treatment compliance will be evaluated by visit and overall during the study. Details will be provided in the SAP.

9.4. Primary and Secondary Analyses

9.4.1. Primary Analyses

The primary objective in Part A is safety (Section 9.5).

The primary endpoint in Part B will be analyzed by a logistic regression model with ACR20 at Week 12 as the dependent variable and treatment, biologic DMARD experience (yes/no), region (Japan vs non-Japan), and baseline DAS28-hsCRP as independent variables. The comparison of each LY3337641 dose to placebo will be presented. Subjects who discontinue from the study earlier than Week 12 and subjects who complete 12 weeks of dosing but do not have sufficient

data to derive the ACR20 response (Section 8.1.1) will be considered as failing to meet the ACR20.

9.4.1.1. Additional Analyses of the Primary Efficacy Measure

The number and percentage of subjects achieving the ACR20 response over time in both parts will be summarized separately by treatment group. All subjects who discontinue study drug at any time for any reason will be defined as nonresponders from time of discontinuation forward for ACR analyses.

The ACR20 will also be analyzed using the per-protocol set (Section 9.2.1) as a sensitivity analysis in Part B. Details will be outlined in the SAP.

Each component of the ACR20 (ie, TJC, SJC, Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, pain score, HAQ-DI, and hsCRP) in both parts will be summarized separately over time by treatment. The change from baseline to postbaseline in Part B will be analyzed by a maximum-likelihood–based mixed model repeated measures (MMRM) analysis of covariance. The change from baseline for each component of the ACR20 to each postbaseline time point in Part B is the dependent variable in the model. Baseline, treatment, weeks of treatment (categorical), the interaction of treatment and weeks, biologic DMARD experience (yes/no), region (Japan vs non-Japan), and baseline DAS28-hsCRP are fixed effects; subjects and error are random effects.

9.4.2. Secondary Analyses

ACR50 and ACR70 will be summarized for both parts separately. Data from Part B will be analyzed using methods similar to those for the primary analysis.

DAS28-hsCRP will be summarized separately for each part by treatment and each postbaseline visit. Change from baseline in DAS28-hsCRP to each postbaseline time point in Part B will be analyzed by the MMRM approach. Subjects with DAS28-hsCRP <2.6 will be considered as having achieved clinical remission; the criterion for achieving LDA will be DAS28-hsCRP ≤3.2. The number and percentage of subjects who achieve clinical remission or LDA will be summarized separately and analyzed using methods similar to those for the primary analysis.

9.5. Safety Analyses

All safety summaries and analyses will be based on the safety population as defined in Section 9.2.1. Safety will be assessed by evaluating all reported AEs, AESIs, changes in vital signs, and changes in laboratory analytes.

Exposure to each study regimen will be calculated for each subject and summarized for both parts separately by treatment group. Safety analyses will be conducted for both parts separately by treatment group.

9.5.1. Adverse Events

Adverse events will be classified by system organ class and preferred term as defined by the *Medical Dictionary for Regulatory Drug Activities*. A TEAE is defined as an event that first

occurs or worsens in severity after baseline and on or prior to the date of the last visit within the dosing period. All pre-existing conditions recorded at Visit 1 (Part A) or Visit 101 (Part B) and any AEs recorded before the first dose of study drug (during the interval between Visits 1 and 2 for Part A or Visits 101 and 102 for Part B and recorded with the time of onset before the first dose of study drug) will be used as baseline. The dosing period will be included as the postbaseline period for analysis. For the Follow-Up Period, a follow-up–emergent adverse event is defined as an event that first occurs or worsens in severity after the last dose of study drug. For events that are sex specific, the denominator and computation of the percentage will only include subjects of the given sex.

Adverse events will be summarized as TEAEs. The frequency and percentage of TEAEs will be presented for each treatment group. All AEs, including pre-existing conditions, will be listed by subject, visit, preferred term, treatment group, severity, and relationship to the treatment.

9.6. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic and exploratory PK/PD analyses will be performed using a nonlinear mixed-effect modeling approach as implemented in NONMEM® on a computer that meets or exceeds the minimum system requirements for this program. It is possible that other validated equivalent PK software programs may be used if appropriate. The version of any software used for the analysis will be documented. Data from Parts A and B may be combined for population PK and PK/PD analyses.

Population PK analyses will be performed to characterize the PK of LY3337641 after qd dosing in subjects with RA. These analyses will include model-based and graphical evaluations of the data. Estimates of PK model parameters and covariate effects and corresponding 95% CIs will be reported. The PK data may be combined with data from other studies in order to obtain improved PK parameter estimates.

