Effects of Baricitinib on Lipid, Apolipoprotein, and Lipoprotein Particle Profiles in a Phase 2b Study in Patients with Active Rheumatoid Arthritis

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ABSTRACT

Objective

To assess the effects of baricitinib on lipid profile in patients with moderate-to-severe rheumatoid arthritis.

Methods

Once-daily baricitinib (1, 2, 4, or 8-mg) or placebo was studied in 301 randomized patients. Changes in lipid profile, particle size, and number were assessed at weeks 12/24; associations with clinical efficacy were evaluated. Apolipoproteins were assessed at weeks 4/12 for the placebo, and 4- and 8-mg baricitinib groups.

Results

Baricitinib treatment resulted in dose-dependent increases by week 12 in serum lipids (low-density lipoprotein cholesterol [LDL-C]: 3.4 mg/dL increase from baseline to week 12 (1-mg) to 11.8 mg/dL (8-mg); high-density lipoprotein cholesterol [HDL-C]: 3.3 mg/dL (1-mg) to 8.1 mg/dL (8-mg); triglycerides: 6.4 mg/dL (1-mg) to 15.4 mg/dL (8-mg) baricitinib). Group-wise mean increases in LDL-C were coincident with mean increases in large LDL particles and mean reductions in small dense LDL particles. Increases from baseline to week 12 in apolipoprotein A-I, B, and total CIII were observed with 4-mg (9.5%, 6.8%, and 23.0%, respectively) and 8-mg (12.2%, 7.1%, and 19.7%, respectively) baricitinib

with no increase in LDL-associated CIII (4-mg: -4.5%; 8-mg: -9.0). Baricitinib reduced HDL-associated serum amyloid A at 4-mg (-36.0%) and 8-mg (-32.0%); a significant reduction in lipoprotein (a) was observed only with 8-mg (-16.6%). Increased HDL cholesterol at week 12 correlated with improved Disease Activity Scores and Simplified Disease Activity Index; changes in total cholesterol, LDL cholesterol, and triglycerides did not reveal a similar relationship.

Conclusion

Baricitinib-associated increases in serum lipids were observed. HDL-C increases correlated with improved clinical outcomes.

Keywords: Rheumatoid arthritis, baricitinib, lipids, HDL, LDL, atherosclerosis

Activation of proinflammatory cytokine pathways contributes to the pathogenesis of rheumatoid arthritis (RA) [1, 2]. Several of these cytokines, including interleukin-6 (IL-6), granulocyte-macrophage colony stimulating factor, IL-23, the IL-2 cytokine family and type 1 and type 2 interferons, utilize the Janus kinase (JAK) intracellular signaling pathway [3]. Accordingly, the development of various inhibitors, each having differing degrees of specificity toward the 4 identified JAKs (JAK1, JAK2, JAK3, TYK2), has been intensively investigated for the treatment of RA [4].

Baricitinib, formerly LY3009104 (INCB028050), is an oral, potent, selective, and reversible inhibitor of JAK1 (IC50 = 5.9 nM) and JAK2 (IC50 = 5.7 nM), with much less activity against TYK2 (IC50 = 53 nM) and JAK3 (IC50 > 400 nM), and inhibits proinflammatory cytokine signaling implicated in RA [5]. In a phase 2b, double-blind, randomized, placebo-controlled study in patients with moderate-to-severe RA, despite treatment with methotrexate and other conventional disease-modifying antirheumatic drugs (DMARDs), significantly more patients in the combined baricitinib 4- and 8-mg groups compared to placebo achieved the primary endpoint of an American College of Rheumatology 20 (ACR20) response at week 12. Baricitinib rapidly improved the signs and symptoms of RA with an acceptable risk profile consistent with what has previously been described [6].

Increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) have been observed in studies with JAK inhibitors [7], with the IL-6 receptor monoclonal antibody tocilizumab [8], and less consistently with anti-tumor necrosis factor (TNF) therapies [9], and with methotrexate in various RA clinical trials [10]. An understanding of the basis for increases in LDL-C is important because low density lipoprotein (LDL) represents a heterogeneous collection of apolipoprotein B-containing particles that transport cholesterol [11]. In addition, the behavior of these different sized particles has implications for particle clearance and atherogenicity [12]. Increases in LDL particle number, particularly small LDL particles, have been associated with an increased risk of cardiovascular events [13]. Here, we assess changes in lipid profile and lipoprotein particle size and number through 24 weeks and apolipoprotein content through 12 weeks in patients with RA. In addition, the relationships between lipid parameters and measures of clinical efficacy were investigated at 12 weeks.

PATIENTS AND METHODS

Patients and study design

Eligible patients met the inclusion criteria for the phase 2b randomized, double-blind, placebo-controlled study as previously described [6]. Qualifying patients (n

= 301) were randomly assigned in a 2:1:1:1:1 ratio to once daily doses of placebo or baricitinib 1, 2, 4, or 8 mg, respectively. Patients initially assigned to baricitinib 2, 4, and 8 mg remained on the same blinded treatment for an additional 12 weeks [6].

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 institutional review board or ethics committee for each center. All patients provided written informed consent. The study (NCT01185353) was designed by the sponsor, Eli Lilly and Company, and Incyte Corporation with input obtained from an academic advisory board in which the non-Lilly authors of this manuscript participated. All authors participated in the preparation and review of this manuscript and approved of the final version.

