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Article type : Full Length

Efficacy, Safety, and Pharmacodynamic Effects of the Bruton's Tyrosine Kinase Inhibitor, Fenebrutinib (GDC-0853), in Systemic Lupus Erythematosus

Results of a Phase II, Randomized, Double-Blind, Placebo-Controlled Trial

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ART.41811

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Running head

The BTK inhibitor, fenebrutinib, in SLE.

Full-length article

Word count (limit - 4,200 word text): 4,193
Abstract (limit - 250 words): 230
Display items (limit - 6 items): 4 tables and 2 figures
References (limit - 50): 39
Supplementary material: 6 tables and 9 figures

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Funding/Support

This study was supported by Genentech, Inc., South San Francisco, CA.

Keywords

Bruton's kinase inhibitor; systemic lupus erythematosus; fenebrutinib; clinical trial

Trial registration

ClinicalTrials.gov identifier: NCT02908100
EudraCT Number: 2016-001039-11

Authorship Criteria

Criterion 1: a) Substantial contributions to study conception and design; and/or

b) Substantial contributions to acquisition of data; and/or

c) Substantial contributions to analysis and interpretation of data.

Criterion 2: Drafting the article or revising it critically for important intellectual content

Criterion 3: Final approval of the version of the article to be published

David Isenberg: 1a, 1b, 1c, 2, 3; Richard Furie: 1a, 1b, 1c, 2, 3; Nicholas S. Jones: 1c, 2, 3; Pascal Guibord: 1c, 2, 3; Joshua Galanter: 1c, 2, 3; Chin Lee: 1c, 2, 3; Anna McGregor: 1a, 1c, 2, 3; Balazs Toth: 1c, 2, 3; Julie Rae: 1c, 2, 3; Olivia Hwang: 1b, 1c, 2, 3; Rupal Desai: 1b, 1c, 2, 3; Armend Lokku: 1c, 2, 3; Nandhini Ramamoorthi: 1c, 2, 3; Jason A. Hackney: 1c, 2, 3; Pedro Miranda: 1b, 2, 3; Viviane A. de Souza: 1b, 1c, 2, 3; Juan J. Jaller-Raad: 1c, 2, 3; Anna Maura Fernandes: 1b, 1c, 2, 3; Rodrigo Garcia Salinas: 1b, 2, 3; Leslie W. Chinn: 1a, 1c, 2, 3; Michael J. Townsend: 1a, 1c, 2, 3; Alyssa M. Morimoto: 1a, 1b, 1c, 2, 3; Katie Tuckwell: 1c, 2, 3

Conflict of interest disclosures

David **Isenberg** has received consulting fees from Genentech/Roche but these are passed onto a local arthritis charity. Richard **Furie received** consulting fees and research support from Genentech/Roche. Nicholas S. **Jones** is an employee and stock holder of Genentech/Roche (>$10,000, each). Pascal **Guibord** is an employee and stock holder of Roche (>$10,000, each). Joshua **Galanter** is an employee and stock holder of Genentech/Roche (>$10,000, each). Chin **Lee** is an employee and stock holder of Genentech/Roche and stockholder of Eli Lilly (>$10,000, each). Anna **McGregor** is a former contractor of Genentech/Roche. Balazs **Toth**, Julie **Rae**, Olivia **Hwang**, and Rupal **Desai** are employees and stock holders of Genentech/Roche (>$10,000, each). Armend **Lokku** is an employee and stock holder of Roche (>$10,000, each). Nandhini **Ramamoorthi** and Jason **Hackney** are employees and stock holders of Genentech/Roche (>$10,000, each). Pedro **Miranda,** Viviane A. **de Souza**, Juan J. **Jaller-Raa**d, Anna **Maura Fernandes,** and Rodrigo **Garcia Salinas** are study investigators who do not have any other disclosures. Leslie W. **Chinn** is an employee of Principia Biopharma and a former employee and

stock holder of Genentech/Roche, and has patent pending at Genentech/Roche (>$10,000, each). Michael J. **Townsend** is an employee and stock holder of Genentech/Roche (>$10,000, each). Alyssa M. **Morimoto** is an employee and stock holder, and has patent pending at Genentech/Roche (>$10,000, each). Katie **Tuckwell** is an employee and stock holder of Genentech/Roche (>$10,000, each).

ABSTRACT

Background: Fenebrutinib (GDC-0853, FEN) is a non-covalent, oral, and highly selective inhibitor of Bruton's tyrosine kinase (BTK). The efficacy, safety, and pharmacodynamics of FEN were assessed in this randomized, placebo-controlled, multi-center phase II study.

Methods: Patients with moderate-to-severely active systemic lupus erythematosus on background standard of care therapy were randomized to placebo, FEN 150 mg QD, or FEN 200 mg BID arms. Corticosteroid taper was recommended from weeks 0 to 12 (W0-W12) and W24-W36. The primary endpoint was SRI-4 at W48.

Results: Patients (*N*=260) were enrolled from 44 sites in 12 countries, with the majority from Latin America, USA, and Western Europe. The SRI-4 response rates at W48 were 51% (p=0.37, versus placebo) for FEN 150 mg QD, 52% (p=0.34, versus placebo) for FEN 200 mg BID, and 44% for placebo. BICLA response rates at W48 were 53% (p=0.086, versus placebo) for FEN 150 mg QD, 42% (p=0.879, versus placebo) for FEN 200 mg BID, and 41% for placebo. Safety results were similar across all arms, although serious adverse events were more frequent with FEN 200 mg BID. By W48, patients treated with FEN had reduced levels of a BTK-dependent plasmablast RNA signature, anti-dsDNA autoantibodies, total IgG, and IgM, as well as increased complement C4, all relative to placebo.