Exploratory graphical PK/PD analyses will be conducted to evaluate the relationship between LY3337641 concentrations (or exposure) and selected measures of clinical response (efficacy measures, PD measures, or biomarkers). These analyses may include analyses of relationships at specific time points as well as the development of longitudinal exposure-response models. Additional model-based analyses may be conducted if deemed appropriate.

9.7. Other Analyses

9.7.1. Health Outcomes and Biomarkers

Health outcomes and biomarkers will be collected throughout the study. These will be summarized. Details will be outlined in the SAP.

9.7.2. Subgroup Analyses

Subgroup analyses will be conducted for ACR20, ACR50, ACR70, and DAS28-hsCRP using the modified intent-to-treat population using Part B data. Subgroups that may be evaluated include

past or ongoing RA treatment at baseline and baseline DAS28-hsCRP. Details will be provided in the SAP.

9.8. Interim Analyses

The Assessment Committee is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their subjects.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

For Part A, two interim analyses are planned. The first interim will take place at least 2 weeks after all subjects have had their last dose. The second will take place when all data from Part A are available. Since all safety data for the primary objective in the Part A treatment period will be completed at the first interim, the study team will be unblinded to all available results for both interims in Part A.

For Part B, an interim efficacy analysis is planned when approximately 40% of the subjects have completed the Week 12 visit. This interim analysis will be conducted for internal decision making to trigger planning activities for future studies associated with LY3337641. The study will not be stopped early for efficacy. No adjustment of type I error will be performed. The PK/PD data will also be reviewed as part of the interim analysis to initiate model development processes. Based on emerging data, additional interim analyses may be conducted by an Assessment Committee to review unblinded safety data.

A second interim analysis in Part B is planned when all subjects in Part B have completed (or discontinued early from) Part B. This interim analysis is planned to be the final analysis for Part B for CSR writing. This interim will include all planned analyses of available data. The study team will be unblinded to all available results for Part B.

If the Assessment Committee determines that an additional efficacy interim analysis may be needed before the Part B final analysis for internal decision-making for future studies, then an additional efficacy interim analysis may be conducted. This study will not be stopped early for efficacy reasons. No adjustment of type I error will be performed. The PK/PD data may be reviewed, and the model may be updated.

Subjects participating in Part B who are positive for HBcAb will continue to have HBV DNA monitoring every 3 months (for 6 months) after the last dose of study drug. Once subjects test positive for HBV DNA, they should be managed as clinically indicated and discontinued from the study (HBV monitoring is no longer required within the study at that point). The final database will be locked when these subjects complete all HBV DNA monitoring. The analyses for HBV DNA will be rerun on the final data.

Details of the planned interim data analyses and the Assessment Committee data review process will be included in an Assessment Committee charter.

10. Study Governance Considerations

10.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

10.1.1. Informed Consent

The investigator is responsible for

- ensuring that the subject understands the potential risks and benefits of participating in the study.
- ensuring that informed consent is given by each subject. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the trial.

10.1.2. Ethical Review

The investigator or an appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Conference on Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

10.1.3. Regulatory Considerations

This study will be conducted in accordance with

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

10.1.4. Investigator Information

Physicians with a specialty in rheumatology or internal medicine will participate as investigators in this clinical trial. Other specialties may be acceptable with approval by the sponsor.

10.1.5. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.1.6. Final Report Signature

The CSR-coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study and accuracy, completeness, and reliability of data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the

investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

10.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.3. Study and Site Closure

10.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

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Appendix 1. Abbreviations and Definitions

Term	Definition
ACPA	anti-citrullinated peptide antibodies
ACR	American College of Rheumatology
ACR20	20% improvement in the American College of Rheumatology criteria
ACR50	50% improvement in the American College of Rheumatology criteria
ACR70	70% improvement in the American College of Rheumatology criteria
ACR90	90% improvement in the American College of Rheumatology criteria
ACR-N	continuous measure of percentage improvement from baseline in American College of Rheumatology criteria: this index is defined operationally as the lowest of either (a) the percentage change in TJC, (b) the percentage change in SJC, or (c) the median percentage change in the remaining 5 ACR core criteria (eg, a patient with an ACR-N of "X" has improvement of at least "X%" in tender and swollen joints and a median improvement of at least "X%" in the 5 remaining ACR core criteria)
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event 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 related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding	A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BTK	Bruton's tyrosine kinase
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CSR	clinical study report
DAS28	Disease Activity Score modified to include the 28 diarthrodial joint count
DMARD	disease-modifying antirheumatic drug