Extended lipid profile

Serum samples were collected at baseline and at weeks 2, 4, 8, 12, 14, 16, 20, and 24 after randomization for conventional lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides). Fasting serum samples were collected at baseline and weeks 12 and 24 for determination of lipoprotein particle subfractions by nuclear magnetic resonance spectroscopy (NMR; LipoScience, Raleigh, NC) [12]. Diameter ranges (nm) for LDL-C were 21.2–23 for large LDL and 18–21.2 for small LDL; ranges for HDL-C were 8.8–13 for large high density lipoprotein

(HDL), 8.2–8.8 for medium HDL and 7.3–8.2 for small HDL [12]. LDL-C was calculated using the Friedewald equation. For apolipoprotein levels as well as LDL-associated apolipoprotein CIII and HDL-associated serum amyloid A (SAA), serum samples were analyzed from the placebo and 4- and 8-mg baricitinib groups at baseline and weeks 4 and 12. Apolipoprotein A-I, apolipoprotein B, apolipoprotein CIII (LDL-associated and total), and lipoprotein (a) (Lp[a]), as well as HDL-associated SAA were quantified using conventional ELISAs (Pacific Biomarkers, Seattle, WA).

The standard cholesterol panel (LDL-C, HDL-C, triglycerides, and total cholesterol) as well as the NMR panel (lipoprotein subfractions) were planned as part of the original study protocol. Assessments at baseline, week 12, and week 24 were planned to assess the effects of the various doses of baricitinib, relative to placebo or to each other, at the end of each study period. Assessments were conducted in a fasting state so as to not be affected by relative timing in relation to meals, as patient visits could be scheduled throughout the day. The specialized lipid panel (apolipoprotein B, apolipoprotein A1, LDL w/apolipoprotein CIII, and HDL-serum amyloid A) was analyzed from stored samples collected during the course of the trial. Because the 4-mg and 8-mg doses of baricitinib were carried into the long-term extension of this study, analysis was limited to patients from

those dose groups. In addition to baseline and week 12, week 4 was selected to understand the kinetics of any observed changes in this specialized panel.

Statistical methodology

Conventional lipid profile, as well as lipoprotein particle size and number assessed by NMR, were summarized by mean changes from baseline and compared for each treatment group to placebo by the *t* test. Within-group changes from baseline values were analyzed with the one-sample *t* test. Apolipoprotein values were summarized by median percent changes from baseline and compared for each treatment group to placebo using the Wilcoxon Mann-Whitney test. Within-group changes from baseline values were analyzed with the Wilcoxon signed-rank test. The strengths of linear associations between lipids and inflammatory markers (high sensitivity C-reactive protein [hsCRP]) and various RA disease improvement and activity measures (28-joint Disease Activity Score [DAS28], Simplified Disease Activity Index [SDAI], and Clinical Disease Activity Index [CDAI]) were assessed through correlations. The Pearson correlation coefficient was used for the relationship with hsCRP and the Pearson and partial correlation coefficients were used within and across treatment groups, respectively, for the relationships with disease activity measures, including tests for increasing or decreasing strength of linear relationship between lipid changes and disease activity measures. For analyses at a given time point, only patients

with data at that time point were included; no missing data imputation was performed.

RESULTS

Demographics and baseline clinical characteristics for the treatment groups were generally comparable [6]. The study's patient population was 74% Caucasian, 83% female, with mean age 51 years and mean duration of disease 5.6 years; 49% of the patients were taking steroids at a mean dose of 6 mg/day. Mean baseline DAS28-CRP was 5.5, with approximately 70% of patients seropositive by rheumatoid factor or anti-citrullinated protein antibodies. Increases in LDL-C, HDL-C, triglycerides, and total cholesterol were observed with baricitinib treatment as early as week 2 and were dose dependent over time. LDL-C increased 3.4, 8.0, 9.5, and 11.8 mg/dL for 1, 2, 4, and 8 mg baricitinib, respectively, from baseline to week 12; HDL-C increased 3.3, 3.0, 7.3, and 8.1 mg/dL, respectively; and triglycerides increased 6.4, 15.3, 8.5 and 15.4 mg/dL, respectively) (Figure 1, Supplementary Table 1). There were no changes in the HDL-C/LDL-C ratio at 12 or 24 weeks at any of the baricitinib doses (Supplementary Table 1). With the exception of patients in the 8-mg baricitinib group at 12 weeks, patients receiving concomitant treatment with a HMG-CoA reductase inhibitor (statin) during the study did not have a significant increase in

LDL-C compared with placebo at 12 or 24 weeks (Supplementary Table 2) though the sample size was small (N=31).

NMR lipoprotein profile demonstrated that the mean increase in LDL-C with baricitinib treatment was coincident with an increase in the total number of large LDL and a decrease in the small dense LDL particles (Table 1). Large LDL particles significantly increased at week 12 for all baricitinib treatment groups versus placebo and at week 24 for the 2-mg group (within treatment). Compared with baseline, very small and medium small LDL particles were significantly reduced at 24 weeks in the 4- and 8-mg baricitinib groups (within treatment) (Table 2). As a result, the total LDL particle number did not change with baricitinib treatment. The mean increase in HDL-C with baricitinib treatment was accompanied by a mean increase in total HDL particle number, which was significant in the 4- and 8-mg groups at week 12 (versus placebo and within treatment) and week 24 (within treatment) (Table 1). The increase in total HDL particle number was accounted for by increases in all HDL particles (large, medium, and small). Finally, the observed mean increase in triglycerides was also coincident with a mean increase in total very low-density lipoproteins (VLDL) particle number (Table 1).

Consistent with LDL-C and HDL-C results, increases in apolipoprotein B and apolipoprotein A-I were observed as early as 4 weeks in patients in the 4- and 8-

mg baricitinib groups (Table 2). With the exception of the 8-mg baricitinib group at week 4, decreases in the apolipoprotein B/apolipoprotein A-I ratio were not significant compared to placebo. A significant increase was observed in total apolipoprotein CIII at weeks 4 and 12 in the 8-mg baricitinib group (versus placebo and within treatment) and at 12 weeks in the 4 mg baricitinib group (versus placebo and within treatment). However, no changes were observed in the amount of apolipoprotein CIII associated with LDL. There were significant reductions in HDL-associated SAA at weeks 4 and 12 in the baricitinib 4- and 8-mg dose groups (versus placebo and within treatment). Finally, a significant reduction in Lp(a) was only observed in the 8-mg treatment group at week 4 (within treatment and versus placebo) and week 12 (within treatment).

