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Absence of Pharmacokinetic Interactions Between the Bruton's Tyrosine Kinase Inhibitor Fenebrutinib and Methotrexate

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Abstract

Fenebrutinib (GDC-0853) is an orally administered small molecule inhibitor of Bruton's tyrosine kinase being investigated for treatment of rheumatoid arthritis (RA) in patients with inadequate responses to methotrexate (MTX). This study interrogated the potential for pharmacokinetic drug interactions between fenebrutinib and MTX. Eighteen healthy male subjects enrolled in the study. They received a single oral dose of MTX (7.5 mg) on Day 1 followed by a 13-day washout period. Subsequently, on Days 15 to 20, subjects received 200 mg fenebrutinib twice daily. On Day 21, subjects received a 7.5 mg dose of MTX and a 200 mg dose of fenebrutinib under fasting conditions. The geometric mean ratios of MTX AUC and C_{max} on Day 21 relative to Day 1 (90% CI) were 0.96 (0.88-1.04) and 1.05 (0.94-1.18), respectively. The geometric mean ratios of fenebrutinib AUC and C_{max} for Day 21 relative to Day 20 (90% CI) were 1.03 (0.95-1.11) and 1.02 (0.90-1.15), respectively. The combination treatment was well tolerated, with an adverse event profile similar to that reported in other methotrexate trials. These results indicate that there is no clinically significant pharmacokinetic interaction between fenebrutinib and MTX.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder associated with functional decline, pain and a reduced quality of life. Between 0.5% and 1% of the world's population is affected, and the economic burden of RA is high (Uhlig et al., 2014). RA is characterized by progressive synovitis, systemic inflammation and the production of characteristic autoantibodies (Lundkvist et al., 2008), which ultimately results in irreversible damage of joint cartilage and bone. Although there are several medications available to treat RA, there is unmet need for safer and more efficacious therapies, ideally leading to full remission of disease (Kjeken et al., 2006; Montag et al., 2011). In response to this need, potential therapies are being evaluated against new molecular targets, including protein kinase inhibitors that interfere with intracellular signaling and the downstream regulation and proliferation of immune cells.

One molecular target of interest is Bruton's tyrosine kinase, or BTK, a cytoplasmic protein tyrosine kinase primarily expressed in hematopoietic cells, including macrophages. BTK is a key signaling kinase during B cell−antigen receptor (BCR) activation and it plays a role in Fc receptor signaling. Inhibition of BTK canresult in the prevention of BCR-dependent cell proliferation as well as reduced production of inflammatory cytokines via these two mechanisms (Kelly and Genovese, 2013). Given that BTK is involved in multiple signaling pathways downstream of the BCR and FcR, it represents an attractive therapeutic target for RA and other inflammatory disorders including systemic lupus erythematosus (SLE) and chronic spontaneous urticaria (CSU).

Fenebrutinib (also known as GDC-0853) is a highly selective, reversible inhibitor of BTK and is being developed by Genentech as an orally administered treatment for patients with RA, SLE, and CSU. Unlike other first-generation BTK inhibitors that act upon several different tyrosine kinases, fenebrutinib binds non-covalently to BTK in an orientation that enables greater selectivity

(Crawford et al., 2018). The *in vitro* cellular potency of fenebrutinib was determined to be 11 nM for the inhibition of BTK auto-phosphorylation in human whole blood obtained from healthy subjects. Additionally, target engagement has been demonstrated in a multiple ascending dose study in healthy subjects, where a maximal inhibition above 90% was seen in BTK auto-phosphorylation and basophil assays (Herman et al., 2018).

As there is currently no cure for RA, treatments focus on providing symptomatic relief of pain and stiffness, thus improving patients' ability to move and their quality of life. Medications known as disease-modifying anti-rheumatic drugs, or DMARDs, combat the inflammation of RA. Methotrexate (MTX), an immunosuppressant, is widely regarded as the preferred first-line conventional DMARD for most patients with RA. One of the targets of MTX associated with efficacy in RA is hypothesized to be 5-aminoimidazole-4-carboxamide ribonucleotide transformylase; inhibition of this enzyme and accumulation of substrates are thought to reduce lymphocyte proliferation (Morgan et al., 2004). Low-dose weekly methotrexate is used in approximately 80% of patients with RA; therefore, it is important to understand the potential for pharmacokinetic drug interactions between methotrexate and candidate compounds being developed for the treatment of RA (Kim et al., 2016).

