Exposure-Response Relationships for Efficacy and Safety of Filgotinib and its metabolite GS-829845 in Subjects with Rheumatoid Arthritis Based on Phase 2 and Phase 3 Studies

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Abstract

Aims:Filgotinib is a potent, oral, JAK1-preferential inhibitor for the treatment of rheumatoid arthritis (RA). This report describes exposure-response (ER) analyses of filgotinib for dose confirmation based on three Phase 3 and two Phase 2 studies in moderate to severe RA patients. Methods:The PK exposures used in ER analyses were derived from population pharmacokinetic analysis. The relationship between filgotinib exposures and various efficacy endpoints (ACR20/50/70 and DAS28) was assessed over octile groups of exposures by using combined exposures of filgotinib and GS-829845 (major, active metabolite). For the ER analyses of safety, exposures were examined between subjects who experienced and who did not experience the evaluated safety events, which was conducted separately for filgotinib and GS-829845. Results:Exposure efficacy relationships consistently revealed high response rates across the exposure range for filgotinib 200 mg once daily dose. A trend of increasing response with increasing exposure was observed over the exposure range for the primary and multiple secondary efficacy endpoints, with exposures associated with the 200 mg dose primarily residing on the curve plateau. For exposure-safety analyses, filgotinib and GS-829845 exposures were similar irrespective of presence/absence of the evaluated safety endpoints, indicating no exposure-safety relationship for common TEAEs, common laboratory abnormalities, serious TEAEs, or serious infections. Conclusions:ER analyses confirmed that filgotinib produced more robust therapeutic effects across the exposure range observed at 200 mg once daily compared to lower doses. The positive exposure-efficacy relationship and a lack of exposure-safety relationship on the evaluated safety endpoints supported the 200 mg once daily dose for commercialization.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that primarily involves the lining of synovial joints and can cause progressive disability [1]. Research efforts are now targeting Janus kinases (JAK)-signal transducer and activator of transcription proteins (STAT) signaling cascade as a therapeutic strategy [2]. EMA (European Medicines Agency) and Pharmaceuticals and Medical Devices Agency have approved four oral, small molecule JAK inhibitors, tofacitinib, baricitinib, upadacitinib, and filgotinib for the treatment of RA [3],[4],[5]. These agents differ in their *in vitro* selectivity profile for JAK subtypes. Newer generations of JAK inhibitors are more selective, specifically targeting inhibition of JAK1 while avoiding potential undesirable effects of inhibiting downstream signaling from JAK2 and JAK3 [3],[6],[7].

Filgotinib is an oral, once-daily, potent JAK1 preferential inhibitor [8], which has demonstrated clinical improvement in RA and was granted marketing approval in European Union and Japan for treatment of moderate to severe RA in adults. Filgotinib has met all the primary endpoints, ACR20 at Week 12 or Week

24, in its Phase 3 clinical trials, FINCH 1, FINCH 2, and FINCH 3 [9],[10]. These studies showed that filgotinib was well tolerated and highly efficacious in patients with moderately to severely active RA, by reducing the signs and symptoms of disease, improving function, and slowing the progression of joint destruction. Filgotinib also showed clinical benefit in ulcerative colitis [11],[12] and is currently being investigated for treatment of other chronic inflammatory diseases such as Crohn's disease [13]. GS-829845, the major circulating metabolite of filgotinib, is also a JAK1 preferential inhibitor and approximately 10-fold less potent than the parent compound [8],[14],[15]. This report describes exposure-efficacy and exposure-safety analyses for filgotinib and its major active metabolite, GS-829845, based on population pharmacokinetic (PopPK) model-derived PK exposures and efficacy and safety data from three Phase 3 studies (FINCH 1, FINCH 2, and FINCH 3) and two Phase 2 studies (DARWIN 1 and DARWIN 2) in patients with moderate to severe RA to support dose recommendation [9],[10],[16],[17],[18].