ECG	electrocardiogram
eCRF	electronic case report form (sometimes referred to as a clinical report form): an electronic form for recording study participants' data during a clinical study, as required by the protocol
EDV	early discontinuation visit
enroll	the act of assigning a subject to a treatment. Subjects who are enrolled in the trial are those who have been assigned to a treatment.
enter	Subjects entered into a trial are those who sign the informed consent form.
ERB	ethical review board
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
GCP	good clinical practice
HAQ-DI	Health Assessment Questionnaire–Disability Index
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C antibody
hsCRP	high-sensitivity C-reactive protein
hybrid ACR	the hybrid ACR (bounded) response measure will be obtained as described by the ACR Committee to Reevaluate Improvement Criteria (Felson et al. 2007)
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Ig	immunoglobulin
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	Investigational product: a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IWRS	interactive web-response system

LDA	low disease activity
Listing of Excluded and Restricted Medications tool	a tabular listing of allowed and excluded/restricted concomitant medications and applicable conditions for use
medical monitor	individual responsible for the medical conduct of the study: Responsibilities of the medical monitor may be performed by a clinical research physician or other medical officer.
MMRM	mixed model repeated measures
modified intent-to-treat	The intent-to-treat principle asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment. The modified intent-to-treat population includes all randomized subjects receiving at least 1 dose of study drug. The analysis population (for applicable treatment outcomes measures) will be all subjects with both a baseline and at least 1 postbaseline data measurement.
MTX	methotrexate
per-protocol set	all subjects randomly assigned to the study drug and using the study drug for 12 weeks (ie, the subset of subjects who sufficiently complied with the protocol); results from this population would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PK/PD	pharmacokinetics/pharmacodynamics
qd	once daily
RA	rheumatoid arthritis
SAE	serious adverse event
safety population	all randomized subjects receiving at least 1 dose of the study drug
SAP	statistical analysis plan
screen	the act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SF-36	Medical Outcomes Study 36-Item Short Form Health Survey
SJC	swollen joint count
study drug	LY3337641 and/or placebo used in the current study
subject	an individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.

SUSARs	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event: any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment
TJC	tender joint count
TST	tuberculin skin test
type I error	rejection of the null hypothesis when it is, in fact, true
ULN	upper limit of normal
VAS	visual analog scale

Appendix 2. Schedule of Activities

Tables presenting the Schedule of Activities for Part A and Part B are provided after the summary of study periods presented below.

Part A:

Screening Period (Visit 1, Weeks –4 to 0)

A screening period to assess subject eligibility will begin at Visit 1 and can last up to 28 days. Subjects will sign the ICF before any study assessments, examinations, or procedures are performed. Details regarding inclusion/exclusion criteria are in Sections 5.1 and 5.2. Refer to the Schedule of Activities table for details regarding screening procedures.

Dosing Period (Visits 2 to 5; Weeks 0 to 4; Study Days 1 to 29)

Subjects will be randomly assigned at baseline (Visit 2) in a 1:1:1:1 ratio to 1 of 4 arms: 3 experimental arms in which LY3337641 will be dosed orally at 5, 10, or 30 mg and 1 placebo comparator arm. Study drug will be administered qd in a blinded fashion from Week 0 through Week 4. Four clinic visits are planned during this period (Visits 2 to 5) at Weeks 0, 1, 2, and 4. At these visits, subjects will undergo safety evaluations, clinical assessments, PK samplings, and other laboratory assessments according to the Schedule of Activities table.

Safety Follow-Up Period (Visit 801, Week 6, Study Day 43)

All subjects will have a safety visit (Visit 801) at least 2 weeks after the final dose of study drug. For subjects who discontinue the study early, an additional safety visit is only required if the EDV occurs less than 2 weeks after the last dose of study drug.

Part B:

Screening Period (Visit 101, Weeks –4 to 0)

A screening period to assess subject eligibility will begin at Visit 101 and can last up to 28 days. Subjects will sign the ICF before any study assessments, examinations, or procedures are performed. Details regarding inclusion/exclusion criteria are in Sections 5.1 and 5.2. Refer to the Schedule of Activities table for details regarding screening procedures.

Dosing Period (Visits 102 to 106; Weeks 0 to 12; Study Days 1 to 85)

Subjects will be randomly assigned at baseline (Visit 102) in a 1:1:1:1 ratio to 1 of 4 arms: 3 experimental arms in which LY3337641 will be dosed orally at 5, 10, or 30 mg and 1 placebo comparator arm. Study drug will be administered qd in a blinded fashion from Week 0 through Week 12. Five clinic visits are planned during this period (Visits 102 to 106) at Weeks 0, 2, 4, 8, and 12. At these visits, subjects will undergo safety evaluations, clinical assessments, PK samplings, and other laboratory assessments according to the Schedule of Activities table.