Methotrexate is a folic acid derivative administered orally or by subcutaneous or intramuscular injection. After oral administration, methotrexate is rapidly absorbed, with anelimination half-life of approximately 5-8 h. Methotrexate is mainly excreted unchanged by the kidney and undergoes both secretion and reabsorption within the renal tubules (Bannwarth et al., 1996), rendering it susceptible to alterations in PK through inhibition of transporter proteins involved in these processes. Clinically relevant effects on methotrexate PK have been reported via the breast cancer resistance protein (BCRP), organic anion transporter 3 (OAT3), and multidrug resistance protein

4 (MRP4) transporters (Ivanyuk et al., 2017). In vitro transporter assay results suggest that fenebrutinib may inhibit BCRP (Jones et al. 2019, manuscript in review). The IC_{50} value for this interaction is substantially higher than the concentrations that would be anticipated following fenebrutinib administration at doses currently under consideration; however, out of an abundance of caution, the potential effect of fenebrutinib on methotrexate was assessed prior to initiation of a Phase 2 study in patients with RA on a background methotrexate regimen.

In order to evaluate the potential for PK interactions between methotrexate and fenebrutinib, a Phase I study was conducted in which single low doses of methotrexate were administered in the presence and absence of steady-state fenebrutinib. The objectives of this study were to evaluate the potential for drug-drug interactions (DDI) and to characterize the pharmacokinetics, tolerability and safety of fenebrutinib and MTX in healthy subjects to assess the feasibility of concurrent administration of fenebrutinib and methotrexate.

Methods

Study Design

This investigation was a Phase I, single center, fixed-sequence study with 3 treatment peroids (methotrexate administered alone, fenebrutinib administered alone, and methotrexate and fenebrutinib administered in combination). GDC-0853 tablets were supplied by Quotient Clinical as 50 mg tablets packaged as per product label. Methotrexate [EBEWE Pharma, Austria, PL 14510/0032] was procured by Quotient Clinical as UK licensed products.

The purposes were to characterize the following: (a) the effect of simultaneous administration of a single dose of methotrexate on the steady-state pharmacokinetics of fenebrutinib and (b) the effect of dosing fenebrutinib on the single dose pharmacokinetics of methotrexate in healthy

subjects. The study population consisted of healthy male subjects between the ages of 18 and 55 years, with normal renal function and no laboratory or clinical history of cytopenias or liver enzyme abnormalities. A single dose of 7.5 mg methotrexate was administered under fasting conditions on Day 1 followed by a 13-day washout period (see Supplemental Figure 1). Subsequently, 200 mg fenebrutinib was administered twice daily under fasting conditions on Days 15 to 20, which was considered sufficient to reach steady state. On Day 21, a single dose of 200 mg fenebrutinib was co-administered with 7.5 mg methotrexate under fasting conditions. There was a 20-day washout period between methotrexate dose administrations (Day 1 and Day 21), based on the half-life of methotrexate which undergoes > 99% elimination from systemic circulation after 13 days. Folic acid (5 mg) was administered orally approximately 24 h after each dose of methotrexate to mitigate the development of potential side effects related to methotrexate. The methotrexate dose of 7.5 mg was selected to give a clinically relevant exposure while minimizing the potential of methotrexate-associated adverse events (AEs). Additionally, this methotrexate dose has been administered to healthy subjects previously (Namour et al., 2012).

This study was conducted at Quotient Sciences (Nottingham, UK) according to the International Council for Harmonisation (Kim et al. 2016) E6 Guideline for Good Clinical Practice (GCP), the E.U. Clinical Trial Directive (2001/20/EC), and applicable local, state, and federal laws. This study was conducted in full conformance with the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted; whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Sample Size Calculation

A sample size of at least 15 subjects was required such that the probability that the 90% CIs for

the geometric mean exposure ratios were contained within 80% and 125% for methotrexate and within 50% and 200% for GDC-0853 was at least 0.8. This sample size calculation assumes a within-subject coefficient of variation of 63% for GDC-0853 and a within-subject coefficient of variation of 28% for methotrexate. To allow for possible dropouts, at least 17 subjects were planned to be enrolled.

