Safety and Efficacy of Poseltinib, Bruton's Tyrosine Kinase-Inhibitor, in Patients With Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled, 2-Part Phase-2 Study

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Conflicts of Interest:
M. C. Genovese is currently an employee of Gilead Sciences Inc. and holds stock options; he reports personal fees and other from Eli Lilly and Company, during the conduct of the study; personal fees and other from AbbVie, Gilead, and other from Galapagos, Pfizer, outside the submitted work;
A Spindler has not conflicts to report;
A Sagawa reports being a paid instructor for ONO Pharmaceutical, Eli Lilly Japan K.K., Takeda, AYUMI Pharmaceutical, Kissei Pharmaceutical, Chugai Pharmceutical, Asahi Kasei Pharma Corporation, and Janssen;
W Park reports consulting fees from Celltrion;
A Dudek has no conflicts to report;
A Kivitz being a shareholder of Pfizer, Sanofi, GlaxoSmithKline, Gilead Sciences, Inc., Novartis, being paid consultant for AbbVie, Boehringer Ingelheim, Flexion, Janssen, Pfizer, Sanofi, Regeneron, SUN Pharma Advanced Research, Gilead Sciences, Inc., and on the speakers bureau: Celgene, Merck, Lilly, Novartis, Pfizer, Sanofi, Genzyme, Flexion, AbbVie.

J Chao, MLS Chan, J Witcher, and A Nirula are employees and stockholders of Eli Lilly;
W Barchuk was an employee of Eli Lilly at the time of this study and currently is an employee of Gilead Sciences, Inc and owns Gilead stock.

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Objectives: To evaluate efficacy and safety of poseltinib (formerly LY3337641/HM71224), an irreversible covalent inhibitor of Bruton's tyrosine kinase from a 2-part, Phase-2 trial (RAjuvenate) in adults with active rheumatoid arthritis (RA).

Methods: In Part A, 36 patients with mildly active RA were randomized 1:1:1:1 to oral poseltinib 5-, 10-, or 30-mg or placebo once-daily for 4 weeks to assess safety/tolerability. No safety signals precluded moving to Part B where 250 patients with moderate-to-severe RA were randomized 1:1:1:1 to oral poseltinib 5- (N=63), 10- (N=62), or 30-mg (N=63) or placebo (N=62) once-daily for 12 weeks. Parts A and B permitted stable doses of background disease-modifying antirheumatic drugs. The primary endpoint in Part B was proportion of patients achieving 20% improvement in American College of Rheumatology criteria (ACR20) at Week 12. Logistic regression compared each poseltinib dose to placebo for primary/secondary endpoints. Nonresponder imputation was used for missing data.

Results: After interim analysis showed low likelihood of demonstrating significant efficacy, the sponsor discontinued Part B of the study. 189 (76%) patients completed 12 weeks in Part B; 61 discontinued study treatment (27 [44%] due to study termination by sponsor). There was no statistically significant difference in ACR20 response between any dose of poseltinib and placebo at Week 12 ($p>0.05$ for all comparisons). Five serious adverse events occurred (n=2, placebo; n=3, 30-mg); there was 1 death due to a fall.

Conclusions: While no safety findings precluded continuation, the study was terminated after interim data demonstrated low likelihood of benefit in RA.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease and the most common type of autoimmune arthritis. Clinical features of RA include chronic joint inflammation typically involving small joints of the hands and feet, and can result in permanent joint deformities. Current treatment strategies for RA include synthetic and biologic disease-modifying antirheumatic drugs (DMARDs), which are often used in conjunction with nonsteroidal anti-inflammatory drugs and/or corticosteroids. Despite multiple therapies available with diverse mechanisms of action, most patients are unable to achieve remission (1). Therefore, the need for additional treatment approaches remains.

Bruton's tyrosine kinase (BTK), a member of the TEC family of cytoplasmic tyrosine kinases, 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 (2,3). BTK is primarily expressed in hematopoietic cells (3), including B-cells, monocytes, and macrophages. In humans, BTK loss-of-function mutations cause nonlethal X-linked agammaglobulinemia, resulting in reduced B-cell and immunoglobulin levels (4). Potential therapeutic benefits of BTK inhibition for RA include reduced pathogenic B-cell autoantibody production, myeloid-cell proinflammatory cytokine production and inhibition of mast cell and basophil degranulation (5).

Poseltinib (formerly LY3337641/HM71224) an orally available, irreversible covalent BTK inhibitor, halted progression of clinical arthritis and significantly diminished structural joint damage in a mouse model of collagen-induced arthritis (6) and improved skin lesions and renal histopathology scores and reduced proteinuria in a mouse model of systemic lupus erythematosus (SLE) (7). Taken together, these results suggest that poseltinib may be useful treatment of autoimmune diseases, including RA.