Methods

Study Design and Population

The protocol and informed consent for each of the studies were approved by the local institutional review boards. All subjects provided written informed consent before study participation. All studies were conducted according to the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference of Harmonisation. The study design, patient eligibility, dose administration statistical analyses, and study outcome details for the studies included in this report have been previously published (FINCH 1: NCT02889796, FINCH 2: NCT02873936, FINCH 3: NCT02886728, DARWIN 1: NCT01888874, DARWIN 2: NCT01894516) [9],[10],[16],[17],[18].

Brief summaries of the study design for each study are as follows. FINCH 1, FINCH 2, and FINCH 3 were the three Phase 3 studies included in this analysis. FINCH 1 was a randomized, double-blind, placebo- and active-controlled study in adults with moderately to severely active RA who had an inadequate response (IR) to methotrexate (MTX; MTX-IR). 1759 subjects were randomized in a 3:3:2:3 ratio to filgotinib 200 mg, filgotinib 100 mg, active comparator (adalimumab), or placebo to match (PTM) administered for up to 52 weeks, all in the context of a weekly stable dose of MTX. FINCH 2 was a randomized, double-blind, placebo-controlled study in adults who had moderately to severely active RA despite conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy (i.e., MTX, hydroxychloroquine, sulfasalazine, leflunomide) and had an inadequate response or are intolerant to at least one biologic disease-modifying antirheumatic drug (bDMARD). 449 subjects were randomized in a 1:1:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or PTM administered for up to 24 weeks, all in the context of a stable dose of permitted csDMARD(s). FINCH 3 was a randomized, double-blind, placebo- and active-controlled study in adult male and female subjects with moderately to severely active RA who were naïve to MTX therapy. 1252 subjects were randomized in a 2:1:1:2 ratio to filgotinib 200 mg with MTX, filgotinib 100 mg with MTX, filgotinib 200 mg alone, or MTX alone for up to 52 weeks [9],[10],[16].

DARWIN 1 and DARWIN 2 were the two Phase 2 studies included in this analysis. DARWIN 1, a multicenter, 24-week double-blind, placebo-controlled, filgotinib add-on Phase 2b dose-finding study, was performed in subjects with moderately to severely active RA who had an inadequate response to MTX alone. A total of 594 subjects were randomized and treated: 86 subjects started in the placebo group and 508 subjects started in 1 of 6 filgotinib dose regimens: 50 mg once daily (82 subjects), 100 mg once daily (85 subjects), 200 mg once daily (86 subjects), 25 mg twice daily (86 subjects), 50 mg twice daily (85 subjects), and 100 mg twice daily (84 subjects) for 24 weeks. DARWIN 2, a multicenter, 24-week double-blind, placebo-controlled, filgotinib monotherapy Phase 2b dose-finding study, was performed in subjects with moderately to severely active RA who had an inadequate response to MTX alone. A total of 283 subjects were randomized and treated: 72 subjects started in the placebo group and 211 subjects started in 1 of 3 filgotinib monotherapy groups (72 subjects, 70 subjects, and 69 subjects were randomized to 50 mg once daily, 100 mg once daily, and 200 mg once daily, respectively, for 24 weeks) [17],[18].

Population PK Analysis

PopPK was performed to provide model predicted individual pharmacokinetic (PK) parameter estimates for exposure-response (ER) analyses. Data from seven Phase 1 studies, four Phase 2 studies, and three Phase 3 studies were analyzed using nonlinear mixed-effects modeling [NONMEM (Version 7.3.0 or later; GloboMax, Hanover, MD)] and Perl-Speaks-NONMEM (PsN; Uppsala University, Sweden). Summary of the data used in the PopPK modeling is shown in supplementary Table 1.

Filgotinib and GS-829845 models were developed separately. Various structural models and random effect models were evaluated to reach the base models. Stepwise forward addition and backward deletion was implemented in the covariate model building process, with evaluated covariates including demographics (age, sex, body weight, race), pathophysiological factors [baseline estimated creatinine clearance (CL_{cr}), baseline bilirubin, baseline alanine aminotransferase, baseline aspartate aminotransferase, RA disease status (subjects with RA vs healthy subjects), baseline C-reactive protein (CRP), and RA duration], and fed status (always fed vs mixed fasted/fed vs always fasting; evaluated on absorption-related parameters). Model selection was done based on a log-likelihood ratio test at an acceptance p-value of 0.01 (forward addition) or 0.001 (backward elimination). The difference in -2 times the log of the likelihood (-2LL) between a full and reduced model was assumed to have a $\chi 2$ asymptotic distribution with degrees of freedom equal to the difference in number of parameters between the 2 models. Model performance evaluation was based on Goodness-of-Fit evaluation, Prediction Corrected Visual Predictive Check (pcVPC), and Bootstrap Resampling Techniques. Individual PK parameter estimates were predicted from the final models for ER analyses.