Safety Follow-Up Period (Visit 802, Week 14, Study Day 99)

All subjects will have a safety visit (Visit 802) at least 2 weeks after the final dose of study drug. For subjects who discontinue the study early, an additional safety visit is only required if the EDV occurs less than 2 weeks after the last dose of study drug.

Additional HBV DNA Monitoring (Visits 803 and 804, Study Days 169 to 253)

HBV DNA will be monitored every 3 months (for 6 months) after the last dose of study drug for those subjects who are HBcAb+ and HBV DNA negative (undetectable) at screening.

Schedule of Activities, Protocol I8K-MC-JPDA – Part A

Perform procedures as indicated.

	Screening	Baseline (Random-ization)	Dosing Period			Safety Follow-Up	Comments
eCRF Visit Number (V)	**V1**	**V2**	**V3**	**V4**	**V5 & EDV**	**V801[a]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**43 +7**	
Study Week		**0**	**1**	**2**	**4**	**6**	
Informed consent	X						Must be completed prior to performing any study-related procedures or tests.
Review and confirm inclusion/exclusion criteria	X	X					
Complete medical history, pre-existing conditions	X						
Complete physical exam	X						
Symptom-directed physical exam (as clinically indicated)		X	X	X	X	X	Symptom-directed physical examinations are not required at each visit but may be conducted at the investigator's discretion at any visit and any time a subject presents with complaints.
Adverse events	X	X	X	X	X	X	AEs will be graded as mild/moderate/severe except rash, which will use CTCAE grading.
Concomitant drugs	X	X	X	X	X	X	
Height	X						Subject should remove shoes.
Body weight	X	X			X		
Vital signs	X	X	X	X	X	X	Vital signs include heart rate and blood pressure.
Temperature	X						May be repeated as clinically indicated.
ECG	X						A local ECG will be collected at screening and may be repeated at the investigator's discretion at any visit.

Schedule of Activities, Protocol I8K-MC-JPDA – Part A

	Screening	Baseline (Random-ization)	Dosing Period			Safety Follow-Up	Comments
eCRF Visit Number (V)	**V1**	**V2**	**V3**	**V4**	**V5& EDV**	**V801[a]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**43 +7**	
Study Week		**0**	**1**	**2**	**4**	**6**	
Chest radiography (PA & lateral)	X						Required only if not already done within 90 days prior to screening. Variations on the view requirements will only be permitted if they differ from local guidelines of care for standard TB screening.
TB test (per local guidelines)	X						Acceptable TB test results: (1) negative TST (defined as a skin induration <5 mm at 48 to 72 hours after the test date, regardless of BCG vaccination history) or (2) negative (not indeterminate) interferon γ release test (eg, QuantiFERON-TB Gold or T-Spot.*TB*). Subjects with known latent TB should not undergo a TST or interferon γ release test and must have documentation of an ongoing/completed course of latent TB therapy. See Exclusion Criterion [21] for details.
Study drug dispensed		X	X	X			First dose (Visit 2) will be given at the site.
Study drug returned			X	X	X		Study drug/packaging should be collected from the subject. Study drug compliance information should be captured in the eCRF. See Section 6.7 regarding compliance.

Schedule of Activities, Protocol I8K-MC-JPDA – Part A

	Screening	Baseline (Randomization)	Dosing Period			Safety Follow-Up	Comments
eCRF Visit Number (V)	**V1**	**V2**	**V3**	**V4**	**V5 & EDV**	**V801[a]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**43 +7**	
Study Week		**0**	**1**	**2**	**4**	**6**	
Laboratory Tests							Visit 2 labs should be collected prior to the first dose of study drug.
FSH (ALL female subjects)	X						
Serum pregnancy test (ALL female subjects)	X						
Urine pregnancy test (female subjects of child-bearing potential)		X			X	X	Refer to Inclusion Criterion [3] regarding definition of nonchildbearing potential.
HIV/HBV/HCV screening tests	X						
HBV DNA (HBcAb+ subjects only)	X				X	X	Subjects who are HBcAb+ at screening, regardless of HBsAb status, will have an HBV DNA obtained by the central laboratory. Subjects who are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Subjects who are HBV DNA negative (undetectable) may be enrolled into the study with HBV DNA monitoring during the study (refer to Section 8.4.7.1 for further details).
Lipid panel (nonfasting)		X			X		
TSH	X						
Serum chemistry	X	X	X	X	X	X	
Creatine kinase	X						
Hematology	X	X	X	X	X	X	
Hemoglobin A1C	X	X			X		