The single dose part of Phase 1 study JPDDdetermined that poseltinib was well tolerated in healthy adult males. In the multiple-dose portion (14 days dosing), poseltinib was generally well tolerated up to 40-mg once-daily, but at ≥80-mg/day, significant treatment-emergent adverse events (TEAEs) (those leading to

discontinuation or deemed significant by the investigator) were reported, most involving skin-related manifestations (8,9). The safety profile of poseltinib, along with the nonclinical efficacy data, supported further investigation in RA patients. RAjuvenate was a multicenter, randomized, double-blind, placebo-controlled, 2-part Phase 2 trial with a long-term extension (LTE) to determine whether oral once-daily dosing of poseltinib is safe and efficacious in adult patients with moderate-to-severe RA.

Material and Methods

Patients

RAjuvenate (NCT02628028) was conducted in 58 centers in 11 countries (See Supplemental File 1). In Part A, adults (ages 18 to 65 years) with RA for ≥6 months, based on the 2010 ACR/EULAR criteria, with active disease defined by ≥3 swollen joints based on 66-joint count, who had either positive rheumatoid factor or anticitrullinated peptide antibodies (ACPA) or had previous radiographs documenting bony erosion in hands or feet consistent with RA were enrolled. Part B enrolled patients with RA for ≥6 months and moderate-to-severe disease activity (defined as ≥6 swollen joints [based on 66-joint count], ≥6 tender joints [based on 68-joint count], and high-sensitivity C-reactive protein [hsCRP] levels greater than the upper limit of normal [defined at 0.999 mg/dL], or positive test results for ACPA) who had an inadequate response, loss of response, or intolerance to at least 1 synthetic (conventional or targeted) or biologic DMARDs. In Part B only, the percentage of patients who were naive to biologic DMARDs was limited to approximately 25% of the study population. In both parts of the study, concurrent treatment with stable doses of methotrexate, hydroxycholoroquine, sulfasalazine and leflunomide was permitted with the exception of concomitant treatment of methotrexate with leflunomide. Key exclusion criteria included use of B-cell–depleting agents (such as rituximab) or other cell-depleting biologics (eg, anti-CD3 antibody) within 12 months of screening in Part A or at any time prior to screening in Part B, concomitant use of biologic DMARDs, and evidence of clinically significant infections, including herpes

zoster and active tuberculosis. Patients that participated in Part A were not eligible to participate in Part B.

Study Design

In Part A, patients were randomized 1:1:1:1 to oral poseltinib 5-, 10-, or 30-mg or placebo once-daily for 4 weeks with safety follow-up at Week 6. Background conventional synthetic DMARDs were permitted at stable doses. The primary objective of Part A was assessment of safety and tolerability. At least 2 weeks after all patients had their last dose of study drug, an internal Assessment Committee conducted an unblinded interim analysis of safety data and determined there were no safety signals to preclude proceeding to Part B. The Assessment Committee was composed of members employed by Lilly who were not members of the RAjuvenate study team to minimize operational and statistical bias.

In Part B, patients were randomized 1:1:1:1 to oral poseltinib 5-, 10-, or 30-mg or placebo once-daily for 12 weeks. Background conventional synthetic DMARDs were permitted at stable doses. Randomization was stratified by biologic DMARD experience (yes/no), region (Japan/non-Japan) and disease severity based on Disease Activity Score of 28 joints with high-sensitivity C-reactive protein (DAS28-hsCRP) (≤5.1 vs >5.1). Safety follow-up occurred at Week 14. Patients who completed the 12-week dosing period of Part B and who, in the opinion of the investigator, had no condition that precluded continued participation in the study were eligible to participate in a 52-week LTE period during which they would continue their current dose of poseltinib or, if initially randomized to placebo, were re-randomized to 1 of the 3 poseltinib doses. The poseltinib dose range of 5- to 30-mg once-daily was supported by nonclinical toxicology and Phase 1 clinical safety data. Doses of poseltinib tested in RAjuvenate were projected to achieve BTK occupancy ranging from approximately 70-90% based on Phase 1 data (8).

Efficacy Outcomes

The primary endpoint of Part B was the proportion of patients achieving 20% improvement in American College of Rheumatology criteria (ACR20) (10) at Week 12. Secondary endpoints included the proportion

of patients achieving ACR50 and ACR70, improvements in disease activity as assessed by DAS28-hsCRP and characterizing the pharmacokinetics (PK) in patients with RA.

This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and approved by the Chesapeake Research Review, Inc (now Advarra IRB, Columbia, MD, USA) (#Pro00018484). Ethics approval was also obtained for all 58 sites. All patients provided written informed consent. Patients signed a separate informed consent form to enroll in the LTE. The study was designed by the sponsor, Eli Lilly and Company, was initiated in August, 2016, and terminated early in February, 2018 prior to completion of Part B. All authors participated in the preparation and review of this manuscript and approved of the final version.