Exposure-efficacy Analysis

The exposure-efficacy analysis was conducted using SAS version 9.4. The analysis dataset for filgotinib and its active metabolite GS-829845 included all subjects from the three Phase 3 and two Phase 2 studies who were (1) randomized/enrolled and had received at least one dose of filgotinib at randomized/enrolled phase; (2), who had at least one nonmissing PK parameter of interest estimated from a PopPK model (described above) for the analyte of interest. ER analyses for efficacy were performed following completion of Phase 3 and Phase 2 studies (FINCH 1, FINCH 2, FINCH 3, DARWIN 1, and DARWIN 2,) to support the dose for commercialization.

The primary objective of the included studies was to evaluate the effect of filgotinib for the treatment of RA as measured by the proportion of subjects achieving ACR20 (primary endpoint) at Week 12 (DARWIN 1, DARWIN 2, FINCH 1, and FINCH 3) or Week 24 (FINCH 2). Secondary efficacy endpoints included the proportion of subjects who achieved ACR50, ACR70, and Disease Activity Score (DAS) 28(CRP) [?] 3.2, or DAS28(CRP) $<$ 2.6 at Week 12 or Week 24, as applicable. Exposure-efficacy analyses were conducted to assess the relationship between filgotinib exposures and the various efficacy endpoints based on pooled Phase 2 and Phase 3 data regardless of the RA population.

As both filgotinib and its metabolite, GS-829845, contribute to efficacy via JAK1 inhibition, their exposures were combined by accounting for relative inhibition potency in the analyses for efficacy. $AUC_{0\text{-}24}$ of filgotinib and $AUC_{0\text{-}24}$ of its active metabolite GS-829845 were combined into AUC_{eff}. AUC_{eff} was calculated by using this equation: $AUC_{eff} = AUC_{FIL} + AUC_{met}$* 1/10 * (425.51/357.43) where AUC_{FIL} and AUC_{met} was the $AUC_{0\text{-}24}$ of filgotinib and GS-829845, respectively, 1/10 is the difference in potency between parent and metabolite [8], and 425.51 and 357.43 are the molecular weights of filgotinib and GS-829845, respectively.

Subjects were grouped into octile subgroups based on the AUC_{eff} in the filgotinib and GS-829845 analysis set. For each subject, the determination of octile subgroup was based on the rankings of AUC_{eff} values from all the subjects in the filgotinib and GS-829845 analysis set with the number of observations approximately equally distributed within the eight octile subgroups. The relationship between exposure (AUC_{eff}) and binary efficacy endpoints [ACR20, ACR50, ACR70, DAS28 (CRP) [?] 3.2, and DAS28(CRP) $<$ 2.6 at Week 12 and Week 24] were explored. Exposure-efficacy relationships were also evaluated by examining AUC_{eff} in subjects who achieved and who did not achieve ACR20/50/70 or DAS28 responses in Phase 2 and Phase 3 studies across all the doses.

Exposure-safety Analysis

ER analyses for safety were pooled from all 5 studies and were performed separately for filgotinib and GS-829845 to characterize the individual safety profile of each analyte. Data were not included in the analysis if they were collected after subjects were rerandomized and were switched to a different treatment group. The evaluated safety endpoints included the 5 most frequent treatment-emergent adverse events (TEAEs) (nausea, nasopharyngitis, upper respiratory tract infection, headache, and hypertension) and Grade 3/4 laboratory abnormalities [glucose increase, lymphocyte decrease, phosphate decrease, lipase increase, and alanine transaminase (ALT) increase] that occurred in the filgotinib 200 mg once daily group based on Phase 2 and Phase 3 studies. Serious TEAEs and serious infections were also evaluated against the exposures. Exposures were compared based on the presence and absence of selected safety event.