Conclusions While FEN had an acceptable safety profile, the primary endpoint, SRI-4, was not met despite evidence of strong pathway inhibition.

INTRODUCTION

Systemic lupus erythematosus (SLE), an autoimmune disease that primarily affects women of childbearing age, is characterized by immunological abnormalities and multisystem involvement. Autoantibody formation can lead to immune complex deposition, thought to be one mechanism leading to tissue damage (1). While the disease is heterogeneous in its clinical presentation, course, and prognosis, predominant manifestations are arthritis, rash, oral or nasal ulcers, Raynaud's phenomenon, and/or severe fatigue. Central nervous system and, in particular, renal involvement, represent severe complications associated with increased disability, morbidity, and mortality (2, 3).

Corticosteroids, antimalarials, and off-label use of immunosuppressive drugs, such as azathioprine and mycophenolate, are the mainstay of SLE treatment. However, because of their toxicities and suboptimal efficacy, a significant unmet need exists for safer and more effective therapy (1). Only one targeted agent, belimumab, has been approved for the treatment of SLE in the past 60 years (4, 5). Although not formally approved, rituximab, a monoclonal anti-CD20 antibody, is also used to treat diverse aspects of SLE (6, 7).

Bruton's tyrosine kinase (BTK) belongs to the Tec family of kinases and is expressed in hematopoietic cells, playing a critical role in B cell (8) and myeloid cell signaling pathways (9). Fenebrutinib (GDC-0853) (Genentech, Inc.) (10) is a highly selective, orally administered, and reversible inhibitor of BTK (11) that has shown clinical activity in the treatment of B cell malignancies (12) and demonstrated efficacy in phase II studies of patients with rheumatoid arthritis (13) and chronic spontaneous urticaria (14). Support for the role of B cells and myeloid cells in the pathogenesis of SLE (15) as well as for BTK inhibition as a treatment strategy in human SLE has been garnered from data generated in preclinical lupus models (10, 16, 17).

The ATHOS trial was the first large phase II dose-ranging study to evaluate fenebrutinib, a highly selective BTK inhibitor therapy, in patients with SLE.

METHODS

Entry criteria

Patients aged 18-75 years with SLE according to either the revised American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria, with ≥1 serologic marker of SLE at screening (antinuclear antibody [ANA], anti-double-stranded DNA [anti-dsDNA] or anti-Smith antibodies), SLEDAI-2K score ≥8 (18), patient global assessment (PGA) score ≥1, and on ≥1 standard oral lupus treatment were eligible to enroll (Supplementary Figure S1). Background standard of care (SOC) therapy (Supplementary Table S1) could consist of an oral corticosteroid (OCS) (stable dose for 2 weeks prior to screening; ≤40 mg/day of prednisone or equivalent), antimalarials (stable dose for 2 months prior to screening), and/or specific oral immunosuppressives (stable dose for 2 months prior to screening). For patients on angiotensin converting enzyme inhibitors or angiotensin receptor blockers at study entry, doses were kept stable for ≥10 days prior to randomization and throughout the trial whenever possible. Patients were excluded if they had proliferative lupus nephritis, recent management of lupus renal disease, central nervous system lupus manifestations, a history of antiphospholipid antibody syndrome, received a solid organ transplant, proteinuria >3.5 g/24h, serum creatinine >2.5 mg/dL, an estimated glomerular-filtration rate of <30 mL/min, recent use of experimental agents or prohibited immunosuppressive therapies (including calcineurin inhibitors and cyclophosphamide), or had received a live attenuated vaccine within 6 weeks of the screening visit.

Study design

This multicenter, phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study evaluated the efficacy, safety, and pharmacokinetics of fenebrutinib in patients with moderate-to-severely active SLE (NCT02908100). The study was 48 weeks long and included two 12-week-intervals, W0–W12 and W24–W36, during which the OCS dose could be reduced (Supplementary Figure S1). At the end of each 12-week-interval, the OCS dose had to remain stable for the next 12 weeks. An increase in OCS dose – a "burst" of up to 40 mg/day (between W0-W10) or 20 mg/day (between W24-W34) prednisone or equivalent – was permitted, following which the OCS dose was tapered within 2 weeks to the dose preceding the increase. "Escape therapy" was defined as treatment with OCS doses exceeding those permitted as a burst, an

increase in OCS dose at a time when burst therapy was not permitted, or an increase in background immunosuppressive dose.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and was approved by the appropriate institutional review boards. All patients provided written informed consent prior to any study-related activities. Patients completing the study were eligible to enroll in an open-label extension study (NCT02908100) and receive 200 mg fenebrutinib twice daily.

Randomization, masking, and dose rationale

Patients were enrolled by investigators listed in Supplementary Table S2. The randomization algorithm for assigning patients to treatment arms was defined by the sponsor and implemented by the interactive response technology vendor (IxRS®), with stratification by region, entry dose of OCS, and disease activity at screening. This was a double-blind study; the investigator could break the treatment code by contacting IxRS if unblinding became necessary for urgent safety reasons. Patients were randomized in a 1:1:1 ratio to oral fenebrutinib (FEN 200 mg twice daily [BID] or FEN 150 mg once daily [QD]) and placebo (PBO) treatment arms, in combination with SOC therapy (Supplementary Figure S1); all treatments were on a twice-daily schedule in order to mask the treatment assignments. The dosing regimens of fenebrutinib were selected based on pharmacokinetic/pharmacodynamic modeling of BTK inhibition generated previously (11). The goal was to achieve plasma concentrations that yielded high levels of BTK inhibition throughout the dosing period, a state associated with the amelioration of disease in both spontaneous and IFNα-accelerated lupus in NZB/W F1 mice (17).