Changes in hsCRP with baricitinib through 12 weeks have been previously reported (placebo: -0.4, 1 mg: -3.3, 2 mg: -0.8, 4 mg: -2.0, and 8 mg: -3.0) [6]; in this secondary analysis, change in HDL-C demonstrated an inverse correlation with changes in hsCRP ($r = -0.37$, $p < 0.0001$) among patients treated with baricitinib. In contrast, LDL-C changes with baricitinib did not correlate with changes in hsCRP ($r = -0.02$, $p = 0.7291$; Supplementary Figure 1). Further correlation analyses with disease activity measures revealed a dose-dependent relationship between change from baseline in HDL-C and change from baseline to week 12 in DAS28-CRP ($p<0.001$ with $p=0.005$ for the dose-response test) as well as with DAS28- erythrocyte sedimentation rate (ESR) ($p=0.004$ with

p=0.019 for the dose-response test) and SDAI (p=0.022 with p=0.003 for the dose-response test), with no apparent relationship observed for placebo and correlations increasing in magnitude as the dose of baricitinib was increased over the 4 studied doses (Table 3). In patients treated with baricitinib, increases in HDL-C were significantly correlated with an improvement in the DAS28-CRP score (all baricitinib: $r = -0.28$, $p < 0.001$; Figure 2, Supplementary Figure 2). Correlations were -0.05, -0.28, -0.14, and -0.55 following treatment with 1, 2, 4, or 8 mg, respectively. In patients treated with placebo, no relationship between HDL-C and DAS28-CRP was apparent ($r = -0.05$, $p = 0.648$). A similar correlation analysis with total cholesterol, LDL-C, and triglycerides with disease activity measures revealed no relationships with total cholesterol and LDL-C (Table 3). Triglycerides were found to have a positive correlation with CDAI ($r = 0.13$, $p = 0.031$) in absolute CDAI score and change from baseline, but not with DAS28 or SDAI (Table 3).

DISCUSSION

Increases in LDL-C, HDL-C, and triglycerides were observed following 2 weeks of baricitinib treatment and persisted through 24 weeks. The increase in LDL-C after treatment with baricitinib was associated with a shift in LDL particle distribution as shown by NMR. It is well established that increased total number

of LDL and small dense LDL particles are both directly associated with incident coronary heart disease (CHD) [14, 15]. However, baricitinib, in the present study, did not increase the total LDL particle number and in fact decreased the number of small dense LDL particles. These results would suggest that the shift in LDL particle size to large LDL is most likely responsible for the increase in LDL-C observed.

In contrast, the increase in HDL-C with baricitinib treatment was concurrent with an increase in the total number of HDL particles, which was mostly due to medium HDL but also all other (large and small) HDL particles. Besides the well-established inverse association of HDL-C with CHD [16], the total number of HDL particles has also been shown to be inversely associated with carotid intima-media thickness and incident CHD, independent of atherogenic lipoproteins (including total number of LDL particles) and HDL-C in the Multi-Ethnic Study of Atherosclerosis [17]. Consistent with the increase in HDL particle number, baricitinib treatment resulted in an increase in apolipoprotein A-I and a reduction in SAA content on the HDL particles. Because SAA negatively impacts HDL function by reducing the ability of these particles to mediate cholesterol efflux [18], a reduction in SAA per HDL particle would likely render these particles more efficient for reverse cholesterol transport [19]. Similar results have also been reported with anti-TNF treatments [20], with tofacitinib [7], and with tocilizumab [21].

The NMR lipoprotein profile also showed no change in intermediate density lipoprotein particles, but an increase in the total number of VLDL particles, which is most likely accountable for the increase in triglyceride levels. Increases in apolipoprotein B and apolipoprotein CIII were also observed with baricitinib treatment. Although TNF inhibitors also increase apolipoprotein B in conjunction with increases in LDL-C [20], their use is associated with a decreased incidence of cardiovascular events [22]. The increases in apolipoprotein B and apolipoprotein CIII in the present study are consistent with the increase observed in VLDL particle number and serum triglycerides. Finally, a reduction in Lp(a) was also observed at 4 (within treatment and compared to placebo) and 12 weeks (within treatment only) in patients treated with 8 mg, but not 4 mg, of baricitinib.

Here we also show that baricitinib-treated patients exhibited a correlation between the increase in HDL-C and change from baseline to week 12 in DAS28-CRP. The increase in HDL-C also correlated with change from baseline to week 12 in DAS28-ESR and SDAI. This association provides additional support for a potential causal relationship between the increase in HDL-C and the reduction in inflammation and disease score. Significant dose-response relationships were identified in the correlation analyses with HDL-C, suggesting that the relationship between HDL-C and disease activity measures became greater in magnitude as a function of the baricitinib dose. The lack of a similar correlation between these disease activity scores and the increases in LDL-C and total cholesterol suggest

the possibility of different mechanisms to explain the increase in HDL-C versus LDL-C. Furthermore, although a positive correlation was observed between triglycerides and CDAI, a similar relationship was not observed with other disease activity scores.