Statistical Analysis

Data from Part A were summarized separately from Part B. No statistical hypothesis testing was performed for Part A. In Part B, a sample size of approximately 61 patients per treatment arm would provide at least 80% power at the 2-sided, 0.05 significance level for the comparison of ACR20 response rates between each poseltinib dose and the placebo group (with assumed placebo response rate of 30%) at Week 12. All randomized patients who received ≥1 dose of study drug and provided both baseline and ≥1 postbaseline data were included in the analysis. At the time of the decision to terminate the study early, the population for categorical analyses was revised to include all randomized patients who received ≥1 dose of study drug and completed or discontinued the study treatment period before sponsor decision with both baseline and ≥1 postbaseline measure. There was no change to the analysis population for continuous endpoints. The primary endpoint, ACR20 at Week 12, was analyzed by a logistic regression model with baseline treatment, region (Japan versus non-Japan), biologic DMARD experience (yes/no), and baseline DAS28-hsCRP. Patients were considered non-responders for analysis if they did not meet the clinical response criteria or had missing clinical response data at Week 12. P-values ≤0.05 (2-sided) were considered statistically significant. Secondary categorical endpoints were

analyzed using the same methods as the primary endpoint. Secondary continuous endpoints were analyzed using mixed-effects model for repeated measures in which baseline treatment, region (Japan versus non-Japan), week of treatment (categorical), the interaction of treatment and week, biologic DMARD experience (yes/no), and baseline DAS28-hsCRP were fixed effects; patients and error were random effects.

Pharmacokinetic (PK) Analysis

Plasma concentrations of poseltinib were determined using venous blood samples of approximately 4-mL based on a sparse sampling design: 4 samples from each patient during Part A and 5 samples during Part B. The plasma concentration data from Parts A and B were combined and analyzed using a population PK modeling approach with nonlinear mixed effects modeling (NONMEM; version 7.4.2, ICON Development Solutions, Ellicott City, Maryland). Data were evaluated using a 2-compartment model with a transit compartment absorption model, which was previously developed from analysis of the Phase 1 Study JPDD. It was necessary to combine the RAjuvenate and JPDD data for this analysis to improve model stability. Clearance was represented separately for each study in the model due to the clearance being approximately 2-fold lower in this study compared to JPDD. The final analysis dataset for RAjuvenate included 788 observations from 209 patients; JPDD data included 1657 observations from 74 patients.

Results

Patients

A total of 57 patients were screened for Part A, of which 36 were randomized to treatment: placebo (N=9); poseltinib 5-mg (N=9), 10-mg (N=10), and 30-mg (N=8). In Part B, 331 patients were screened and 250 patients were randomly assigned to placebo (n=62), poseltinib 5-mg (n=63), 10-mg (n=62), and 30-mg (n=62). The sponsor, Eli Lilly and Company, terminated the study early prior to completion of Part B, including the long-term extension, based on results of an interim analysis that showed a low likelihood

of demonstrating significant efficacy at the conclusion of the trial.Overall in Part B, the mean age was 51 years, the majority of patients were female (86.4%), and mean time from RA diagnosis was 11.2 years. There were no meaningful differences in baseline demographics across the treatment groups (Table 1); mean hsCRP was somewhat lower in the placebo and poseltinib 5-mg groups (14.7 and 14.1 mg/L, respectively) than in the poseltinib 10-mg and poseltinib 30-mg groups (17.8 and 17.6 mg/L, respectively)

Thirty-five (97.2%) patients completed Part A and 1 patient (poseltinib 10-mg) discontinued the study (withdrawal by patient). 189 (76%) patients completed Part B and 180 (93%) of those patients elected to enter the LTE. Of the 61 patients who discontinued study treatment in Part B, the most common reason for discontinuation was study termination by sponsor (n=27, 44%) (Figure 1). Other discontinuation reasons included AEs (n=8, 13%), withdrawal by patient (n=8, 13%), and lack of efficacy (n=4, 6.6%). Full disposition details for Part B are in Figure 1. Only 1 patient completed the LTE.

Efficacy Outcomes

Efficacy data are presented from Part B only as the primary objective in Part A was safety and tolerability. Results are based on the patients who completed the study or discontinued early the Part B dosing period before or on the date of study termination. There were no statistically significant differences in the ACR20 response between any treatment group of poseltinib and placebo at the primary endpoint of Week 12 (response rates of 48%, 55%, 44%, and 51% in the placebo, 5-mg, 10-mg, and 30-mg groups, respectively) or any other time point (Figure 2A); similarly, there were no significant increases in ACR50 or ACR70 (Figure 2B and 2C) over placebo for any dose arm of poselitinib. There were no statistically significant differences in change from baseline of DAS28-hsCRP scores at any time point for any poseltinib treatment group versus placebo (change from baseline to Week 12 was -1.62, -1.55, -1.24, and -1.80 in the placebo, 5-mg, 10-mg, and 30-mg groups, respectively), nor were there any

statistically significant differences in the proportion of patients achieving DAS28-hsCRP ≤3.2 or DAS28-hsCRP <2.6 for any poseltinib treatment group versus placebo (Figure 3).