Analytical Methods

Blood samples for the measurement of methotrexate were obtained up to 24 h after the administration of methotrexate on Days 1 and 21. Of note, methotrexate metabolites have not been conclusively associated with activity (safety or efficacy). Therefore, quantification of methotrexate metabolites was not performed in this study. Blood samples for the measurement of fenebrutinib were obtained prior to the morning dose of fenebrutinib on Days 17, 18 and 19, and for up to 24 h after the morning dose of fenebrutinib on Days 20 and 21.

Plasma concentrations of fenebrutinib and methotrexate were determined using validated bioanalytical methods at Covance Laboratories (Madison, WI). The concentrations of fenebrutinib and methotrexate in human plasma containing K_2EDTA as an anticoagulant were measured using supported-liquid extraction followed by analysis with high performance liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS). The lower limit of quantification (LLOQ) was 0.5 ng/mL for fenebrutinib and 1 ng/mL for methotrexate. Analysis runs were determined to have a high degree of reproducibility (97.9% of repeated results were within 20% of the original results) and a low degree of inter-run carryover (<5%), which was considered acceptable for pharmacokinetic quantitation.

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Determination of pharmacokinetic parameters

Plasma concentrations of fenebrutinib and methotrexate and sampling times after dosing were used to estimate pharmacokinetic (PK) parameters of both fenebrutinib and methotrexate using Phoenix WinNonlin PK software (v6.3, Certara USA, Inc., St. Louis, MO, USA). Profiles of mean plasma concentrations against sampling times after dosing were generated. The estimated PK parameters included: area under the plasma concentration-time curve (AUC), the maximal concentration observed in plasma (C_{max}) and the time after dosing at which C_{max} was apparent (t_{max}) for fenebrutinib and methotrexate. Summary statistics (i.e., mean, median, CV%, n, minimum, maximum, and geometric mean) were calculated for fenebrutinib and methotrexate PK parameters as applicable. Concentrations below the LLOQ (lower limit of quantification) were set to zero for the calculation of summary statistics except for calculation of geometric summary statistics, where values were set to 0.5 × LLOQ. Mean concentration-time curves by treatment/analyte were generated.

Safety Assessment

The incidence of AEs was monitored throughout the study. An AE was defined as any unfavorable or untoward medical occurrence in a clinical investigational subject administered a pharmaceutical product, regardless of causal attribution. AEs were assessed based on severity, duration and relationship to study drug.

Statistical analysis

Formal statistical analysis was performed on the following plasma PK parameters: $AUC_{0\text{-}12,ss}$ and $C_{max,ss}$ for fenebrutinib and $AUC_{0\text{-}24}$ and C_{max} for methotrexate. The PK parameters were logarithmically transformed and were subsequently analyzed using ANOVA modeling techniques.

The model included terms for treatment as a fixed effect and subject as a random effect. The following pairwise treatment comparisons were analyzed: a) comparison of fenebrutinib at steady state co-administered with methotrexate (Day 21) versus fenebrutinib administered alone at steady state (Day 20) and b) comparison of methotrexate co-administered with fenebrutinib (Day 21) versus methotrexate administered alone (Day 1). Adjusted geometric mean ratios (GMRs) and 90% CIs for the adjusted GMRs for the pairwise treatment comparisons were calculated. No adjustment for multiple comparisons was performed.