There were some limitations in this study. This study restricted enrollment to the anti-TNF/biologic-naïve population on background methotrexate, thus limiting interpretation to this patient subset. Although the increase noted in LDL-C was not observed in a subgroup of baricitinib-treated patients (n=31) who were receiving a statin at any time during the study, the number of patients receiving statins varied across treatment groups, and no attempt was made to evaluate the effects of statin initiation or dosage on the lipid profile of baricitinib-treated patients. To this extent it is noted that, by chance, a higher percentage of patients in the baricitinib 4 and 8 mg arms were on concomitant statins than the lower baricitinib doses. Therefore, it is possible that the increases in total cholesterol in these two higher doses would have been higher than the lower doses as suggested in the subset analysis of the non-statin versus statin users (Supplementary Table 2). However, caution in interpretation of this subgroup analysis is appropriate due to the small sample size per treatment arm once non-statin and statin users are subdivided. In addition, the use of other lipid-lowering medications was not restricted; however, the initiation of new medications and/or treatments during the course of the study was prohibited unless required to treat an adverse event or

ongoing medical condition. The placebo-controlled period was limited to 12 weeks duration for ethical concerns of continuing placebo in patients with active RA. Evaluation of the changes in lipid profile and lipoprotein particle size and number was limited to 24 weeks with a total enrollment of 301 patients based on the phase 2 dose-ranging study design. Lastly, as with any post hoc analyses and especially with evaluations in small subgroups, the number of statistical comparisons performed without control of the type I error rate may lead to some spurious findings.

The results in this study are most consistent with those reported in tocilizumab-treated patients in whom increases in total cholesterol, LDL-C, HDL-C, and triglycerides and reductions in HDL-associated SAA and Lp(a) have been reported [8]. These similarities suggest the possibility that the inhibition of IL-6 signaling may explain, in part, the mechanism(s) by which baricitinib modulates lipoprotein particle distribution and metabolism. Treatment with the JAK inhibitor tofacitinib has resulted in increases in LDL-C, HDL-C, and total cholesterol, as well as in triglycerides with increases in HDL particle number and LDL particle size similarly observed by NMR [7]. This same study also reported that tofacitinib decreased the fractional catabolic rate for cholesterol esters, which in part may explain the similar qualitative changes observed in the current study in serum lipids. The current study reports a series of changes in lipid particle size and apolipoproteins in patients with RA receiving treatment with baricitinib.

Longer-term observational studies tracking actual cardiovascular events and lipid changes on baricitinib will be needed before the clinical impact of the lipid changes described can be better understood.

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Table 1. Lipoprotein Particle Subfractions (Mean ± SD)

		Baricitinib			
	Placebo	**1 mg QD**	**2 mg QD**	**4 mg QD**	**8 mg QD**
	N = 98	**N = 49**	**N = 52**	**N = 52**	**N = 50**
Total LDL particles (nmol/L)					
Baseline	1251 ± 385	1269 ± 474	1324 ± 504	1319 ± 373	1285 ± 397
Week 12	1191 ± 374	1243 ± 441	1275 ± 512	1306 ± 404	1248 ± 414
Week 24	--	--	1309 ± 474	1233 ± 422	1270 ± 429
Mean change from baseline at week 12	-80 ± 280†	-55 ± 307	-56 ± 294	-4 ± 287	-35 ± 303
Mean change from baseline at week 24	--	--	-18 ± 344	-69 ± 301	-67 ± 366
Large LDL (nmol/L)					
Baseline	521 ± 293	463 ± 283	476 ± 207	512 ± 242	490 ± 234
Week 12	507 ± 226	494 ± 293	536 ± 265	564 ± 271	555 ± 284
Week 24	--	--	568 ± 302	544 ± 262	581 ± 251
Mean change from baseline at week 12	-29 ± 200	45 ± 193*	61 ± 168†,*	56 ± 163†,*	61 ± 250*
Mean change from baseline at week 24	--	--	88 ± 212†	42 ± 220	69 ± 229
Small LDL (nmol/L)					
Baseline	693 ± 425	765 ± 552	801 ± 501	771 ± 397	754 ± 451
Week 12	648 ± 416	706 ± 536	690 ± 527	700 ± 514	645 ± 490

Week 24			697 ± 502	640 ± 507	642 ± 494
Mean change from baseline at week 12	-50 ± 257	-99 ± 311†	-119 ± 268†	-64 ± 302	-103 ± 410
Mean change from baseline at week 24			-103 ± 397	-123 ± 337†	-139 ± 433†
Medium Small LDL (nmol/L)					
Baseline	146 ± 88	159 ± 114	163 ± 101	158 ± 85	157 ± 93
Week 12	136 ± 85	147 ± 115	143 ± 111	145 ± 102	134 ± 100
Week 24			146 ± 106	131 ± 99	129 ± 96
Mean change from baseline at week 12	-10 ± 56	-20 ± 66	-21 ± 57†	-12 ± 61	-22 ± 82
Mean change from baseline at week 24			-17 ± 84	-27 ± 66†	-33 ± 89†
Very small LDL (nmol/L)					
Baseline	546 ± 339	607 ± 439	638 ± 403	613 ± 314	597 ± 360
Week 12	512 ± 333	559 ± 422	547 ± 418	555 ± 413	511 ± 392
Week 24	--	--	551 ± 396	509 ± 409	512 ± 398
Mean change from baseline at week 12	-39 ± 208	-79 ± 250†	-97 ± 217†	-52 ± 244	-81 ± 330
Mean change from baseline at week 24	--	--	-86 ± 317	-96 ± 275†	-106 ± 348†
Total HDL particles (µmol/l)					
Baseline	32 ± 6	33 ± 7	32 ± 8	33 ± 7	31 ± 8