Schedule of Activities, Protocol I8K-MC-JPDA – Part A

	Screening	Baseline (Random-ization)	Dosing Period			Safety Follow-Up	Comments
eCRF Visit Number (V)	**V1**	**V2**	**V3**	**V4**	**V5 & EDV**	**V801[a]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**43 +7**	
Study Week		**0**	**1**	**2**	**4**	**6**	
Urinalysis	X	X			X		
hsCRP	X	X	X	X	X		
Total Ig and Ig classes (IgG, IgA and IgM)	X						
RF and ACPA	X						ACPA may be reported by central laboratory as CCP.
BTK-occupancy samples		X	X	X	X		Samples will be drawn only at sites that meet assay requirements.
pBTK samples		X	X	X	X		Samples will be drawn only at sites that meet assay requirements.
LY pharmacokinetics samples		X	X	X	X		At Visit 2, this sample should be collected 0.5-2 hours postdose.
Exploratory storage samples		X	X	X	X		
Pharmacogenetic sample		X					May be drawn at any time during the study if not drawn at Visit 2.
Clinical Measures							
Physician's Global Assessment of Disease Activity (VAS)		X	X	X	X		
Tender/swollen joint count	X	X	X	X	X		
Patient's Global Assessment of Disease Activity (VAS)		X	X	X	X		Should be completed prior to other study procedures.

Schedule of Activities, Protocol I8K-MC-JPDA – Part A

	Screening	Baseline (Randomization)	Dosing Period			Safety Follow-Up	Comments
eCRF Visit Number (V)	**V1**	**V2**	**V3**	**V4**	**V5 & EDV**	**V801[a]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**8 ±3**	**15 ±3**	**29 ±3**	**43 +7**	
Study Week		**0**	**1**	**2**	**4**	**6**	
Patient's Global Assessment of Arthritis Pain (VAS)		X	X	X	X		Should be completed prior to other study procedures, especially the tender and swollen joint counts.
HAQ-DI		X	X	X	X		Should be completed prior to other study procedures.
Morning joint stiffness		X	X	X	X		Should be completed prior to other study procedures.

Abbreviations: ACPA = anti-citrullinated peptide antibodies; AEs = adverse events; BCG = Bacillus Calmette-Guérin; BTK = Bruton's tyrosine kinase; CCP = cyclic-citrullinated peptide; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; eCRF = electronic case report form; EDV = early discontinuation visit; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; LY = LY3337641; PA = posteroanterior; pBTK = phosphorylated BTK; RF = rheumatoid factor; TB = tuberculosis; TSH = thyroid-stimulating hormone; TST = tuberculin skin test; V = visit; VAS = visual analog scale.

[a] For subjects who discontinue the study early, the safety visit will be at least 2 weeks after the final dose of study drug and is required only if the EDV occurs less than 2 weeks after the final dose.

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

Perform procedures as indicated.

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
Informed consent	X									Must be completed prior to performing any study related procedures or tests.
Review and confirm inclusion/exclusion criteria	X	X								
Complete medical history, pre-existing conditions	X									
Complete physical exam	X									
Symptom-directed physical exam (as clinically indicated)		X	X	X	X	X	X	X	X	Symptom-directed physical examinations are not required at each visit but may be conducted at the investigator's discretion at any visit and any time a subject presents with complaints.
Adverse events	X	X	X	X	X	X	X	X	X	AEs will be graded as mild/moderate/severe except rash, which will use CTCAE grading.
Concomitant drugs	X	X	X	X	X	X	X	X	X	
Height	X									Subject should remove shoes.
Body weight	X	X				X				
Vital signs	X	X	X	X	X	X	X	X	X	Vital signs include heart rate and blood pressure.
Temperature	X									May be repeated as clinically indicated.

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
ECG	X									A local ECG will be collected at screening and may be repeated at the investigator's discretion at any visit.
Chest radiography (PA & lateral)	X									Required only if not already done within 90 days prior to screening. Variations on the view requirements will only be permitted if they differ from local guidelines of care for standard TB screening.
TB test (per local guidelines)	X									Acceptable TB test results: (1) negative TST (defined as a skin induration <5 mm at 48 to 72 hours after the test date, regardless of BCG vaccination history) or (2) negative (not indeterminate) interferon γ release test (eg, QuantiFERON-TB Gold or T-Spot.*TB*). Subjects with known latent TB should not undergo a TST or interferon γ release test and must have documentation of an ongoing/completed course of latent TB therapy. See Exclusion Criterion [21] for details.
Study drug dispensed		X	X	X	X					First dose will be given at the site.