Results

Patient Demographics and Baseline Characteristics

A total of 18 healthy male subjects with a mean age of 32 years (range: 20-55 years) participated, and 12 of them successfully completed the study. All 18 subjects received at least 1 dose of methotrexate or fenebrutinib and were therefore included in the safety population. Six subjects discontinued the study (two withdrew consent and four discontinued due to mild treatment-emergent adverse events, TEAEs). Thirteen subjects completed all treatments (one subject completed all doses but was lost to follow-up prior to the final assessment and was therefore considered a study discontinuation), and they contributed at least 3 quantifiable post-dose plasma concentrations on Days 1, 20, and 21. They constituted the PK population for assessment of a DDI. Fifteen subjects were white Caucasians whereas 2 subjects were of African ethnic origin and 1 subject was Asian (Bangladeshi). Baseline inflammatory markers (ESR and CRP) were within the normal range for all subjects and creatinine clearance results were recorded for all subjects and were > 90 mL/min. Baseline demographics are described in the supplementary materials (Supplemental Table 1).

Pharmacokinetics of Fenebrutinib

Overall, a single dose of 7.5 mg methotrexate produced no significant effect on the steady-state plasma concentrations of fenebrutinib; the mean fenebrutinib concentration-time profiles in the presence and absence of methotrexate are presented on a linear/linear scale in Fig. 1.

The key PK parameters for fenebrutinib following multiple oral doses of 200 mg fenebrutinib and co-administration with 7.5 mg methotrexate in the fasting state are shown in Table 1. Observation of mean pre-dose fenebrutinib concentrations indicated that a steady state was reached by Day 19. At steady state, the fenebrutinib t_{max} ranged from 0.50 - 2 h, with a median value of 1 h. The geometric mean (CV%) steady state fenebrutinib C_{max} and AUC_{0-12} values were 659 ng/mL (54.1%) and 3270 ng.h/mL (45.2%), respectively. Following C_{max}, plasma fenebrutinib concentrations declined with a geometric mean terminal half-life of 4.63 h (16.0%). On Day 21, following co-administration with 7.5 mg methotrexate, the fenebrutinib t_{max} ranged from 0.50 - 2 h, with a median value of 0.50 h. The geometric mean (CV%) fenebrutinib C_{max} and AUC_{0-12} values at steady state were 673 ng/mL (51.4%) and 3360 ng.h/mL (39.2%), respectively, and the geometric mean (CV%) terminal half-life was 6.87 h (28.5%). The geometric mean ratios (90% CI) for fenebrutinib $C_{max,ss}$ and $AUC_{0-12,ss}$ were 1.02 (0.90 - 1.15) and 1.03 (0.95 - 1.11), respectively, in the presence of methotrexate compared to administration alone.

Pharmacokinetics of methotrexate

The mean plasma methotrexate concentration-time profiles following oral administration of a single dose of 7.5 mg methotrexate on Day 1 and with co-administration of 200 mg fenebrutinib on Day 21 could be superimposed (Fig. 2).

The key PK parameters for methotrexate following a single oral dose of 7.5 mg methotrexate in the presence and absence of steady-state concentrations of fenebrutinib are shown in Table 2. Following a single oral dose of 7.5 mg methotrexate, methotrexate plasma concentrations were measured at the first post-dose time point (0.50 h) and remained quantifiable until at least 16 h post-dose in all subjects. The methotrexate t_{max} occurred between 0.50 and 2 h with a median of 1 h post-dose. The geometric mean (CV%) methotrexate C_{max} and AUC_{0-24} were 191 ng/mL (28.2%) and 730 ng.h/mL (15.2%), respectively. Following C_{max}, methotrexate plasma concentrations declined in a monophasic or a biphasic manner with a geometric mean (CV%) terminal half-life of 3.42 h (20.4%), consistent with expected pharmacokinetics (Bannwarth et al., 1996).

Following co-administration with 200 mg fenebrutinib on Day 21, the methotrexate t_{max} occurred between 1.00 and 2.00 h with a median of 1.00 h post-dose. The geometric mean (CV%) methotrexate C_{max} and AUC_{0-24} were 220 ng/mL (27.8%) and 724 ng.h/mL (23.6%), respectively. After reaching Cmax, plasma methotrexate concentrations declined in a monophasic or a biphasic manner with a geometric mean (CV%) terminal half-life of 3.57 h (14.9%).

The geometric mean ratios (90% CI) for methotrexate C_{max} and AUC_{0-24} were 1.05 (0.94-1.18) and 0.96 (0.88-1.04), respectively, in the presence of fenebrutinib compared to administration of methotrexate alone.