Pharmacokinetic Outcomes

The observed plasma concentration versus time data were primarily within the model prediction intervals, and PK data appeared consistent across dose levels (Figure 4A-C). The PK model was used to simulate the average steady-state plasma concentration ($C_{ss,avg}$) for each patient in Part B (Figure 4D). The $C_{ss,avg}$ increased in a manner that was generally proportional over the 5 to 30-mg dose range. The plasma concentration data from the LTE were compared graphically and were consistent with the treatment period data (not shown).

Safety Outcomes

During Part A, there were no deaths, SAEs or discontinuations due to adverse events. Over the 4-week dosing period, the proportion of patients who reported at ≥1 TEAE was 3/9 (33.3%) of the placebo group and 9/27 (33.3%) of all poseltinib groups combined. All TEAEs were mild or moderate during the dosing period. The only TEAE that occurred in >1 patient was headache (3 patients; Supplemental Table S1). There was 1 severe TEAE of squamous cell carcinoma reported during the safety follow-up period for (10-mg).

In Part B through 12 weeks there was no dose-dependent trend in the proportion of patients with ≥1 TEAE (Table 2). The most common TEAEs (reported by ≥5 patients treated with poseltinib) were nasopharyngitis, RA, rash, and influenza, (Supplemental Table S2); majority of events were mild/moderate in severity. Rates of infections and rash were higher in patients treated with poseltinib 10-mg (24.2% and 8.1%, respectively) and 30-mg (31.7% and 12.7%) versus placebo (11.3% and 6.5%) (Table 2). The most common infection-related TEAEs occurring in ≥5 poseltinib-treated patients were nasopharyngitis and influenza. There were dose-dependent increases in rates of anemia (1.6% and 4.8%

in the 10- and 30-mg groups, respectively) all of which were mild; no patients in the poseltinib 5-mg group or the placebo group reported anemia.

There were 5 SAEs in Part B: 2 in placebo (joint dislocation and cholecystitis acute) and 3 in poseltinib 30-mg (foot fracture, multiple injuries and venous thrombosis). There was 1 death in the study: a patient receiving poseltinib 30-mg during Part B sustained multiple injuries after a 4-story fall down an elevator shaft and died 13 days later. Overall, 11 (4.4%) patients discontinued the study due to adverse events: menorrhagia, aspartate aminotransferase elevation, arthralgia, erythema annulare, multiple injuries, rash (n=3), and urticaria in the poseltinib groups; RA and basal cell carcinoma in the placebo group. There were no reports of tuberculosis or systemic opportunistic infections.

In the LTE overall, 5 (2.8%) patients reported ≥1 SAE: alanine aminotransferase increased, patella fracture, multiple SAEs of ankle, hand, pubis, and wrist fractures (result of motor vehicle accident), nephrolithiasis, and pneumonia. All SAEs reported during the LTE were considered by the investigator to be severe, except for pneumonia, which was considered moderate.

There were no clinically significant changes in safety laboratory values during Part A. In Part B through 12 weeks, there was a trend toward decreasing hemoglobin levels from baseline with higher doses of poseltinib. There were higher rates of worsening Common Terminology Criteria for Adverse Events (CTCAE) grade for hemoglobin levels for 10-mg and 30-mg (24.2% and 22.6%, respectively) versus placebo and 5-mg groups (14.5% and 15.9%, respectively). Most differences were in Grade 1 CTCAE changes. While there was no clear trend in mean changes in Week 12 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) versus baseline, 3 patients had increases ≥3 to ≤5× the upper limit of normal of ALT or AST (all poseltinib 30-mg); no events met Hy's law criteria. No clinically meaningful changes were noted in other safety laboratory parameters through 12 weeks. In the LTE, the lack of a placebo group, fewer patients in the study over time, and smaller patient numbers across treatment groups limit the ability to make conclusions.

Discussion

RAjuvenate was the first clinical trial to assess the efficacy and safety of poseltinib in adult patients with active RA. In these patients , once-daily oral poseltinib produced no statistically significant differences between placebo and any active treatment group in primary or secondary endpoints. The sponsor discontinued Part B of RAjuvenate, and the LTE, based interim analysis results that showed low likelihood of demonstrating significant efficacy at the conclusion of the trial.