Efficacy assessments

The primary efficacy analysis evaluated the proportion of patients achieving SLE Responder Index-4 (SRI-4) at W48 with fenebrutinib (150 mg QD or 200 mg BID) compared to placebo. Powering and statistical analyses are described in Supplementary Methods. Secondary objectives assessing response rates in each fenebrutinib dose group compared to placebo included SRI-4 at W24, BICLA, SRI-6, and SRI-4 response with sustained reduction of OCS dose at W24 and W48 (OCS dose <10 mg/day and ≤ day 1 dose from W12–W24 and W36–W48), and SRI-4 response at W48 in patients with high baseline levels of plasmablast signature (with/without a reduction in

OCS dose). Exploratory endpoints included an evaluation of responses in individual components of the SRI-4 (SLEDAI-2K, British Isles Lupus Assessment Group 2004 Index [BILAG-2004], and PGA), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), 28-joint count, and SELENA-SLEDAI Flare Index (SFI-flare). Fatigue was assessed using the functional assessment of chronic illness therapy-fatigue scale (FACIT fatigue).

Safety assessments

The incidence and severity of adverse events (AEs) as well as laboratory results were assessed at each study visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). An Internal Monitoring Committee and Scientific Oversight Committee conducted an unblinded safety review on a bimonthly basis during the 48-week treatment period.

Biomarker assessments

Biomarkers were evaluated in serum, plasma, peripheral blood mononuclear cell protein lysate, or blood samples at screening, baseline, and weeks 4, 12, 24, and 48. Serologically active patients were defined as being positive for anti-dsDNA antibodies and having one or both complement components (C3 or C4) below the lower limit of normal at baseline. Anti-dsDNA antibodies (Inova Diagnostics, San Diego, CA; Covance, Indianapolis, IN), C3, C4, total hemolytic complement (CH50), total immunoglobulin G (IgG), and total immunoglobulin M (IgM), (Siemens, Washington, D.C; Covance), CCL4 (Singulex, Alameda, CA; EMD Millipore, Temecula, CA), phosphorylated (Y223) BTK and BTK protein (Genentech, South San Francisco, CA) levels were analyzed using immunoassays. $CD19^+$ B cells and $CD3^+$ T cells were measured by flow cytometry (Covance, Princeton, NJ). The BTK-dependent (17) plasmablast gene signature immunoglobulin J chain (IgJ), marginal zone B and B1 cell-specific protein (MZB1), thioredoxin domain containing 5 (TXNDC5), and the housekeeping gene transmembrane 55b (TMEM55B) were measured in blood RNA samples from patients and healthy control subjects (n=20) using qRT-PCR. The level of signature is the average of expression of the three genes normalized to TMEM55B.

Pharmacokinetic assessments

Samples for pharmacokinetic assessments were obtained at predefined timepoints. Plasma fenebrutinib concentrations were determined using liquid chromatography/mass spectrometry (Covance, Madison, WI); the lower limit of quantification was 0.5 ng/mL. Summary statistics of plasma fenebrutinib concentrations by timepoint were performed using SAS (SAS Institute).

RESULTS

Patients and treatments

Between January 2017 and July 2019, 260 patients were enrolled at 44 sites in 12 countries, the majority in Latin America, USA, and Western Europe. Three hundred and fifty-six patients failed screening mainly due to absence of serologic markers (anti-Smith, anti-dsDNA, or anti-ANA) (21%) or positive TB testing (12%) (Supplementary Figure S2). Patients were stratified by baseline OCS dose (≥10 vs. <10 mg/day), SLEDAI-2K score (≥10 vs. <10) and geographic region (US and Western Europe vs. Rest of World). Baseline demographic and clinical characteristics were similar across the three arms (Table 1). The majority of patients were white (65%), female (97%), and of Hispanic or Latino ethnicity (68%); the median age was 41 years (range 18-72) and median disease duration was 7 years (range 0.1-38). Eighty percent of patients were on background antimalarials, and 49% were receiving immunosuppressives. In addition, 80% of patients entered the study receiving treatment with OCS at a mean prednisone dose of 10.7 mg/day. A subset of patients had low baseline levels of C3, C4, or CH50 (30%, 14%, and 3%, respectively). Most patients had positive ANA tests (98%); many were also positive for anti-Smith (26%) or anti-dsDNA (52%).

Primary and secondary outcomes

There were no significant differences in SRI-4 response rates at W48 between treatment groups, which were 44% for PBO, 51% for FEN 150 mg QD (p= 0.37 versus placebo), and 52% for FEN 200 mg BID (p= 0.34 versus placebo) (Table 2; Supplementary Figure S3). SRI-4 responses in all treatment groups were driven mainly by improvements in SLEDAI-2K; few patients experienced PGA or BILAG worsening (Supplementary Table S3). BICLA response rates at W48 were not different between treatment arms, with 41% attaining a response for PBO, and 53% and 42% achieving response for FEN 150 mg QD and FEN 200 mg BID, respectively (Table 2). Similarly, responses for SRI-6 and SRI-4 with OCS taper did not show differences among arms (Table 2). Fenebrutinib also failed to demonstrate a treatment benefit over placebo for SRI-4 in patients with high baseline plasmablast signature levels (Supplementary Figure S4).