Week 12	32 ± 7	34 ± 7	33 ± 8	38 ± 8	36 ± 9
Week 24	--	--	35 ± 7	37 ± 8	37 ± 7
Mean change from baseline at week 12	1 ± 6	2 ± 6	1 ± 6	4 ± 6††,*	4 ± 6††,**
Mean change from baseline at week 24	--	--	2 ± 6†	3 ± 5††	5 ± 6††
Large HDL (µmol/L)					
Baseline	10 ± 4	10 ± 5	10 ± 4	9 ± 3	9 ± 4
Week 12	11 ± 4	10 ± 5	10 ± 5	10 ± 5	11 ± 5
Week 24			10 ± 4	10 ± 4	11 ± 5
Mean change from baseline at week 12	0	1†	0	1†	1†
Mean change from baseline at week 24			1†	1	1†
Medium HDL (µmol/L)					
Baseline	4 ± 4	4 ± 5	4 ± 4	3 ± 3	4 ± 5
Week 12	3 ± 3	4 ± 3	5 ± 7	4 ± 5	5 ± 7
Week 24	--	--	5 ± 5	4 ± 4	6 ± 6
Mean change from baseline at week 12	-1 ± 3	-1 ± 4	1 ± 5*	2 ± 5†,*	1 ± 4*
Mean change from baseline at week 24	--	--	1 ± 3†	1 ± 3†	1 ± 5
Small HDL (µmol/L)					

Baseline	18 ± 7	19 ± 5	19 ± 7	22 ± 6	18 ± 7
Week 12	19 ± 7	21 ± 6	19 ± 6	23 ± 7	20 ± 6
Week 24			19 ± 7	23 ± 7	20 ± 6
Mean change from baseline at week 12	1 ± 5	2 ± 4†	-1 ± 5	1 ± 6	2 ± 5†
Mean change from baseline at week 24			0 ± 5	2 ± 6	2 ± 7†
IDL (nmol/L)					
Baseline	37 ± 40	40 ± 52	46 ± 58	37 ± 34	41 ± 50
Week 12	36 ± 42	43 ± 63	48 ± 69	42 ± 45	48 ± 58
Week 24			43 ± 51	48 ± 53	48 ± 58
Mean change from baseline at week 12	-1 ± 39	-1 ± 47	1 ± 53	4 ± 46	7 ± 45
Mean change from baseline at week 24			-4 ± 54	12 ± 49	3 ± 55
Total VLDL (nmol/L)					
Baseline	62 ± 40	73 ± 49	63 ± 41	60 ± 28	58 ± 34
Week 12	55 ± 32	81 ± 58	70 ± 48	72 ± 37	69 ± 46
Week 24	--	--	72 ± 36	76 ± 38	73 ± 46
Mean change from baseline at week 12	-7 ± 27†	5 ± 31*	6 ± 33*	12 ± 28†,**	12 ± 38†,*
Mean change from baseline at week 24	--	--	8 ± 31	15 ± 35†	13 ± 38†

Medium VLDL (nmol/L)					
Baseline	25 ± 24	32 ± 28	26 ± 26	20 ± 17	23 ± 22
Week 12	21 ± 16	41 ± 37	31 ± 40	28 ± 23	28 ± 25
Week 24			29 ± 24	30 ± 24	28 ± 28
Mean change from baseline at week 12	-3 ± 19	8 ± 22†,*	5 ± 25*	8 ± 21†,*	5 ± 26*
Mean change from baseline at week 24			4 ± 20	8 ± 25†	4 ± 24
Small VLDL (nmol/L)					
Baseline	35 ± 19	38 ± 23	35 ± 18	36 ± 17	32 ± 15
Week 12	32 ± 20	36 ± 23	35 ± 20	39 ± 19	37 ± 22
Week 24			39 ± 16	43 ± 20	42 ± 23
Mean change from baseline at week 12	-4 ± 15†	-3 ± 20	1 ± 20	3 ± 18*	5 ± 18†,*
Mean change from baseline at week 24			4 ± 16	7 ± 18†	9 ± 21†

SD – standard deviation; QD – once-daily; LDL - low-density lipoprotein; HDL- high-density lipoprotein; IDL- intermediate density lipoprotein; VLDL- very low density lipoprotein.

†$p<0.05$ (within treatment)

††$p<0.001$ (within treatment)

*$p<0.05$ vs. placebo

**$p<0.001$ vs. placebo

Table 2. Percent Change from Baseline in Apolipoprotein Results

		Baricitinib	
	Placebo	**4 mg QD**	**8 mg QD**
	N = 96	**N = 52**	**N = 50**
Apolipoprotein A-I (mg/dL)			
Baseline	184.0 ± 5.5	188.0 ± 10	178.5 ± 8.5
Percent change from baseline at week 4	-1.9 ± 3.0	5.1 ± 4.1†,*	11.6 ± 3.9††,**
Percent change from baseline at week 12	1.1 ± 2.5	9.5 ± 3.8†,*	12.2 ± 3.0††,*
Apolipoprotein B (mg/dL)			
Baseline	105.0 ± 3	110.5 ± 6.5	100.0 ± 6.5
Percent change from baseline at week 4	-4.5 ± 2.6†	3.6 ± 2.44*	0.85 ± 3*
Percent change from baseline at week 12	-4.5 ± 0.93†	6.8 ± 3.55*	7.14 ± 3.83*
Apolipoprotein B/ Apolipoprotein A-I Ratio (mg/dL)			
Baseline	0.6 ± 0.03	0.6 ± 0.03	0.6 ± 0.03
Percent change from baseline at week 4	-3.4 ± 2.5†	-2.69 ± 3.0	-9.8 ± 5.3*
Percent change from baseline at week 12	-6.6 ± 2.7†	-5.33 ± 2.7	-4.9 ± 6.2
Apolipoprotein CIII (mg/dL)			