Placebo response rates for the primary and secondary endpoints were relatively high compared to those observed in other clinical trials of similar populations (11-13) and may explain why the vast majority of patients entered the LTE despite negative study results. No differences in baseline characteristics could clearly account for high placebo response and rates in placebo patients were generally similar across regions in this global study. Evaluation of other variables, including previous biologic exposure and baseline hsCRP levels, did not clearly identify a sub-population of patients driving the placebo response. Patterns of increasing placebo responses over time in RA trials were observed in a review of Phase 2/3 trials of primarily bDMARD-naïve patients from 1999 to 2018 (13). Statistically significant increases were noted in ACR response rates over time in placebo patients even after controlling for potential confounders such as demographics, disease duration, baseline joint counts, CRP and time to primary outcome (13). Potential hypotheses for this trend included changes in disease course/treatment and expectation bias. While these hypotheses could have contributed to the results in our trial, additional work is needed to understand mechanisms driving higher placebo response rates and how to mitigate them in future trials.

Despite the high placebo response, the level of response in poseltinib arms relative to placebo were neither clinically meaningful nor statistically significant. It is possible that higher doses of poseltinib are required to demonstrate a treatment effect in RA. In a rat collagen-induced arthritis model, BTK occupancy of approximately 80% was sufficient to achieve efficacy (internal data). The dose range

selected for this study was projected to result in BTK occupancy ranging from 70% (5-mg) to 90% (30-mg) based on Phase 1 data (8). However, no clear dose response was observed to inform the relationship between BTK occupancy and clinical efficacy in humans. It is possible that near complete BTK occupancy is required to demonstrate clinical benefit. In the present study, the maximum dose of 30-mg was selected based on toxicology and Phase 1 safety data. Higher doses of poseltinib could be efficacious, however, there is potential for increased toxicity leading to an undesirable risk/benefit profile for RA patients and multiple approved treatments already exist with well-characterized safety and efficacy. Another consideration is that targeting B-cells through BTK inhibition requires more time to demonstrate efficacy, and 12 weeks of treatment might not have been long enough to observe a response. However, given that available treatments have demonstrated benefit at 12 weeks in RA, longer duration to achieve efficacy would not bring meaningful improvement to current standard of care.

There were no significant safety findings that precluded continuation of the trial. No clinically meaningful differences were observed in proportions of patients reporting SAEs or discontinuations due to AEs in the poseltinib treatment groups versus placebo. While there were dose-dependent increases in rates of infections, rash and anemia, the majority of these events were mild or moderate in severity. These data add to the growing body of literature of BTK inhibition in RA, which has demonstrated variable results. In a Phase 2 study of fenebrutinib, a noncovalent BTK inhibitor, ACR50 responses for the highest dose (200-mg twice/day) were significantly higher versus placebo, and comparable versus adalimumab in methotrexate inadequate responders (14). Other BTK inhibitors have not been as successful. Spebrutinib (CC-292), a covalent BTK inhibitor, did not meet its primary endpoint (ACR20 at 4 weeks), in RA patients on background methotrexate(15). Other BTK inhibitor studies are ongoing (16-18); publication of these data will contribute to the collective understanding of targeting BTK to treat RA

and factors (compound potency, kinase specificity, and covalent bonding status) that may contribute to a given BTK-inhibitor's benefit/risk profile.

Another consideration for the relevance of BTK as a target is whether it plays a pivotal role in immunologic indications other than RA. In a Phase 2, multiple sclerosis study, patients taking evobrutinib 75-mg once-daily, but not 25-mg once-daily, had fewer enhancing lesions versus placebo patients during Weeks 12-24; no dose demonstrated significant differences from placebo for annualized relapse rates or disability progression (19). A Phase 2 study of fenebrutinib, in patients with moderate-to-severe SLE, did not meet its primary endpoint, SLE responder index-4, at Week 48 (20). Additional studies are needed to understand the role of targeting BTK and how different characteristics among individual BTK inhibitors affect the benefit/risk profiles in each indication.

Limitations include that this study was discontinued before completion of Part B; therefore the final analysis included fewer patients than originally planned. However, at study discontinuation, the trial was near completion and conclusions were expected to correlate with results had the trial continued to completion. Another limitation was the requirement for hsCRP to be elevated in ACPA-negative patients, however >90% of patients were ACPA-positive, thus not requiring baseline elevated hsCRP. While mean baseline hsCRP values were elevated across treatment groups, this could introduce additional heterogeneity to the patient population allowing inclusion of patients who may not respond to an immunomodulating agent.

In conclusion, poseltinib was generally well-tolerated in adult patients with active RA. Although no safety findings precluded continuation, the study was terminated after interim data demonstrated low likelihood of benefit in RA.

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Figure Legends

Figure 1. Patient Disposition in Part B of the study

Figure 2. Proportion of patients achieving ACR20 (A), ACR50 (B), and ACR70 (C) through 12 weeks of Part B of the study. ACR20/50/70=American College of Rheumatology 20%/50%/70% response; *p<0.05 vs placebo; NRI-non-responder imputation. Note: Response rates were based on the number of patients who completed or discontinued the dosing period before or on the date of study termination

Figure 3. Change from baseline in DAS28-hsCRP scores through 12 weeks in Part B of the study (A) and the proportion of patients who achieved low-disease activity (≤3.2) or remission (<2.6) based on the DAS28-hsCRP (B). DAS28-hsCRP=Disease Activity Score based on 28 joints with high sensitivity C-reactive protein; NRI=non-responder imputation.