Exploratory outcomes

There were no differences among treatment arms for time to flare using BILAG or SFI definitions of flare (Supplementary Figure S5). The percentage of patients with a disease flare by BILAG (one new "A" or two "B's") was 9.6% across the study and 14.2% by SFI (all flares), with similar numbers of patients experiencing flares in the FEN and PBO arms. Most improvements in SLEDAI-2K scores from baseline were generated in the musculoskeletal and mucocutaneous domains, with slight improvements in laboratory parameters. Changes to more detailed assessments (CLASI, joint count, FACIT-fatigue) are described in Supplementary Table S3.

Few patients (3%) received an OCS burst in each of the two burst windows, while 58% maintained the same OCS dose throughout the trial (Supplementary Table S4), with no appreciable differences in percentage of patients receiving OCS burst or keeping stable OCS dose among treatment arms. Twenty-five (10%) patients received escape therapy during the study, with rates balanced across treatment arms (Table 2). The proportion of patients achieving an OCS dose <7.5 mg/day among those who started on ≥10 mg/day prednisone equivalent dose was 38% in the placebo arm compared to 38% and 55% in the low and high dose fenebrutinib arms, respectively.

Serologically active patients (anti-dsDNA positive plus low C3 and/or C4 – 27% of ATHOS patients) treated with fenebrutinib had greater SRI response rates relative to those on placebo (SRI-4 at WK48 of 18% for PBO, 52% for FEN 150 mg QD, and 37% for FEN 200 mg BID). Similarly, post-hoc exploratory subgroup analyses based on baseline disease subgroups suggested that SRI-4 response to fenebrutinib was greater compared to placebo in several patient subsets with more severe disease. For example, among patients with SLEDAI arthritis and a swollen joint count of 4 or greater at baseline, SRI-4 response was achieved in 39%, 50%, and 57% of patients for PBO, FEN 150 mg QD, and FEN 200 mg BID arms, respectively (Table 3).

Safety

The majority (75%) of patients completed the 48-week study (Table 4). Overall, AEs were balanced across treatment arms (Table 4; Supplementary Table S5). Three deaths were reported, two in the PBO arm and one (due to a salivary gland neoplasm) in the FEN 150 mg QD arm. More patients in the FEN 200 mg BID arm (*n*=12, 14%) experienced serious AEs (SAEs) than in the PBO arm (*n*=8, 10%) or the FEN 150 mg QD arm (*n*=4, 5%); no clear pattern in SAEs was observed. More AEs led to treatment withdrawal in the FEN 200 mg BID group (*n*=17, 19%) than with FEN 150 mg QD (*n*=7, 8%) or PBO (*n*=7, 8%). The reasons for treatment withdrawal

were variable, but the most common reason for discontinuation was lymphopenia (*n*=3 for FEN 200 mg BID arm, *n*=1 for FEN 150 mg QD arm, *n*=0 for PBO arm). The overall rates of any infection (51%, 56%, and 47% in the PBO, FEN 150 mg QD, and FEN 200 mg BID arms, respectively) and serious infection (4 in PBO, 1 in the FEN 150 mg QD arm, and 3 in the FEN 200 mg BID arm) were balanced across treatment groups. IgG levels were decreased by 1.51 and 1.25 g/L in the FEN 200 mg BID and FEN 150 mg QD arms, respectively, relative to a decrease of 0.2 g/L in the PBO group by W48. More patients in the FEN 200 mg BID arm (*n*=40, 48%) experienced elevations in alanine aminotransferase (ALT) than in the PBO arm (*n*=15, 17%) or the FEN 150 mg QD arm (*n*=18, 20%). However, the proportion of patients who experienced grade 2 elevations was balanced across treatment arms (2 patients each in the PBO and FEN 150 mg QD arms and 3 patients in the FEN 200 mg BID arm). One patient in the FEN 200 mg BID arm experienced a grade 3 (≥5x to 20x ULN) ALT and aspartate aminotransferase (AST) elevation. A non-clinically meaningful but consistent increase in serum creatinine was observed in the FEN 200 mg BID arm, which reverted towards baseline level following study drug discontinuation. Nine patients in the FEN 200 mg BID arm had grade 2 elevations in creatinine compared to 4 patients in the FEN 150 mg and 2 patients in the placebo arm.

Three pregnancies were reported overall; one in the PBO arm resulted in a spontaneous abortion while two others in the FEN 150 mg QD arm included an induced abortion and a birth of a reportedly healthy male at term.

Biomarkers

Levels of phosphorylated BTK (pBTK) were reduced in both fenebrutinib treatment groups relative to placebo by W4; this inhibition was sustained to W48 in the subset of patients (*n*=11) evaluated to this timepoint (Supplementary Figure S6). As BTK inhibition leads to reduced differentiation of memory cells to plasmablasts (17), the effect of fenebrutinib treatment on genes enriched in plasmablasts relative to naïve and activated memory B cells (plasmablast signature; Supplementary Figure S7) was assessed. The plasmablast signature for patients in the fenebrutinib groups showed significant reductions relative to placebo by W4, with sustained reductions to W48 (Figure 1); fenebrutinib treatment resulted in plasmablast signature levels below the median level observed in healthy volunteers (Figure 1).