Results

Summaries of baseline characteristics in the ER analysis population stratified by study are shown in Table 1. The baseline characteristics were summarized by continuous variables (age, body weight, CL_{cr}, CRP, and RA duration) and categorical variables (sex and race). The baseline characteristics were as expected in a population with moderately to severely active RA.

Population PK Analysis

The final PopPK model development dataset for filgotinib included 13376 PK datapoints from 3125 subjects (details by study are provided in supplementary Table 1). Plasma concentrations of filgotinib were best described by a 2-compartment model with a mixture model for absorption and linear elimination. The two subpopulations for absorption, rapid versus slower, were described respectively by a first-order [with absorption rate constant (k_a) being fixed to a high value to mimic an almost instantaneous absorption profile] and a sequential zero- first-order absorption. The model included a difference in bioavailability (F) between tablets and capsules. Weight effects were included on apparent central clearance (CL/F), apparent intercompartmental clearance (Q/F), central volume of distribution (V_c/F), and peripheral volume of distribution (V_p/F) using standard fixed allometric exponents of 0.75 for the clearance and 1 for the volume of distribution parameters. Moreover, baseline CRP and sex were identified as statistically significant covariates on filgotinib CL/F, whereas race (white and Asian versus black or African American versus other) was identified as a statistically significant covariate on V_c/F (supplementary Table 2). Although the final filgotinib model had a tendency to modestly underpredict C_{max} (GMRs of 0.76-0.79 based on different populations), the model was able to adequately predict AUC_{tau} with geometric mean ratio (GMR) = 0.98, and thus could be used to predict individual exposures for ER analyses.

For GS-829845, the final model development dataset included 14896 PK datapoints from 3155 subjects (details by study are provided in supplementary Table 1). Plasma concentrations of GS-829845 were best described by a 1-compartment model with first-order absorption, and first-order elimination. Statistically significant covariates included the effects of baseline CL_{cr}, baseline CRP, patient status, and sex on CL/F; Asian race versus non-Asian race and duration of RA on V/F; and formulation on F and k_a(supplementary Table 3).

The final models adequately described the plasma concentrations of filgotinib and GS-829845 separately, as assessed by diagnostic plots/metrics including Goodness-of-Fit evaluation, pcVPC, and Bootstrap Re-sampling (supplementary Tables 2-3 and supplementary Figures 2-5). Thus, the predicted individual PK exposures were deemed adequate to be used in the ER analyses.

Exposure-efficacy Analysis

Exposure-Response for Efficacy Supporting Dose Confirmation

The Analysis Set for exposure-efficacy included pooled Phase 2 and Phase 3 subjects with RA who received filgotinib and had evaluable PopPK-based exposure estimates ($AUC_{0\text{-}24}$) for both filgotinib and GS-829845 (N = 2678).

Exposure-efficacy analysis across the Phase 2 and Phase 3 program confirmed that filgotinib produced robust therapeutic effects across the exposure range observed at 200 mg once daily at both Week 12 and Week 24 (Figure 1 and Figure 2). In this ER analysis over a wide dose/exposure range, high response rates (approximately 70% to 80% for ACR20, the primary endpoint) were demonstrated across octile groups associated with 200 mg in subjects with RA receiving filgotinib at Week 12 (Figure 1). ACR20 responses in the filgotinib 200 mg group appeared to be on the plateau of the ER curve in the analysis, with the filgotinib 100 mg group being slightly lower than the curve plateau. For multiple secondary efficacy endpoints including ACR50, ACR70, DAS28 (CRP) [?] 3.2, and DAS28 (CRP) < 2.6, a trend of increasing response with increasing exposure was observed over the first 4 octiles (corresponding to 100 mg and lower doses) and a plateau was observed over the last 4 octiles (corresponding to 200 mg exposures). The analysis on Week 24 data showed similar findings to the Week 12 analysis (Figure 2).