Baseline	8.3 ± 0.4	7.6 ± 0.65	7.4 ± 0.6
Percent change from baseline at week 4	-4.2 ± 4.3	17.0 ± 13.0	22.3 ± 10.5††,*
Percent change from baseline at week 12	-8.9 ± 4.3	23.0 ± 6.9†,*	19.7 ± 3.8††,**
LDL-Associated Apolipoprotein CIII (mg/dL)			
Baseline	1.1 ± 0.08	1.2 ± 0.17	1.2 ± 0.12
Percent change from baseline at week 4	-20.8 ± 14.8	-4.7 ± 18.7	-1.3 ± 18.1
Percent change from baseline at week 12	0 ± 8.3	-4.5 ± 10.8	-9.0 ± 18.9
HDL-Associated Serum Amyloid A (mg/L)			
Baseline	5.7 ± 0.6	6.4 ± 0.9	11.1 ± 3.5
Percent change from baseline at week 4	12.0 ± 14.3	-51.3 ± 5.3††,**	-50.2 ± 7.5†,**
Percent change from baseline at week 12	11.3 ± 6.5	-36.0 ± 3.5†,*	-32.0 ± 16.1†,*
Lipoprotein (a) (mg/dL)			
Baseline	8.4 ± 1.5	10.7 ± 3.0	11.1 ± 2.3
Percent change from baseline at week 4	0.7 ± 5.4	2.53 ± 7.4	-8.1 ± 6.5†,*
Percent change from baseline at week 12	-2.4 ± 3.9	-4.62 ± 4.5	-16.6 ± 2.6†

QD – once-daily; LDL - low density lipoprotein; HDL- high density lipoprotein; SE - standard error.

Data are median ± SE due to skewed distribution.

†p<0.05 (within treatment)

††p<0.001 (within treatment)

*p<0.05 vs. placebo

**p<0.001 vs. placebo

Table 3. Correlation Analysis Between Lipid Changes and Changes from Baseline to Week 12 in Clinical Endpoints

Clinical Endpoint	HDL-C		LDL-C		Triglycerides		Total Cholesterol	
	r[§]	p-value	r[§]	p-value	r[§]	p-value	r[§]	p-value
DAS28-CRP	-0.23	<0.001	0.02	0.806	0.07	0.234	-0.03	0.572
DAS28-ESR	-0.17	0.004	0.09	0.143	0.07	0.273	0.05	0.419
SDAI	-0.14	0.022	0.00	0.980	0.12	0.059	0.00	0.984
CDAI	-0.08	0.185	0.01	0.921	0.13	0.031	0.03	0.590

DAS28 - Disease Activity Score based on 28-joint assessment; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; SDAI - Simplified Disease Activity Index; CDAI - Clinical Disease Activity Index; HDL-C - high-density lipoprotein cholesterol; LDL-C - low-density lipoprotein cholesterol.

[§]r-values shown are the Pearson partial correlation (with associated p-value)

Figure Legends

Figure 1. Dose and time-dependent changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides relative to placebo over 24 weeks, with values obtained at baseline, week 12, and week 24 in a fasting state. QD – once-daily.

Only patients in 2, 4, and 8 mg treatment groups continued treatment for an additional 12 weeks.
Mean change from baseline analysis:

*p<0.05 vs. placebo

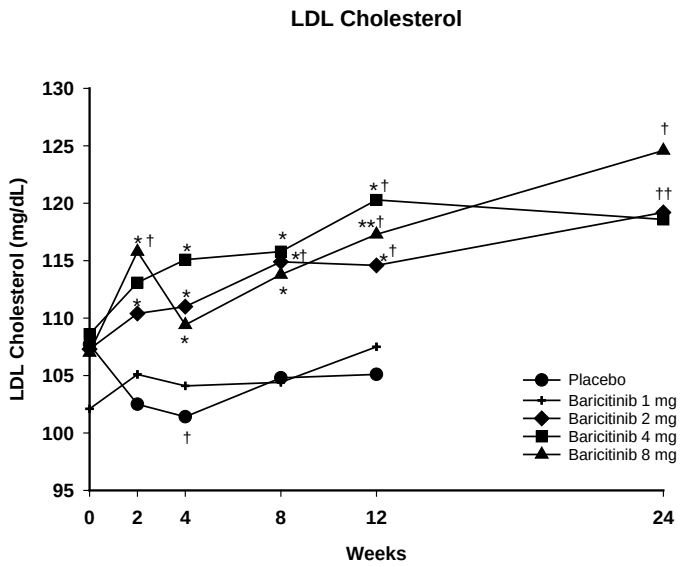
**p<0.001 vs. placebo

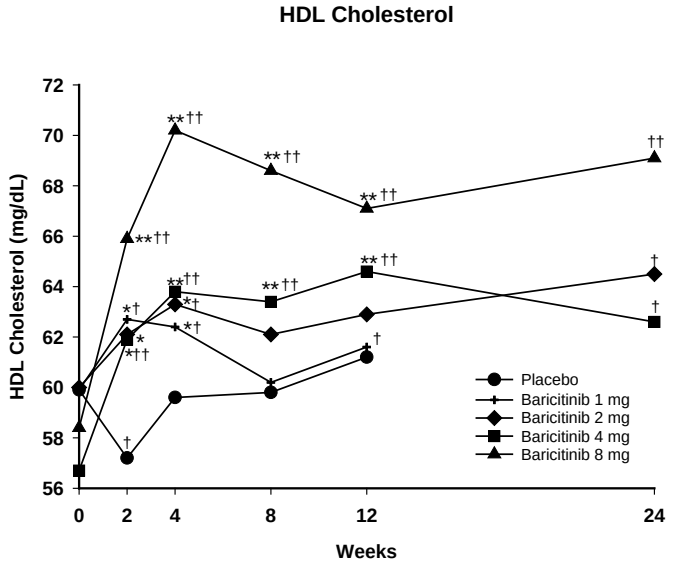
†p<0.05 (within treatment)