Patients treated with fenebrutinib had a transient and early accumulation of peripheral CD19+ B cells at W4 compared to placebo (median increase of 30.0 and 29.0 cells/μL for FEN 200 mg BID and FEN 150 mg QD, respectively; −1.0 for PBO). At W48, significant reductions in CD19+ B cells were observed with both fenebrutinib treatment groups relative to placebo (median reductions of 64.5 and 65.0 cells/μL for FEN 200 mg BID and FEN 150 mg QD, respectively; −4.5 for PBO (Figure 2). These changes appeared to reflect increases in naïve and double-negative B cell subsets at W4 and reductions in memory, IgD transitional and plasmablast B cell subsets at W48, notably with FEN 200 mg BID (Supplementary Table S6). No significant reductions in CD3+ T cells were observed at W48 with fenebrutinib treatment (Supplementary Figure S8). Consistent with the observed reduction of absolute B cells at W48, significant reductions in levels of anti-dsDNA autoantibodies, IgG, and IgM were also detected at weeks 12, 24, and 48 in patients treated with fenebrutinib, relative to placebo (Figure 2; Supplementary Figure S8). By W48, anti-ds DNA autoantibody levels were decreased by 75.7 and 38.3 IU/mL in the FEN 200 mg BID and FEN 150 mg QD arms, respectively, relative to an increase of 6.9 IU/mL for the PBO group (Figure 2). Small increases in complement C3 levels were observed at W12 and W24 in patients treated with fenebrutinib (200 mg BID) relative to placebo; modest improvements in complement C4 levels were observed at weeks 12, 24, and 48 with both doses of fenebrutinib relative to placebo (Supplementary Figure S9). Lastly, fenebrutinib also decreased levels of a myeloid-enriched biomarker, CCL4, relative to placebo (Supplementary Figure S8).

Pharmacokinetics

The mean fenebrutinib concentrations across the three steady-state pre-dose pharmacokinetics assessments ranged from 25.5 ng/mL to 56.6 ng/mL for the 150 mg QD group, and 137 ng/mL to 197 ng/mL for the 200 mg BID group (11). These concentrations were associated with reductions in pBTK levels consistent with those predicted based on pharmacokinetic/pharmacodynamic modeling using healthy volunteer data (Supplementary Figure S6). Inter-individual variability (CV%) was high, ranging from 110% to 204% for the FEN 150 mg QD group and from 67.2% to 97.1% for the FEN 200 mg BID group.

DISCUSSION

Fenebrutinib in two dosing regimens given to patients with moderate-to-severely active SLE failed to demonstrate clinical efficacy, even though strong inhibition of pBTK and the BTK-dependent plasmablast signature were achieved. In line with previous studies (19-21), the placebo response rate in in this trial was lower in serologically active patients relative to the entire study population. While higher response rates were seen in serologically active patients within the fenebrutinib arms, these were not dose-dependent and did not translate into clinically meaningful benefit. The primary efficacy results were notably similar to those observed in another recently completed BTK inhibitor trial (22).

BTK is known to play an important role in B cell receptor signaling pathways with relevance to B cell development, as evidenced in humans with X-linked agammaglobulinemia, an immunodeficiency resulting in complete loss of BTK, and in murine models of lupus lacking B cell inhibitory signaling molecules (15). Accordingly, serologic changes observed in this study (immunoglobulins and autoantibodies reductions) were expected, and have also been observed in fenebrutinib-treated patients with rheumatoid arthritis (RA) (13). Unlike genetic mutation leading to complete absence of BTK function, therapeutic targeting with fenebrutinib in patients led to limited cases of leukopenia. Moreover, the types of safety events that might be expected with BTK modulation were generally consistent with other therapies used in SLE, including immunosuppressives, as suggested by the overall similarities in the rates of infections seen in the FEN and PBO groups.

The mechanism(s) by which fenebrutinib elicits transient increases in B cells is currently not clear. A significant transient increase in B cells (but not T cells) was also observed in patients with RA treated with fenebrutinib (13); therefore, it is possible that these aggregated observations in RA and SLE may reflect BTK's role in B cell homing and retention (23-25). The reduction of total peripheral B cells in patients with SLE at WK48 was not observed in patients with RA treated with fenebrutinib for 12 weeks (13), suggesting that longer term inhibition of BTK can elicit B cell reductions, consistent with the key role of BTK in B cell activation and proliferation (15).

As there were notable serologic and biomarker changes, we conducted post-hoc efficacy analyses to gain further insights into the impact of BTK inhibition (26, 27). Interestingly,

fenebrutinib treatment was shown to be associated with improved FACIT-fatigue score relative to placebo. Enhanced efficacy was also observed in certain subgroups of patients with more active disease at baseline, including those who were autoantibody positive with BILAG A, and patients with higher baseline tender or swollen joint counts. This suggests that patients with more severe SLE may be more likely to show a treatment benefit with fenebrutinib. However, it is difficult to draw any definitive conclusions as low numbers of patients were included in these subgroups. Additionally, it is unclear why patients in other subgroups with high baseline disease activity (BILAG A or high SLEDAI score) did not demonstrate a potential treatment effect with fenebrutinib. While these post-hoc clinical findings do not change the conclusion that fenebrutinib is clinically ineffective in our overall patient population, the results suggest that certain patient subgroups may have the potential to derive a treatment benefit with fenebrutinib.