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
Study drug returned			X	X	X	X				Study drug/packaging should be collected from the subject. Study drug compliance information should be captured in the eCRF. See Section 6.7 regarding compliance.
Laboratory Tests										Visit 102 labs should be collected prior to the first dose of study drug.
FSH	X									Required only to confirm postmenopausal status.
Serum pregnancy test (female subjects of childbearing potential)	X									Refer to Inclusion Criterion [3] regarding definition of nonchildbearing potential.
Urine pregnancy test (female subjects of child-bearing potential)		X		X	X	X	X			Refer to Inclusion Criterion [3] regarding definition of nonchildbearing potential.
HIV/HBV/HCV screening tests	X									

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
HBV DNA (HBcAb+ subjects only)	X			X	X	X		X	X	Subjects who are HBcAb+ at screening, regardless of HBsAb status, will have an HBV DNA obtained by the central laboratory. Subjects who are found to be HBV DNA positive (detectable) at screening will be excluded from the trial. Subjects who are HBV DNA negative (undetectable) may be enrolled into the study with continued HBV DNA monitoring during the dosing period and every 3 months (for 6 months) after the last dose of study drug (refer to Section 8.4.7.1 for further details).
Lipid panel (nonfasting)		X				X				
TSH	X									
Serum chemistry	X	X	X	X	X	X	X			
Creatine kinase	X									
Hematology	X	X	X	X	X	X	X			
Hemoglobin A1C	X	X		X	X	X				
Urinalysis	X	X				X				
hsCRP	X	X	X	X	X	X				
Total Ig and Ig classes (IgG, IgA and IgM)	X					X				

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
RF and ACPA	X					X				ACPA may be reported by central laboratory as CCP.
Flow cytometry: lymphocyte subset samples (T cells and B cells)		X	X	X	X	X				
BTK-occupancy samples		X	X	X	X	X				Samples will be drawn only at sites that meet assay requirements.
pBTK samples		X	X	X	X	X				Samples will be drawn only at sites that meet assay requirements.
LY pharmacokinetics samples		X	X	X	X	X				At Visit 102, this sample should be collected 0.5-2 hours postdose.
Exploratory storage samples		X		X	X	X				
Pharmacogenetic sample		X								May be drawn at any time during the study if not drawn at Visit 102.
Clinical Measures										
Physician's Global Assessment of Disease Activity (VAS)		X	X	X	X	X				
Tender/swollen joint count	X	X	X	X	X	X				

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
Patient's Global Assessment of Disease Activity (VAS)		X	X	X	X	X				Should be completed prior to other study procedures.
Patient's Global Assessment of Arthritis Pain (VAS)		X	X	X	X	X				Should be completed prior to other study procedures, especially the tender and swollen joint counts.
HAQ-DI		X	X	X	X	X				Should be completed prior to other study procedures.
SF-36		X	X	X	X	X				Should be completed prior to other study procedures.
FACIT-F		X	X	X	X	X				Should be completed prior to other study procedures.
Morning joint stiffness		X	X	X	X	X				Should be completed prior to other study procedures.
Sexual function (VAS)		X	X	X	X	X				Should be completed prior to other study procedures.

Abbreviations: ACPA = anti-citrullinated peptide antibodies; BCG = Bacillus Calmette-Guérin; CCP = cyclic-citrullinated peptide; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; eCRF = electronic case report form; EDV = early discontinuation visit; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FSH = follicle-stimulating hormone; HAQ-DI = Health Assessment Questionnaire–Disability Index; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBV/HCV = hepatitis B/C virus; hsCRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; LY = LY3337641; PA = posteroanterior; pBTK = phosphorylated Bruton's tyrosine kinase; RF = rheumatoid factor; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; TB = tuberculosis; TSH = thyroid-stimulating hormone; TST = tuberculin skin test; V = visit; VAS = visual analog scale.

[a] For subjects who discontinue the study early, the safety visit will be at least 2 weeks after the final dose of study drug and is required only if the EDV occurs less than 2 weeks after the final dose.

[b] Additional HBV monitoring (V803 and V804) is only for subjects who are HBcAb+.

Appendix 3. Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology[b,c]

CBC with differential**:**
- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC) with absolute counts:
  - Neutrophils, segmented
  - Lymphocytes
  - Monocytes
  - Eosinophils
  - Basophils
- Platelets
- Cell morphology
- Flow cytometry (lymphocyte subsets)

Urinalysis[b,c]
- Specific gravity
- pH
- Protein
- Glucose
- Color
- Bilirubin
- Urobilinogen
- Urinary nitrate
- Ketones
- Blood
- Urine leukocyte esterase
- Microscopic exam of sediment (when indicated)[e]

Hepatitis
- Hepatitis B surface antigen
- Hepatitis B surface antibody
- Hepatitis B core antibody
- Hepatitis B virus DNA
- Hepatitis C antibody
- Hepatitis C virus RNA [h]

Human immunodeficiency virus

Tuberculosis

QFT[i] or T-Spot.*TB*[f] or TST[f]

Clinical Chemistry[b,c]