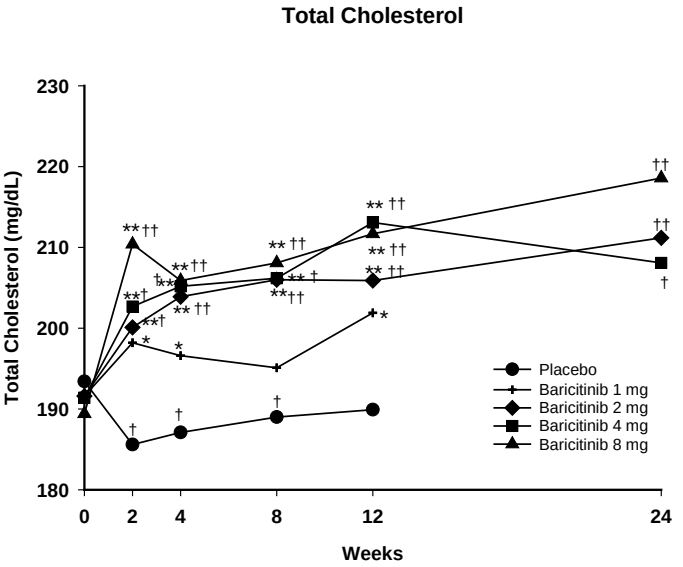
††p<0.001 (within treatment)

Figure 2. Correlation analysis: change from baseline to week 12 in high-density lipoprotein cholesterol (HDL-C) versus change from baseline to week 12 in Disease Activity Score based on 28-joint assessment and C-reactive protein (DAS28-CRP). Patients across the entire study were divided into tertiles of change in HDL-C (1^{st} tertile ≤0.0 mg/dL, 2^{nd} tertile >0.0 but ≤7.7 mg/dL, 3^{rd} tertile >7.7 mg/dL) and tertiles of improvement from baseline to Week 12 in DAS28-CRP [1^{st} tertile <1.07 (least improvement), 2^{nd} tertile ≥1.07 but <1.97, 3^{rd} tertile ≥1.97 (most improvement)]. Higher peaks along the east-west diagonal represent an increased relationship between HDL-C and DAS28-CRP changes.

Figure 1.


LDL Cholesterol
LDL Cholesterol (mg/dL)
130
125
120
115
110
105
100
95
0
2
4
8
12
24
Weeks
Placebo
Baricitinib 1 mg
Baricitinib 2 mg
Baricitinib 4 mg
Baricitinib 8 mg


HDL Cholesterol
HDL Cholesterol (mg/dL)
72
70
68
66
64
62
60
58
56
0
2
4
8
12
24
Weeks
Placebo
Baricitinib 1 mg
Baricitinib 2 mg
Baricitinib 4 mg
Baricitinib 8 mg


Total Cholesterol
Total Cholesterol (mg/dL)
230
220
210
200
190
180
0
2
4
8
12
24
Weeks
Placebo
Baricitinib 1 mg
Baricitinib 2 mg
Baricitinib 4 mg
Baricitinib 8 mg

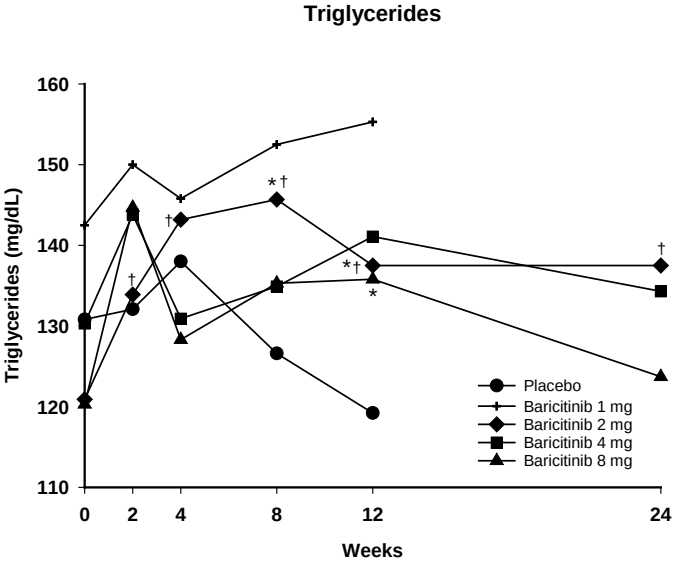
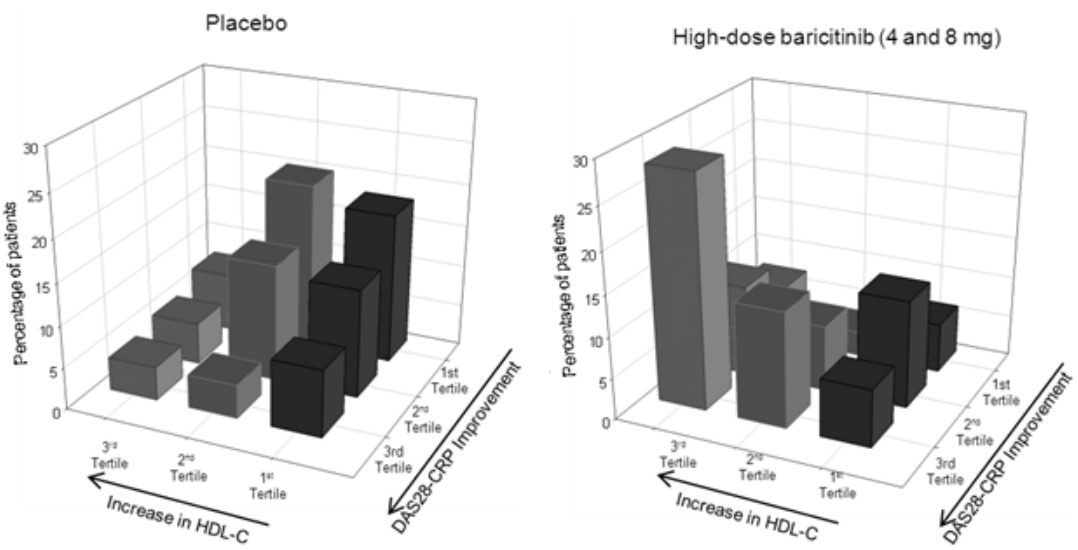

Triglycerides
Triglycerides (mg/dL)
160
150
140
130
120
110
0
2
4
8
12
24
Weeks
Placebo
Baricitinib 1 mg
Baricitinib 2 mg
Baricitinib 4 mg
Baricitinib 8 mg

Figure 2.