There are inherent challenges in conducting SLE trials (28), and this one was not exempt. For instance, determining how, how much, and when to permit the use of background immunosuppressive medications and corticosteroids represents an important consideration. Many key features of the current study were consistent with prior trial designs, which permitted use of SOC therapies, included OCS taper and stability windows prior to W24 and W48, and gave investigators the latitude to apply their clinical judgment in managing OCS tapering (4, 5, 29-31). However, given that 80% of patients received OCS at baseline, it was unexpected that only 27% would attempt taper during the trial. This is one of several factors that likely contributed to the relatively low rates of SLE flares observed during the study (9.6%) compared to other trials (32). Although the mean cumulative W48 corticosteroid doses were reduced in the FEN 200 mg BID arm compared to the PBO arm, corticosteroid reduction did not appear to have any notable impact on the SRI-4 with OCS taper outcome. Introduction of potential confounding on the primary endpoint due to differential application of OCS tapering across treatment arms remains a possibility.

Implementing a baseline OCS dose cap, alongside a mandated OCS tapering schedule with adequate provision for rescue therapy could better allow a new therapeutic to demonstrate prevention of disease worsening (33). Adherence to the protocol defined OCS taper by investigators likely contributed to a lower placebo response rate in another SLE trial (5). Given that there is geographic variability in the management of SLE (34, 35), it is possible that some

patients were more aggressively treated than others, which may in part underlie the lower SLE flare rate.

The ATHOS study sample size was similar to other recent phase 2 randomized, controlled SLE trials (5, 30, 36), and was adequately powered to see a treatment response. The 44% placebo response rate seen in this trial was high, but clearly in line with rates observed in a recent SLE trial meta-analysis (37). Since clinical trials with lower placebo rates have been able to demonstrate potential efficacy of new therapeutics over SOC (5), this should be a goal when designing new trials (28). Non-adherence to medications is all too frequent for patients with SLE (38, 39) so that well-intentioned dosing reminders within a clinical trial setting could improve SOC adherence but at the same time increase placebo response rates. Enrolling patients with more active disease could reduce the placebo response, as shown in a post-hoc analysis of patient subsets in the belimumab studies (20). While patients were adjudicated prior to entry into the ATHOS study, baseline characteristics suggest that eligible patients with lower disease activity than desired were enrolled.

Other limitations of the study may reduce its applicability and interpretability. As in any clinical study evaluating efficacy, results are limited to the range of doses studied. Due to the strong pathway inhibition observed, and the estimated suppression of BTK for the entire dosing interval for patients receiving 200 mg fenebrutinib BID, it is expected that higher doses would not have had any added benefit. Additionally, while the treatment duration of 48 weeks should be informative, and high study discontinuation rates were commensurate with those seen in other SLE studies, effects of longer-term fenebrutinib treatment are not known. Further, given that White and Hispanic or Latino patients represented the predominant racial and ethnic composition of our study population, respectively, the results may not be as readily generalizable to other patient groups whose enrollment numbers were comparatively limited in this trial. Finally, subgroup analyses were performed in a post-hoc fashion and were not statistically powered, nor were adjustments for multiple comparisons performed.

The findings from this phase II trial of patients with moderate-to-severe SLE indicate that fenebrutinib did not demonstrate a treatment benefit over placebo despite compelling BTK pathway inhibition evidenced by sustained decreases in levels of phosphorylated BTK, reductions in plasmablast signature levels, and distinct changes in the B cell profile accompanied by reductions in immunoglobulins, including autoantibodies, and directionally favorable

improvements in complement levels. Nevertheless, these study results offer further insights into the pathology of SLE, particularly with respect to BTK inhibition and B cell biology, as well as provide findings that may have utility in designing future SLE trials.

ACKNOWLEDGEMENTS

We thank the patients and their families, study investigators, and site staff for participation. This study was funded by Genentech, Inc., South San Francisco, CA. Medical writing and editing assistance was provided by A. Daisy Goodrich, Ph.D., (Genentech, Inc.) according to Good Publication Practice guidelines. The authors thank Emily Tse for help with figures.

DATA SHARING STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Table 1. Demographics and baseline characteristics

	PBO (*n*=86)	FEN 150 mg QD (*n*=87)	FEN 200 mg BID (*n*=87)	Total (*N*=260)
Age, median years (range)	40 (21-71)	44 (18-72)	39 (18-68)	41 (18-72)
Sex, *n* (%) female	85 (99)	82 (94)	84 (97)	251 (97)
Race, *n* (%)				
American Indian or Alaska native	11 (13)	8 (9)	17 (20)	36 (14)
Asian	7 (8)	1 (1)	2 (2)	10 (4)
Black/African-American	11 (13)	15 (17)	13 (15)	39 (15)
White	56 (65)	62 (71)	52 (60)	170 (65)
Multiple	1 (1)	1 (1)	3 (3)	5 (2)
Ethnicity, *n* (%)				
Hispanic or Latino	54 (63)	61 (70)	61 (70)	176 (68)
Not Hispanic or Latino	32 (37)	25 (29)	26 (30)	83 (32)
Not Stated	0	1 (1)	0	1 (0)
Duration of SLE, median years (range)	7 (1-29)	7 (0.1-32)	7 (0.7-38)	7 (0.1-38)
Physician's global assessment score, median (range)	1.6 (1-3)	1.7 (1-3)	1.8 (1-3)	1.7 (1-3)
Serological parameters, *n* (%)				
ANA ≥ 1:80	80 (95)	87 (100)	86 (98)	253 (98)
Anti-Smith positive[1]	20 (24)	21 (24)	25 (28)	66 (26)
Anti-dsDNA positive[2]	41 (49)	47 (54)	47 (53)	135 (52)
Low C3 complement[3]	22 (26)	25 (29)	31 (35)	78 (30)
Low C4 complement[3]	12 (14)	11 (13)	13 (15)	36 (14)
Low CH50[3]	2 (2)	5 (6)	1 (1)	8 (3)
Serological parameters, mean (SD)				
Anti-dsDNA (IU/mL)	141 (284)	160 (333)	253 (613)	