There were no statistically significant differences in the total or peak exposures of fenebrutinib or methotrexate following co-administration compared to administration of fenebrutinib or methotrexate alone.

Safety and Tolerability

This study assessed the safety and tolerability of multiple 200 mg oral doses of fenebrutinib and a single dose of methotrexate administered in the presence of steady state fenebrutinib in healthy male subjects. Fenebrutinib was well-tolerated when given as 200 mg oral doses twice daily in the fasting state for 6 days and with a single 7.5 mg oral dose of methotrexate. The majority of adverse events were mild and not considered related to fenebrutinib. Two moderate severity unrelated TEAEs, a hand fracture and ligament sprain, were reported in one subject. There were no serious or severe adverse events and no deaths.

Twelve out of 18 subjects (66.7%) reported 26 AEs (tabulated in Supplemental Table 2). Adverse events were reported most commonly during the period of twice daily dosing with fenebrutinib (7/16, 43%) with only one adverse event (rash) reported after the addition of the single dose of methotrexate. Overall, the most common events were reported in the skin and subcutaneous disorders system organ class (SOC) (6/26, 33.3%) and consisted of mild AEs of rash (rash (2), rash maculopapular (1) and rash pruritic (1)), generalized pruritus (1), petechiae and papules (1). Adverse event terms were reported once only with the exception of rash and headache in two subjects each. Four subjects (22.2%) experienced six mild treatment-emergent adverse events (TEAEs) that resulted in study drug withdrawal and the subjects' discontinuation from the study. Three of these subjects withdrew during the period of fenebrutinib dosing, one after the initial methotrexate dosing and none in the period after dosing with methotrexate in the setting of steady state fenebrutinib. These TEAEs leading to withdrawal were generalized pruritus, folliculitis, petechiae, pyrexia, influenza-like symptoms and diarrhea of which only petechiae was considered related to study drug. All AEs had resolved by the end of the study. There were no clinically significant changes in laboratory parameters, vital signs, ECGs, or physical examination findings recorded during the study.

Discussion

This Phase I, single center, fixed-sequence study with 2 treatments (methotrexate and fenebrutinib, alone and in combination) in healthy subjects demonstrated that fenebrutinib was well tolerated when a single dose of methotrexate was co-administered. The effects on the steady state PK of 200 mg fenebrutinib were minimal when dosed with 7.5 mg methotrexate on Day 21; fenebrutinib t_{max}, C_{max} and AUC were comparable with and without methotrexate, and formal statistical analysis confirmed no significant difference in exposure parameters. The geometric mean half-life for fenebrutinib when co-administered with methotrexate was 1.5-fold longer than that for a fenebrutinib tablet administered without methotrexate (6.87 and 4.63 h, respectively). However, this was likely due to the longer sampling period on Day 21 resulting in better definition of the terminal phase and half-life.

Methotrexate is a cornerstone of therapy in the treatment of rheumatoid arthritis. Hence, determining whether concomitant administration of fenebrutinib affects the PK of methotrexate was a crucial step prior to conducting a clinical study in RA patients. Minimal effect was seen on the PK of methotrexate when co-administered with fenebrutinib at steady state on Day 21, and formal statistical analysis confirmed no significant differences in exposure parameters. MTX t_{max}, C_{max} and AUC were comparable in the presence and absence of fenebrutinib. Therefore, fenebrutinib did not appear to significantly impact the PK of methotrexate.

The safety profile observed during co-administration of fenebrutinib with methotrexate was typical of that expected from similar methotrexate drug-drug interaction studies (Namour et al., 2012; Mohamed et al., 2016; Lee et al., 2017) and from methotrexate monotherapy (Salliot and van der Heijde, 2009). Fenebrutinib was well tolerated when administered as multiple 200 mg oral doses of tablet formulation BID and with a single 7.5 mg oral dose of methotrexate. Almost all the

TEAEs reported were mild, with no serious adverse events (SAEs) or severe AEs, and no clinically significant changes in laboratory or other parameters recorded during the study. These results combined with the lack of significant changes in pharmacokinetic parameters suggest that fenebrutinib can be administered to RA patients receiving methotrexate as a background therapy without restrictions or dosage adjustments.