Serum concentrations of the following:
- Sodium
- Potassium
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- ALT
- AST
- Blood urea nitrogen
- Bicarbonate
- Chloride
- Creatinine with calculated eGFR[d]
- Calcium
- Glucose (nonfasting)
- Albumin
- Total protein
- Amylase
- Lipase
- Creatine kinase

Lipid panel (nonfasting)
- Cholesterol (total)
- HDL-C
- LDL-C
- Triglycerides

Endocrine
- TSH
- FSH

Pregnancy Test (female subjects only)
- Pregnancy urine[f]
- Pregnancy serum[b]

Other Tests
- ACPA
- Rheumatoid factor
- pBTK[g]
- BTK occupancy[g]
- hsCRP
- Exploratory storage samples (serum, plasma, Whole Blood, and RNA)
- LY pharmacokinetics samples
- Pharmacogenetic sample
- Total Ig, IgG, IgM, and IgA
- Hemoglobin A1C

Clinical Laboratory Tests[a]

Abbreviations: ACPA = anti-citrullinated peptide antibodies; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BTK = Bruton's tyrosine kinase; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; hsCRP = high-sensitivity C-reactive protein; HDL-C = high-density lipoprotein cholesterol; Ig = immunoglobulin; LDL-C = low-density lipoprotein cholesterol; LY = LY3337641; pBTK = phosphorylated BTK; QFT = QuantiFERON-TB Gold; RBC = red blood cell count; TB = tuberculosis; TSH = thyroid-stimulating hormone; WBC = white blood cells.

[a] Refer to the Schedule of Activities (Appendix 2).

[b] Assayed by the Lilly-designated (central) laboratory.

[c] Unscheduled blood chemistry (including creatine kinase), hematology, and urinalysis panels may be performed at the discretion of the investigator. If tests are done to evaluate laboratory results for resuming study drug, samples must be assayed centrally.

[d] Estimated glomerular filtration rate for serum creatinine will be calculated by the central laboratory using the Modification of Diet in Renal Disease method.

[e] Microscopic examination of sediment will be performed only if abnormalities are noted on the routine urinalysis.

[f] Testing will be performed by a local or investigator-designated laboratory.

[g] Samples will be drawn only at sites that meet assay requirements.

[h] Hepatitis C Virus RNA will only be measured to confirm positive Hepatitis C virus antibody.

[i] QFT to be performed by a local laboratory but may be performed at the Lilly-designated (central) laboratory.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be requested for subject follow-up after consultation with the Lilly medical monitor or designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Partial thromboplastin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline phosphatase isoenzymes[a]**
CK	
	Anti–smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GGT = γ-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Protocol Amendment I8K-MC-JPDA(d) Summary
A Randomized, Double-Blind, Placebo-Controlled, 2-Part Phase 2 Study to Evaluate the Safety and Efficacy of LY3337641 in Adult Subjects with Rheumatoid Arthritis: The RAjuvenate Study

Overview

Protocol I8K-MC-JPDA (A Randomized, Double-Blind, Placebo-Controlled, 2-Part Phase 2 Study to Evaluate the Safety and Efficacy of LY3337641 in Adult Subjects with Rheumatoid Arthritis: The RAjuvenate Study) has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I8K-MC-JPDA Amendment (d)

Section # and Name	Description of Change	Brief Rationale
Section 4.5 (Benefit/Risk Assessment)	Removed renal effects from a list of observed nonclinical effects	There was no evidence of significant renal effects in the 26-week rat (Study 31488) and 39-week monkey (Study 31489) repeat-dose studies, conducted at doses up to 120 mg/kg and 24 mg/kg. This change is an update to be consistent with the Investigator's Brochure, which has already had the possible risk of renal injury removed.
Section 5.1 (Inclusion Criteria)	Modified inclusion criterion [2] to clarify that pregnancy testing is required only for women of childbearing potential	Pregnancy testing is required only for women of childbearing potential.
Section 5.1 (Inclusion Criteria)	Updated inclusion criterion [3] to require that women of childbearing potential agree to use a reliable method of birth control for 28 days (instead of 2 weeks) after the last dose of study drug.	This revision is based on a new internal recommendation that contraception requirements for current and future clinical trials of LY3337641 be guided by duration of BTK occupancy by LY3337641 instead of the pharmacologic half-life of LY3337641 . The overall risk/benefitbenefit/risk assessment of LY3337641 has not changed.