Exposure-efficacy relationships were also evaluated by examining AUC_{eff} in subjects who achieved and who did not achieve ACR20/50/70 or DAS28 responses in Phase 2 and Phase 3 studies across all the doses. In Figure 3, AUC_{eff} overlapped between those who achieved (black) and those who did not achieve (gray) ACR20/50/70 or DAS28 responses, however, those who achieved responses had numerically higher median AUC_{eff} compared with those who did not achieve responses at both Week 12 and Week 24.

Overall, filgotinib exposure-efficacy analysis across the Phase 2 and Phase 3 program confirmed that filgotinib produced more robust therapeutic effects across the exposure range observed at 200 mg once daily compared to lower doses. This analysis supported 200 mg for most adult patients and 100 mg for special populations who may have elevated PK exposures [e.g. elder patients aged 75 years and older and patients with moderate to severe renal impairment (RI)].

Exposure-safety Analysis

The ER analyses for safety were based on the pooled population in Phase 2 and Phase 3 program and were performed separately for filgotinib and GS-829845 to characterize the individual safety profiles of each analyte.

The Most Frequent TEAEs

The 5 evaluated TEAEs were: nausea, nasopharyngitis, upper respiratory tract infection, headache, and hypertension. The Analysis Set for exposure-safety included pooled Phase 2 and Phase 3 subjects with RA who received filgotinib and had evaluable PopPK-based exposure estimates ($AUC_{0\text{-}24}$) (N = 2678 for filgotinib and N = 2707 for GS-829845). Data were not included in the analysis if they were collected after subjects were rerandomized and were switched to a different treatment group. As shown in Figure 4 (filgotinib) and Figure 5 (GS-829845), filgotinib or GS-829845 exposures ($AUC_{0\text{-}24}$) in subjects with RA were similar regardless of the presence (black) or absence (gray) of the evaluated TEAEs up to Week 52.

The Most Frequent Grade3/4 Laboratory Abnormalities

The 5 evaluated Grade 3/4 laboratory abnormalities included: glucose increase, lymphocyte decrease, phosphate decrease, lipase increase, and ALT increase. As shown in Figure 6 (filgotinib) and Figure 7 (GS-829845), filgotinib or GS-829845 exposures ($AUC_{0\text{-}24}$) were highly overlapping between subjects who experienced (black) and who did not experience (gray) the selected Grade 3/4 laboratory abnormalities up to Week 52.

Serious TEAEs and Serious Infections

Serious TEAEs and serious infections are also evaluated against the filgotinib and GS-829845 exposures and no exposure-driven patterns were present based on the safety data up to Week 52 (Supplementary Figure 1).

Overall, the exposure-safety relationships for either filgotinib and GS-829845 demonstrate no trend toward increasing incidence of common TEAEs, common laboratory abnormalities, serious TEAEs, or serious infections with increasing exposure.

Discussion

In the PopPK analysis, plasma concentrations were adequately described by the final models of filgotinib and GS-829845 separately and thus the predicted individual PK exposures were further used in the ER analyses. The final filgotinib model was able to adequately predict AUC_{tau} with geometric mean ratio (GMR) = 0.98, but it still had a tendency to modestly underpredict C_{max} (GMRs of 0.76-0.79 based on different populations). Various efforts were made to address this issue both on the structural (e.g., different absorption models, 2 vs 3-compartment models) and the stochastic model (e.g., separate IIV by sampling density or phase, skewed ETA distributions, IOV on absorption parameters and volume of distribution, full omega blocks, etc.). However, none of these additional modifications to the PopPK model resulted in further improvement of the C_{max}underprediction. Overall, the bias is acknowledged and taken into consideration when using model-derived exposures in the context of exposure-response analyses with particular attention to the use of C_{max}. In all, estimated filgotinib AUC_{tau} is adequate for the intended purpose to support exposure-response analyses in subjects with RA.

The pharmacokinetic-pharmacodynamic relationship of filgotinib was studied previously. Dose-dependent inhibition of the JAK1-related IL-6-induced pSTAT1 by filgotinib was demonstrated at doses of 50 mg of filgotinib and higher with maximum inhibition of pSTAT1 (˜78%) plateaued at or above 200 mg total daily dose and intermediate inhibition (˜47%) observed at a total daily dose of 100 mg [19].