There are several reports of interactions of small molecule drugs with low-dose methotrexate, although the clinical relevance of such interactions in the overall RA patient population is unknown (Hall et al., 2017). Typically, methotrexate is the victim of these interactions, and there is no compelling evidence of CYP inhibition by methotrexate (Baumhäkel et al., 2001). Nonselective NSAIDs (nonsteroidal anti-inflammatory drugs), particularly salicylates, have been reported to interact with methotrexate when administered concomitantly, resulting in increased plasma concentrations and decreased renal clearance of methotrexate. Some drugs (NSAIDs) elevate and prolong serum methotrexate levels by reducing tubular secretion via OAT3 and MRP4 (Bannwarth et al., 1996; Ivanyuk et al. 2017). Other drugs (e.g. salicylates, phenylbutazone, phenytoin, and sulfonamides) are reported to increase methotrexate toxicity by displacing albumin-bound methotrexate, but protein binding changes in general are rarely considered clinically significant (Benet and Hoener, 2002). Methotrexate is eliminated primarily via renal excretion. This occurs predominantly via glomerular filtration and with an additional active secretory process via OATs (Songsiridej and Furst, 1990). It is thought that the BCRP transporter is responsible for methotrexate secretion in the kidneys during the process of renal excretion. A study by Breedveld et al. suggested that competition for BCRP may explain the DDI between methotrexate and benzimidazoles (e.g. proton pump inhibitors) (Breedveld et al., 2004). In the context of planned evaluation of fenebrutinib in patients with RA, for whom methotrexate is

commonly prescribed, and given several reports about the interaction between small molecules and methotrexate via renal transporters, this study was conducted in order to assess whether there would be a pharmacokinetic interaction between fenebrutinib and methotrexate at clinically relevant doses. As fenebrutinib could potentially be used in combination with methotrexate, it was important to understand the potential for DDIs between these 2 compounds.

In conclusion, this study demonstrated that concomitant administration of fenebrutinib and methotrexate resulted in no statistically significant differences in the exposure of fenebrutinib following administration of a single dose of methotrexate, or in the exposure of methotrexate following administration of multiple doses of fenebrutinib. These data indicate that fenebrutinib does not substantially affect the systemic exposure of methotrexate, and that methotrexate does not significantly change the systemic exposure of fenebrutinib. A favorable tolerability and safety profile also support concomitant use of methotrexate and fenebrutinib in patients with autoimmune diseases.

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Authorship contributions:

Participated in research design: Winter, Katsumoto, Florero, Murray, and Chinn
Conducted experiments: Walker and Singh
Performed data analysis: Jones, Winter, Katsumoto, Florero, Murray, Walker, Singh, and Chinn
Wrote or contributed to the writing of the manuscript: Jones, Winter, Katsumoto, Florero, Murray, Walker, Singh, and Chinn

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Footnotes:

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Figure Legends

Figure 1. Mean (± SD) plasma fenebrutinib concentration-time profiles over 12 h in healthy subjects (n = 13) on Day 20 and Day 21 following multiple twice daily doses of 200 mg fenebrutinib under fasting conditions on Days 15 to 20, and a single final dose of 200 mg fenebrutinib co-administered with 7.5 mg methotrexate) under fasting conditions on Day 21.

Figure 2. Mean (± SD) plasma methotrexate concentration-time profile in healthy subjects (n = 13) following a single dose of 7.5 mg methotrexate under fasting conditions on Day 1, and a single dose of 7.5 mg methotrexate co-administered with 200 mg fenebrutinib under fasting conditions on Day 21.

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Tables

Table 1. Steady-state fenebrutinib pharmacokinetic parameters (geometric mean, CV%) for twice daily fenebrutinib administered alone on Day 20, and in combination with a single dose of 7.5 mg methotrexate on Day 21.