C3 Complement (g/L)	1.04 (0.3)	1.03 (0.3)	1.02 (0.3)	
C4 Complement (g/L)	0.19 (0.08)	0.19 (0.09)	0.16 (0.09)	
SLEDAI-2K, median (range)	9 (6-22)	10 (6-22)	10 (4-26)	
BILAG, patients, n (%)				
≥1 BILAG-A domain	41 (49)	39 (45)	47 (53)	127 (49)
No BILAG A and ≥1 BILAG-B domain	38 (45)	46 (53)	37 (43)	121 (47%)
No BILAG A or B	5 (6)	2 (2)	4 (5)	11 (4)
CLASI activity, median (range)	4 (0-28)	4 (1-26)	5 (0-28)	
Swollen joints, median (range)	4 (0-24)	4 (0-24)	4 (0-18)	
Tender joints, median (range)	8 (0-28)	8 (0-28)	7 (0-28)	
Background standard of care treatments				
Systemic corticosteroids, *n* (%)	70 (83)	69 (79)	70 (80)	
Avg. prednisone equivalent dose/day, mean (range)	9.3 (2.5-30)	11.1 (2.5-25)	11.7 (2.5-40)	
Antimalarials, *n* (%)	72 (86)	61 (70)	75 (85)	
Immunosuppressants, *n* (%)	41 (49)	37 (43)	49 (56)	
Azathioprine	13 (16)	14 (16)	20 (23)	47 (18)
Methotrexate	19 (23)	11 (13)	19 (22)	49 (19)
Mycophenolate sodium or mycophenolate mofetil	8 (10)	9 (10)	8 (9)	25 (10)

[1]Defined as above the upper limit of normal for testing laboratory.

[2]Defined as >25% by Farr assay or above normal range for testing laboratory;

[3]Defined as below the lower limit of normal for testing laboratory.

Table 2. Key efficacy data at W48

	PBO	FEN 150 mg QD	FEN 200 mg BID
SRI-4 response at W48	(*n*=86)	(*n*=87)	(*n*=87)
Responder, *n* (%)	38 (44)	44 (51)	45 (52)
Treatment difference vs. PBO (%)		6.4	7.5
95% CI		−8.5, 21.2	−7.3, 22.4
P-value		0.373	0.339
SRI-6 response at W48	(*n*=86)	(*n*=87)	(*n*=87)
Responder, *n* (%)	24 (28)	34 (39)	31 (36)
Treatment difference vs. PBO (%)		11.2	7.7
95% CI		(-2.8, 25.1)	(-6.1, 21.6)
P-value		0.105	0.286
SRI-4 with OCS[1] tapering response at W48	(*n*=86)	(*n*=87)	(*n*=87)
Responder, *n* (%)	36 (42)	44 (51)	39 (45)
Treatment difference vs. PBO (%)		8.7	3.0
95% CI		−6.1, 23.5	−11.8, 17.7
P-value		0.223	0.737
BICLA response at W48	(*n*=80)	(*n*=85)	(*n*=83)
Responder, *n* (%)	33 (41)	45 (53)	35 (42)
Treatment difference vs. PBO (%)		11.7	0.9
95% CI		−3.4, 26.8	−14.2, 16.1
P-value		0.086	0.879
Received escape therapy[2], *n* (%)	8 (10)	7 (8.2)	10 (12)

[1]Oral corticosteroid.

[2]Escape therapy defined as receipt of SLE medications exceeding the limits permitted by the protocol.

Table 3. Exploratory subgroup analyses on SRI-4[a] at W48

	PBO	FEN 150 mg QD	FEN 200 mg BID
Total N for subgroup **(% responders)**			
All patients	86 (44)	87 (51)	87 (52)
BILAG A	42 (48)	39 (54)	46 (59)
BILAG A + SLEDAI dsDNA binding	19 (37)	17 (53)	26 (65)
SLEDAI arthritis +SJC≥4	57 (39)	54 (50)	54 (57)
SLEDAI arthritis +TJC≥4	71 (39)	70 (53)	69 (59)
CLASI ≥10	14 (21)	11 (36)	16 (31)
Serologically active[b]	17 (18)	25 (52)	27 (37)

For inclusion in each subgroup, patients must have had the relevant BILAG score, CLASI score, 28-joint count value, and/or SLEDAI-2K manifestation at baseline. SJC=swollen joint count; TJC= tender joint count

[a] All analyses were post-hoc except for serologically active subgroup.