Figure 4. Poseltinib plasma concentrations versus time from last dose. Observed concentrations shown in symbols and 90% prediction interval shown by orange lines. Model prediction intervals are consistent with the observed data.

Figure 5. Average steady-state plasma concentration for poseltinib 5-, 10-, and 30-mg once daily dose groups. The boxplots show the 25th, median, and 75th percentile; the whiskers show the 5th and 95th percentile.

Table 1. Baseline demographics and disease characteristics in Part B

	Placebo	Poseltinib		
	(N=62)	5-mg (N=63)	10-mg (N=62)	30-mg (N=63)
Age, years	50 (9)	50 (9)	52 (9)	52 (9)
Female, n (%)	54 (87)	53 (84)	56 (90)	53 (84)
Duration of RA[a], years	9.3 (7.7)	13.3 (9.4)	11.8 (7.9)	10.4 (6.3)
ACPA positive, n (%)	58 (94)	58 (92)	59 (95)	61 (97)
RF positive, n (%)	52 (84)	53 (84)	55 (89)	51 (81)
Swollen joint count, of 66	13.7 (9.6)	13.9 (7.5)	13.5 (6.5)	13.9 (6.7)
Tender joint count, of 68	25.1 (13.5)	22.8 (13.4)	23.0 (13.3)	23.6 (11.7)
hsCRP, mg/L	14.7 (20.8)	14.1 (17.7)	17.8 (28.4)	17.6 (30.7)
DAS28-hsCRP	5.6 (1.0)	5.5 (1.1)	5.6 (1.0)	5.5 (1.0)
HAQ-DI	1.5 (0.8)	1.5 (0.8)	1.6 (0.7)	1.4 (0.6)
Physician's global assessment of disease activity (0-100)	61.7 (20.5)	59.8 (19.7)	61.1 (20.4)	65.1 (18.2)
Patient's assessment of pain (0-100)	64.2 (22.6)	62.3 (24.3)	62.2 (23.2)	62.3 (25.1)
Patients on corticosteroids, n (%)	40 (64.5)	40 (63.5)	44 (71.0)	48 (76.2)
Daily dose corticosteroids	6.3 (2.3)	5.9 (2.2)	5.7 (2.7)	5.7 (2.9)
Patients on methotrexate, n (%)	54 (90.0)	60 (98.4)	58 (96.7)	60 (98.4)

Weekly dose methotrexate	15.4 (4.9)	15.7 (5.4)	17.4 (8.2)	14.6 (5.6)
Number of cDMARDs being used	1.6 (0.8)	1.9 (1.3)	1.9 (1.0)	1.9 (1.2)

[a]Time from RA diagnosis
Data are mean (SD) unless otherwise stated.
ACPA=anti-citrullinated peptide antibody; cDMARDs=conventional disease-modifying antirheumatic drugs; DAS28=Disease Activity Score 28 joints; HAQ-DI=Health Assessment Questionnaire- Disability Index; hsCRP=high sensitivity C-reactive protein; RF=rheumatoid factor

Table 2. Safety outcomes at Week 12

	Placebo	Poseltinib		
	(N=62)	5-mg (N=63)	10-mg (N=62)	30-mg (N=63)
Treatment emergent adverse events	31 (50.0)	22 (34.9)	37 (59.7)	34 (54.0)
Serious adverse events	2 (3.2)	0	0	3 (4.8)
Deaths	0	0	0	1 (1.6)
Adverse events leading to discontinuation	2 (3.2)	1 (1.6)	3 (4.8)	5 (7.9)
Infections	7 (11.3)	6 (9.5)	15 (24.2)	20 (31.7)
Herpes zoster	0	0	1 (1.6)	0
Serious infections	0	0	0	1 (2.1)
Rash	4 (6.5)	2 (3.2)	5 (8.1)	8 (12.7)
Venous thrombosis	0	0	0	1 (1.6)

Data are n (%)