Exposure-response analyses based on Phase 2 and Phase 3 clinical studies were further conducted to confirm the dose. Exposure-efficacy analyses consistently revealed high response rates (approximately 70%-80% for ACR20 at Week 12) across the exposure range for the filgotinib 200 mg doses. A trend of increasing response with increasing exposure was observed over the exposure range for multiple secondary efficacy endpoints including ACR50, ACR70, DAS28 (CRP) [?] 3.2, and DAS28 (CRP) $<$ 2.6, with a plateau in response corresponding to filgotinib 200 mg exposures (5^{th} to $95^{th}AUC_{eff}$ percentiles approximately 10,000 – 20,000 h[?]ng/mL). An analysis of those who achieved and those who did not achieve responses across dose groups demonstrated that subjects who achieved responses had numerically higher exposures, consistent with numerically higher response rates at the 200 mg dose versus the 100 mg dose observed in Phase 2 and Phase 3 studies. Exposure-safety relationships established that filgotinib and GS-829845 exposures ($AUC_{0\text{-}24}$) were similar regardless of the presence or absence of the most frequent TEAEs, the most frequent Grade 3/4 laboratory abnormalities, serious TEAEs, or serious infections, indicating no exposure-safety relationship.

This exposure-response analysis based on pooled data from Phase 2 and Phase 3 studies supported 200 mg for most adult patients and 100 mg for special populations who may have elevated PK exposures (e.g. elder patients aged 75 years and older and patients with moderate to severe RI). Filgotinib and its metabolite were shown to be moderately higher (1.45- and 1.33-fold, respectively) in the elderly subjects ([?]75 years) compared with younger subjects; in subjects with severe RI, filgotinib was 1.54 fold higher and 2.74 fold higher for the metabolite [15]. It is also suggested that modest changes in filgotinib and GS-829845 exposures due to the influence of other intrinsic/extrinsic factors, such as moderate hepatic impairment and food intake, are not clinically meaningful [20],[21].

Collectively, the ER analyses indicate robust therapeutic effects across the exposure range observed at 200 mg once daily in subjects with moderately to severely active RA. The trend towards greater efficacy with higher exposures observed for the primary and secondary endpoints [ACR20, ACR50, ACR70, DAS28 (CRP) [?] 3.2, and DAS28 (CRP) $<$ 2.6] and a lack of exposure-safety relationship based on the evaluated TEAEs and common laboratory abnormalities indicates an advantage to the 200 mg filgotinib dose relative to the 100 mg filgotinib dose for most adult patients.

Conclusions

Based on the exposure-efficacy analyses, exposures associated with 200 mg once daily filgotinib corresponded to numerically higher ACR responses compared with those associated with filgotinib 100 mg once daily or lower doses, showing a plateau over higher exposures corresponding to 200 mg for multiple efficacy endpoints [ACR20, ACR50, ACR70, DAS28 (CRP) [?] 3.2, and DAS28 (CRP) $<$ 2.6]. For the safety analyses, it was

shown that filgotinib was generally well tolerated with no exposure-dependent effects on the evaluated safety endpoints. Overall, the exposure-response analyses supported 200 mg once daily doses for commercialization.

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Declaration of Conflicting Interests :

A Meng, KA, CN, LN, SMC, BK, BB, and A Mathias are/were employees and shareholder of Gilead Sciences, Inc and FB, PC, and CC were under a work contract with Gilead Sciences, Inc when this research work was conducted.