[b]Defined as anti-dsDNA >=30 IU/mL and (C3 < 0.9 or C4 < 0.1g/L)

Table 4. Key safety and disposition data

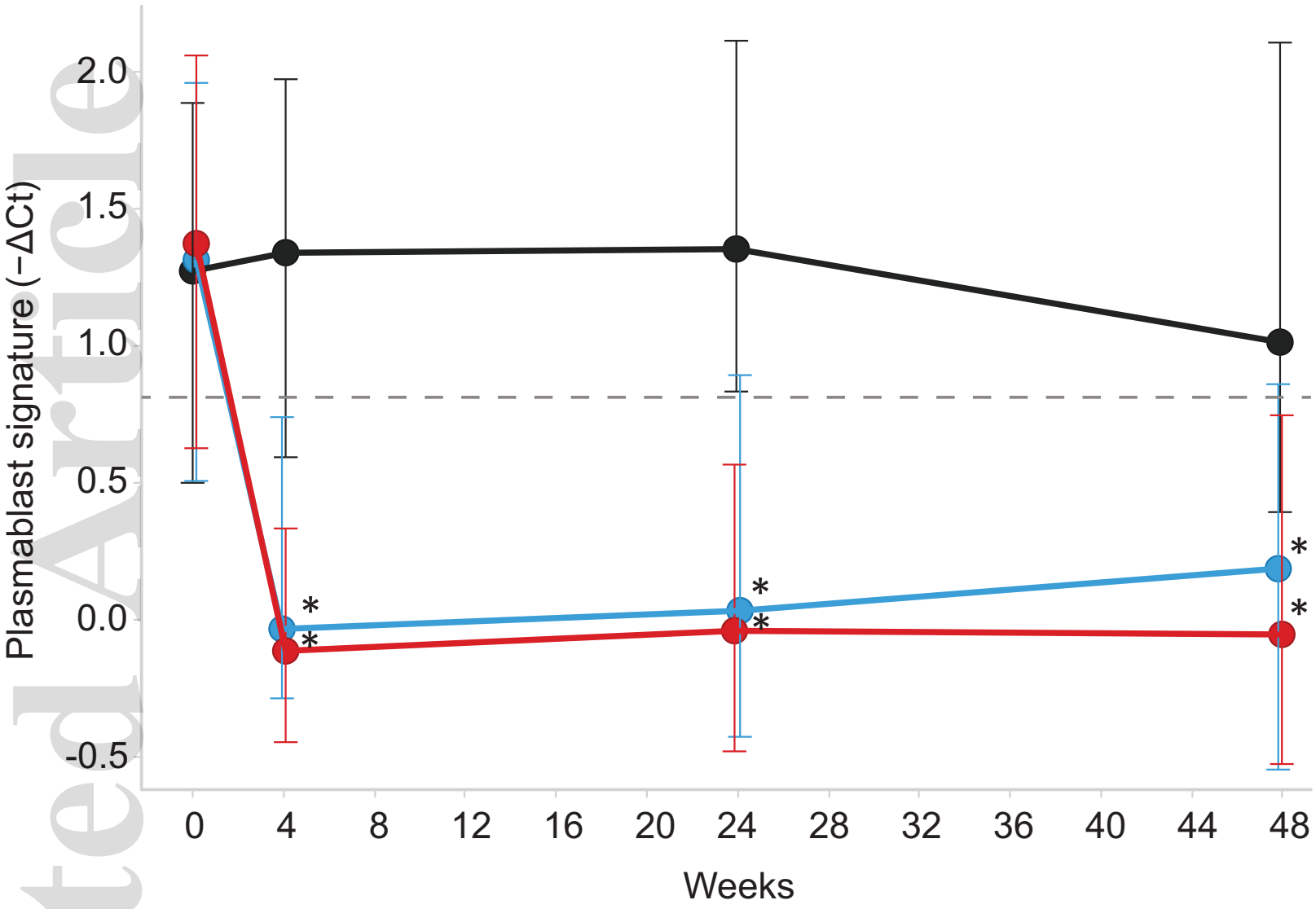
	PBO (*n*=84)	FEN 150 mg QD (*n*=87)	FEN 200 mg BID (*n*=88)
Patients with ≥1 event, *n* (%)			
Adverse event	64 (76)	77 (89)	69 (78)
Serious adverse event	8 (10)	4 (5)	12 (14)
Grade ≥3 adverse event	12 (14)	7 (8)	16 (18)
Transaminase (ALT/AST) elevation			
Grade 2	2 (2)	3 (3)	3 (3)
Grade 3	0	0	1 (1)
Serious infection adverse event	4 (5)	1 (1)	3 (3)
Adverse event leading to death[1]	2 (2)	1 (1)	0
Study discontinuations, *n* (%)	22 (26)	21 (24)	21 (24)
Adverse event	7 (8)	6 (7)	9 (10)
Death	2 (2)	0	0
Lack of efficacy	2 (2)	3 (3)	3 (3)
Lost to follow-up	0	1 (1)	2 (2)
Non-compliance with study drug	1 (1)	1 (1)	2 (2)
Other	1 (1)	0	0
Physician decision	0	1 (1)	0
Pregnancy	1 (1)	2 (2)	0
Withdrawal by subject	8 (10)	7 (8)	5 (6)

[1]Deaths due to salivary gland tumor (150 mg QD, death occurred after study completion); respiratory failure (PBO); infected skin ulcer (PBO).

FIGURE LEGENDS

Figure 1. Change from baseline in plasmablast gene signature. The –ΔCt value of the plasmablast gene signature expression over time (median with interquartile range) is shown. The dotted line represents the median –ΔCt value observed in healthy volunteers (*n*=20). Significance versus placebo is indicated by a "*".

Figure 2. Changes from baseline in biomarkers. Change from baseline in levels of (A) CD19+ B cells, (B) anti-dsDNA antibodies and (C) IgG over time are shown (median with interquartile range). Significance versus placebo is indicated by "*". Anti-dsDNA analysis included patients who were positive at screening.



ARM	Week 0	Week 4	Week 24	Week 48
Placebo	*n*=85	*n*=80	*n*=65	*n*=52
FEN 150 mg QD	*n*=87	*n*=82	*n*=66	*n*=53
FEN 200 mg BID	*n*=87	*n*=85	*n*=68	*n*=57

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