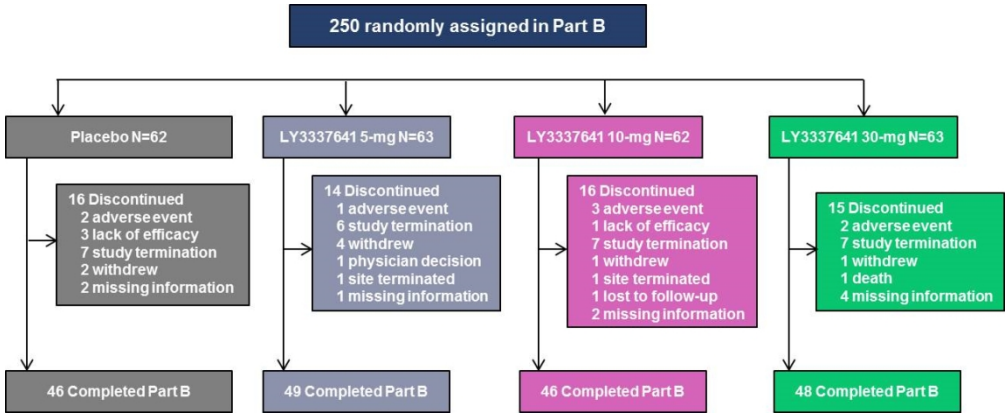

Figure 1. Patient Disposition in Part B of the study

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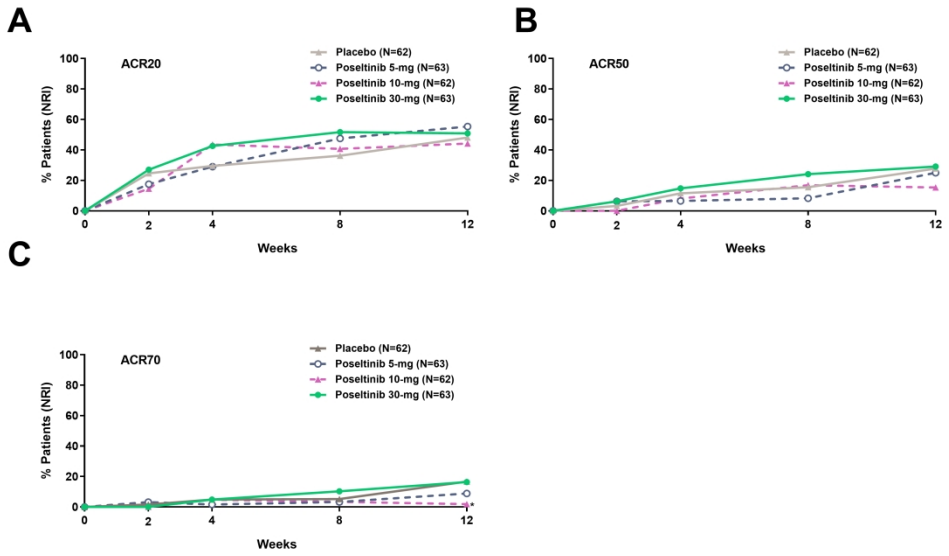

Figure 2. Proportion of patients achieving ACR20 (A), ACR50 (B), and ACR70 (C) through 12 weeks of Part B of the study. ACR20/50/70=American College of Rheumatology 20%/50%/70% response; *p<0.05 vs placebo; NRI-non-responder imputation. Note: Response rates were based on the number of patients who completed or discontinued the dosing period before or on the date of study termination

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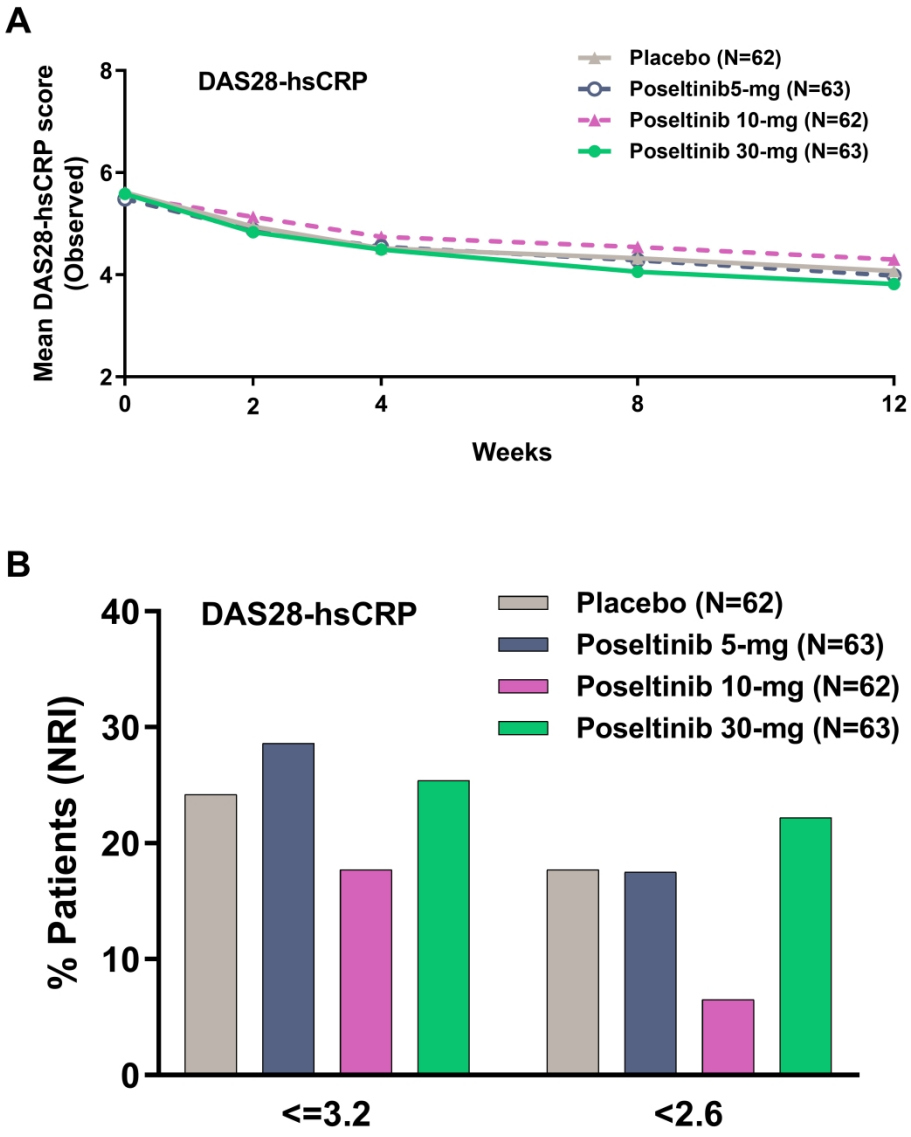