PK Parameter	200 mg Fenebrutinib tablet Day 20 Fasting[a], n = 13	200 mg Fenebrutinib tablet with 7.5 mg Methotrexate Day 21 Fasting[b], n = 13
$t_{max,ss}$ [c] (h)	1.00 (0.50 – 2.00)	0.50 (0.50 – 2.00)
$C_{max,ss}$ (ng/mL)	659 (54.1)	673 (51.4)
$AUC_{0-12,ss}$ (ng.h/mL)	3270 (45.2)	3360 (39.2)
$t_{1/2,ss}$ (h)	4.63 (16.0)	6.87 (28.5)
Geometric mean ratio of $AUC_{0-12,ss}$ (90% CI)	NA	1.03 (0.95-1.11)
Geometric mean ratio of $C_{max,ss}$ (90% CI %)	NA	1.02 (0.90-1.15)

[a]Single dose of 200 mg fenebrutinib BID on Days 15 to 20 under fasting conditions (an overnight fast for the morning dose and a 2 h fast for the evening dose)

[b]Single dose of 200 mg fenebrutinib (along with 7.5 mg methotrexate) on Day 21 under fasting conditions

[c]Median (range)

NA: Not Applicable, BID: Twice Daily

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Table 2. Single dose methotrexate pharmacokinetic parameters (geometric mean, CV%) following oral administration of 7.5 mg methotrexate on Day 1 and in combination with steady-state administration of fenebrutinib (200 mg twice daily) on Day 21

PK Parameter	7.5 mg Methotrexate Day 1 Fasting[a], n = 13	7.5 mg Methotrexate with 200 mg Fenebrutinib Day 21 Fasting[b], n = 13
t_{max}[c] (h)	1.00 (0.50 – 2.00)	1.00 (1.00 – 2.00)
C_{max} (ng/mL)	191 (28.2)	220 (27.8)
AUC_{0-t} (ng.h/mL)	725 (15.8)	718 (24.2)
AUC_{0-24} (ng.h/mL)	730 (15.2)	724 (23.6)
AUC_{0-inf} (ng.h/mL)	736 (15.5)	729 (23.8)
$t_{1/2}$ (h)	3.42 (20.4)	3.57 (14.9)
Geometric mean ratio of AUC_{0-24} (90% CI)	NA	0.96 (0.88-1.04)
Geometric mean ratio of C_{max} (90% CI)	NA	1.05 (0.94-1.18)

[a]Single dose of 7.5 mg methotrexate administered as 3 x 2.5 mg tablets under fasting conditions

[b]Single dose of 7.5 mg methotrexate (administered as 3 x 2.5 mg tablets) co-administered with fenebrutinib under fasting conditions

[c]Median (range)

NA: Not Applicable, BID: Twice Daily

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Figure 1

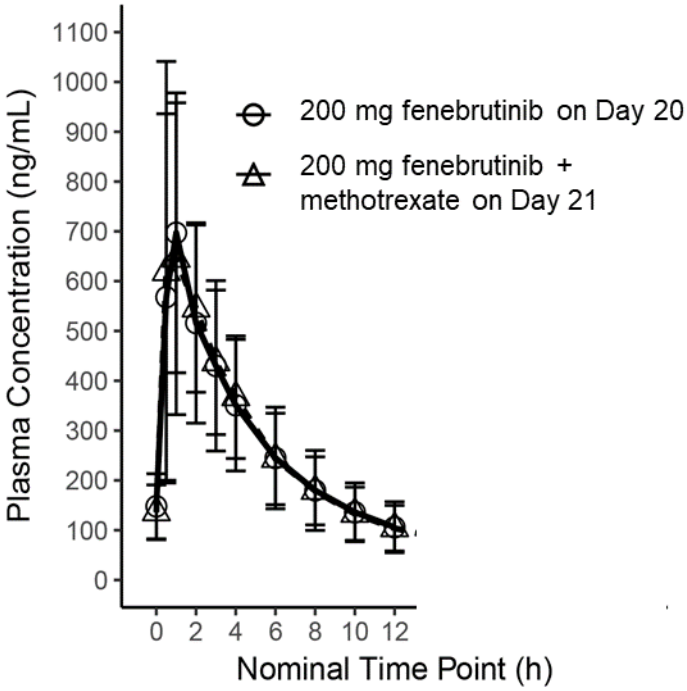

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Figure 2