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Figure Legends

Figure 1. Exposure-response relationship of AUCeff based on filgotinib and GS-829845 against ACR and DAS28 (CRP) responses at Week 12 in subjects with RA in pooled Phase 2 and Phase 3 studies. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies DARWIN 1, DARWIN 2, FINCH 1, FINCH 2, and FINCH 3, and had at least 1 nonmissing PK parameter of interest. Each symbol represents the proportion of subjects achieving the ACR response with the vertical line showing the 95% confidence interval within each group based on the Clopper-Pearson method. Circles show ACR20, triangles show ACR50, and squares show ACR70 in the left panel. Hollow circles show DAS28 [?] 3.2 and hollow triangles show DAS28 < 2.6 in the right panel. Shaded areas with blue stripes show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUCeff

for filgotinib 200 mg once daily in Phase 2 and Phase 3 subjects with RA; shaded areas with pink cross pattern show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUCeff for filgotinib 100 mg once daily in Phase 2 and Phase 3 subjects with RA. AUCeff is based on the population PK-predicted exposure in Phase 2 and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

Figure 2. Exposure-response relationship of AUCeff based on filgotinib and GS-829845 against ACR and das28 (CRP) responses at Week 24 in subjects with RA in pooled Phase 2 and Phase 3 studies. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies DARWIN 1, DARWIN 2, FINCH 1, FINCH 2, and FINCH 3, and had at least 1 nonmissing PK parameter of interest. Each symbol represents the proportion of subjects achieving the ACR response with the vertical line showing the 95% confidence interval within each group based on the Clopper-Pearson method. Circles show ACR20, triangles show ACR50, and squares show ACR70 in the left panel. Hollow circles show DAS28 [?] 3.2 and hollow triangles show DAS28 $<$ 2.6 in the right panel. Shaded areas with blue stripes show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUCeff for filgotinib 200 mg once daily in Phase 2 and Phase 3 subjects with RA; shaded areas with pink cross pattern show median (dashed vertical line) and fifth and 95th percentiles (dotted vertical lines) of AUC_{eff} for filgotinib 100 mg once daily in Phase 2 and Phase 3 subjects with RA. AUC_{eff} is based on the population PK-predicted exposure in Phase 2 and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

Figure 3. Boxplot of AUC_{eff} in subjects who achieved and did not achieve ACR20/50/70 and DAS28 (CRP) responses in pooled Phase 2 and Phase 3 studies. PK/PD analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies FINCH 1, 2, 3, and had at least 1 nonmissing PK parameter of interest. For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 x the interquartile range) are displayed as small squares. ACR and DAS28 responses at Week 12 are shown in the upper panel and ACR and DAS28 responses at Week 24 are shown in the lower panel.

Figure 4. Filgotinib $AUC_{0\text{-}24}$ by the 5 most frequent TEAEs in subjects with RA up to Week 52 data. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies FINCH 1, FINCH 2 FINCH 3, DARWIN 1, DARWIN 2, DARWIN 3, and had at least 1 nonmissing PK parameter of interest. For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 x the interquartile range) are displayed as small squares. $AUC_{0\text{-}24}$ is the population PK-predicted exposure in Phase 2and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

Figure 5. GS-829845 $AUC_{0\text{-}24}$ by the 5 most frequent TEAEs in subjects with RA up to Week 52 data. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies FINCH 1, FINCH 2 FINCH 3, DARWIN 1, DARWIN 2, DARWIN 3, and had at least 1 nonmissing PK parameter of interest. For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 x the interquartile range) are displayed as small squares. $AUC_{0\text{-}24}$ is the population PK-predicted exposure in Phase 2and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

Figure 6. Filgotinib $AUC_{0\text{-}24}$ by the 5 most frequent Grade 3/4 laboratory abnormalities in subjects with RA. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies FINCH 1, FINCH 2 FINCH 3, DARWIN 1, DARWIN 2, DARWIN 3 and had at least 1 nonmissing PK parameter of interest. For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 x the interquartile range) are displayed as small squares. $AUC_{0\text{-}24}$ is the population PK-predicted exposure in Phase 2 and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

Figure 7.GS-829845 $AUC_{0\text{-}24}$ by the 5 most frequent Grade 3/4 laboratory abnormalities in subjects with RA. The analysis set includes subjects with RA who were enrolled/randomized, received at least 1 dose of filgotinib in studies FINCH 1, FINCH 2 FINCH 3, DARWIN 1, DARWIN 2, DARWIN 3, and had at least 1 nonmissing PK parameter of interest. For each box, the bottom and top edges are located at the sample 25th (Q1) and 75th (Q3) percentiles, respectively; the center horizontal line is drawn at the 50th percentile (median); and outliners (beyond 1.5 x the interquartile range) are displayed as small squares. $AUC_{0\text{-}24}$ is the population PK-predicted exposure in Phase 2 and Phase 3 subjects with rheumatoid arthritis receiving filgotinib.