Appendix 2 (Schedule of Activities)	Modified to clarify that pregnancy testing is required only for women of childbearing potential	Pregnancy testing is required only for women of childbearing potential.
Appendix 2 (Schedule of Activities)	Modified to clarify that FSH testing is required only to confirm post-menopausal status.	FSH testing is required only to confirm post-menopausal status.
Section 9.8 (Interim Analyses)	Added an optional additional efficacy interim analysis in Part B before the final analysis.	An optional additional efficacy interim analysis was added in Part B before the final analysis if the Assessment Committee determines that this the information may be needed for internal decision-making purposes for future studies prior to the Part B final analysis.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

4.5. Benefit/Risk Assessment

There are currently no human data regarding the efficacy of LY3337641 in RA. Nonclinical data and safety data in Phase 1 support further development of LY3337641 in RA at the proposed doses.

The safety profile for LY3337641 has been informed by the results from nonclinical toxicology and safety pharmacology studies and the Phase 1 clinical study (JPDD). The primary toxicity observed in animal studies was gastrointestinal tract injury. Pancreatic~~, renal,~~ and immune system effects were also observed (see Section 5.2.1 of the IB). In humans, the drug was generally well tolerated at dosages up to 40 mg per day. At total daily dosages of 80 mg and higher in the multiple dose portion of the study, significant TEAEs were reported in some subjects. The majority involved skin manifestations, the most common being skin rash. Associated signs and symptoms ranged from pruritus to systemic features such as fever and elevated levels of acute phase reactants. The highest dosage in Study JPDA is 30 mg qd, which is below the doses at which skin rashes or significant TEAEs were reported in Study JPDD. However, adverse events (AEs) of skin rash will be monitored over the course of the study by the medical monitor using blinded data. In addition, skin rash will be monitored by an Assessment Committee using unblinded data. The Assessment Committee members will be independent from the Lilly study team (Section 8.4.7).

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of LY3337641 can be found in the IB.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria:

[1] are male or female between the ages of 18 and 65 years (inclusive) at the time of initial screening and are able and willing to provide written informed consent as a legal adult according to local regulations

[2] female subjects of childbearing potential ~~(regardless of childbearing potential)~~: test negative for pregnancy at screening and agree not to breastfeed from the start of screening until 2 weeks after the last dose of study drug

[3] female subjects: agree to use a reliable method of birth control (eg, intrauterine contraceptive devices, hormonal contraceptives, or complete abstinence from sexual intercourse with men) from the start of screening until ~~2 weeks~~ 28 days after the last dose of study drug or be classified as female subjects of nonchildbearing potential, defined as meeting at least 1 of the following criteria:

- are postmenopausal with spontaneous amenorrhea for at least 12 months and have a follicle-stimulating hormone level >40 mIU/mL (>40 IU/L) at screening
- have undergone bilateral tubal ligation, bilateral oophorectomy, and/or hysterectomy at least 6 weeks prior to screening
- have another medical cause of female infertility that has been discussed with and accepted in writing by the sponsor

9.8. Interim Analyses

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For Part B, an interim efficacy analysis is planned when approximately 40% of the subjects have completed the Week 12 visit. This interim analysis will be conducted for internal decision making to trigger planning activities for future studies associated with LY3337641. The study will not be stopped early for efficacy. No adjustment of type I error will be performed. The PK/PD data will also be reviewed as part of the interim analysis to initiate model development processes. Based on emerging data, additional interim analyses may be conducted by an Assessment Committee (AC) to review unblinded safety data.

A second interim analysis in Part B is planned when all subjects in Part B have completed (or discontinued early from) Part B. This interim analysis is planned to be the final analysis for Part B for CSR writing. This interim will include all planned analyses of available data. The study team will be unblinded to all available results for Part B.

If the AC determines that an additional efficacy interim analysis may be needed before the Part B final analysis for internal decision-making for future studies, then an additional efficacy interim analysis may be conducted. This study will not be stopped early for efficacy. No adjustment of type I error will be performed. The PK/PD data may be reviewed, and the model may be updated.

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Appendix 2. Schedule of Activities

Schedule of Activities, Protocol I8K-MC-JPDA – Part B

	Screening	Baseline (Randomi-zation)	Dosing Period				Safety Follow -Up	Additional HBV DNA Monitoring		Comments
eCRF Visit Number (V)	**V101**	**V102**	**V103**	**V104**	**V105**	**V106 & EDV**	**V802[a]**	**V803[b]**	**V804[b]**	
Study Day (±day(s))	**≤28 Days from V2**	**1**	**15 ±2**	**29 ±2**	**57 ±3**	**85 ±3**	**99 +7**	**169 ±7**	**253 ±7**	
Study Week		**0**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	
FSH ~~(ALL female subjects)~~	X									Required only to confirm postmenopausal status.
Serum pregnancy test (~~ALL female subjects)~~female subjects of child bearing potential)	X									Refer to Inclusion Criterion [3] regarding definition of nonchildbearing potential.

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