Figure 3. Mean observed DAS28-hsCRP scores through 12 weeks in Part B of the study (A) and the proportion of patients who achieved DAS28-hsCRP ≤3.2 or <2.6 (B). DAS28-hsCRP=Disease Activity Score based on 28 joints with high sensitivity C-reactive protein; NRI=non-responder imputation.

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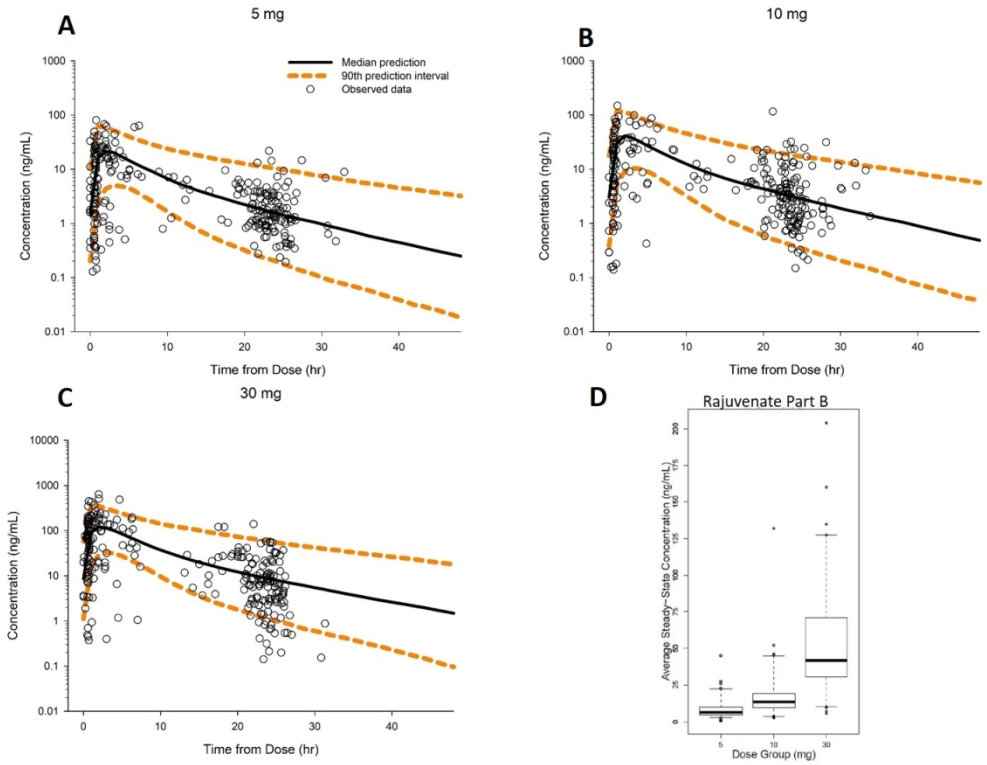

Figure 4. Poseltinib plasma concentrations versus time from last dose (Figure A-C). Observed concentrations shown in symbols and 90% prediction interval shown by orange lines. Model prediction intervals are consistent with the observed data. Average steady-state plasma concentration for poseltinib 5-, 10-, and 30-mg once daily dose groups (Figure D). The boxplots show the 25th, median, and 75th percentile; the whiskers show the 5th and 95th percentile.

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