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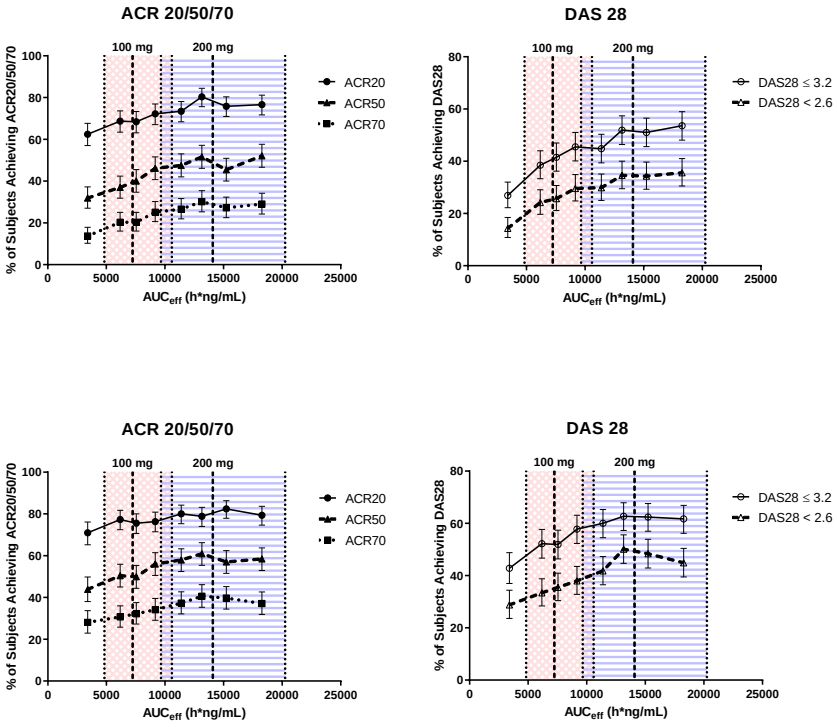
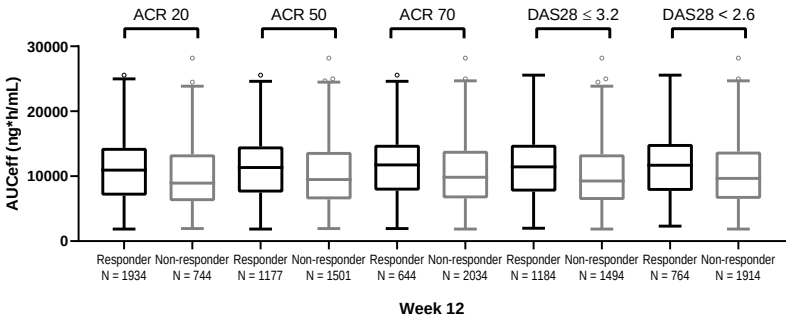
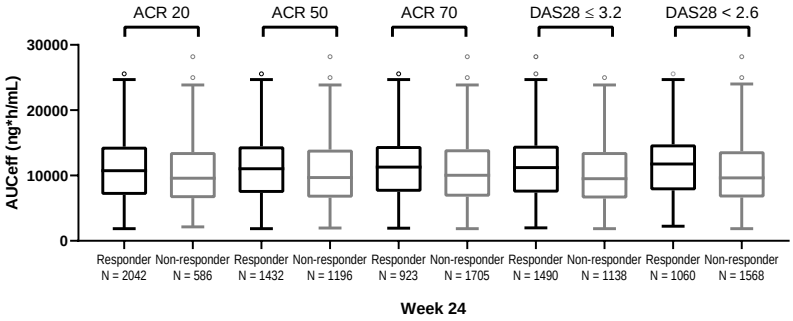




Week 12



Week 24