Placebo
High-dose baricitinib (4 and 8 mg)
Percentage of patients
30
25
20
15
10
5
0
3rd Tertile
2nd Tertile
1st Tertile
Increase in HDL-C
DAS28-CRP Improvement

Supplemental Appendix – Online Only

Supplementary Table 1. Lipid profiles after treatment with placebo or baricitinib

		Baricitinib			
	Placebo	**1 mg QD**	**2 mg QD**	**4 mg QD**	**8 mg QD**
	N = 98	**N = 49**	**N = 52**	**N = 52**	**N = 50**
LDL-C (mg/dL)					
Baseline	108 ± 34	102 ± 35	107 ± 31	109 ± 33	107 ± 30
Week 12	105 ± 31	108 ± 35	115 ± 40*,†	120 ± 33*,†	117 ± 31**,†
Week 24	--	--	119 ± 37††	119 ± 32	125 ± 33†
HDL-C (mg/dL)					
Baseline	60 ± 18	60 ± 18	60 ± 17	57 ± 14	58 ± 16
Week 12	61 ± 17	62 ± 20†	63 ± 22†	65 ± 19**,††	67 ± 19**,††
Week 24	--	--	65 ± 19†	63 ± 17†	69 ± 18††
Total Cholesterol (mg/dL)					
Baseline	193 ± 40	192 ± 44	192 ± 38	191 ± 39	189 ± 37
Week 12	190 ± 34	202 ± 42*	206 ± 49**,††	213 ± 39**,††	212 ± 39**,††
Week 24	--	--	211 ± 45††	208 ± 39†	219 ± 37††
Triglycerides (mg/dL)					
Baseline	131 ± 73	143 ± 86	121 ± 65	130 ± 65	120 ± 58
Week 12	119 ± 72	155 ± 93	138 ± 87*,†	141 ± 71	136 ± 84*
Week 24	--	--	138 ± 69†	134 ± 55	124 ± 76
HDL-C/LDL-C ratio					

Baseline	0.65 ± 0.52	0.67 ± 0.29	0.63 ± 0.38	0.56 ± 0.20	0.59 ± 0.25
Week 12	0.65 ± 0.32	0.69 ± 0.58	0.67 ± 0.60	0.59 ± 0.27	0.62 ± 0.25
Week 24	--	--	0.60 ± 0.30	0.57 ± 0.23	0.60 ± 0.24

HDL-C - high-density; QD – once-daily; LDL-C - low-density lipoprotein cholesterol;

lipoprotein cholesterol; SD – standard deviation.

Data are mean ± SD, unless noted otherwise.

Only patients in 2, 4, and 8 mg treatment groups continued treatment for an additional 12 weeks.

Change from baseline analysis:

†$p<0.05$ (within treatment)

††$p<0.001$ (within treatment)

*$p<0.05$ vs. placebo (only conducted at week 12)

**$p<0.001$ vs. placebo (only conducted at week 12)

Supplementary Table 2. LDL-C (mg/dL) in Patients Receiving Concomitant Statins (Mean ± SD)

With Statin Use[a]	**Placebo**	**1 mg QD**	**2 mg QD**	**4 mg QD**	**8 mg QD**
	n = 19	**n = 6**	**n = 3**	**n = 11**	**n = 11**
Baseline	122 ± 30	113 ± 43	97 ± 56	108 ± 37	131 ± 28
Week 12	n=18	n=6	n=3	n=10	n=10
	105 ± 28	126 ± 46	98 ± 66	110 ± 33	135 ± 35
Week 24	--	--	n=2	n=10	n=10
			81 ± 49	123 ± 33	124 ± 34
Mean change from baseline at week 12	-19 ± 31†	13 ± 40	2 ± 35	-4 ± 24	8 ± 32*
Mean change from baseline at week 24	--	--	-10 ± 28	8 ± 32	-9 ± 40
Without Statin Use	**Placebo**	**1 mg QD**	**2 mg QD**	**4 mg QD**	**8 mg QD**
	n = 79	**n = 41**	**n = 49**	**n = 41**	**n = 39**
Baseline	104 ± 35	101 ± 34	108 ± 30	109 ± 33	100 ± 28
Week 12	n=64	n=37	n=46	n=39	n=37
	105 ± 32	105 ± 32	116 ± 39	123 ± 33	113 ± 29

Week 24	--	--	n=47 121 ± 36	n=38 118 ± 32	n=34 125 ± 34
Mean change from baseline at week 12	-1 ± 22	2 ± 21	8 ± 24†,*	13 ± 31†,*	13 ± 21††,*
Mean change from baseline at week 24	--	--	12 ± 22††	9 ± 33	21 ± 25††

LDL-C - low-density lipoprotein-cholesterol; QD – once-daily; SD – standard deviation

[a]The numbers of patients who initiated statins after baseline were as follows for each treatment group: placebo (5/19), baricitinib 1 mg (3/6), baricitinib 2 mg (1/3), baricitinib 4 mg (2/11), baricitinib 8 mg (9/11).

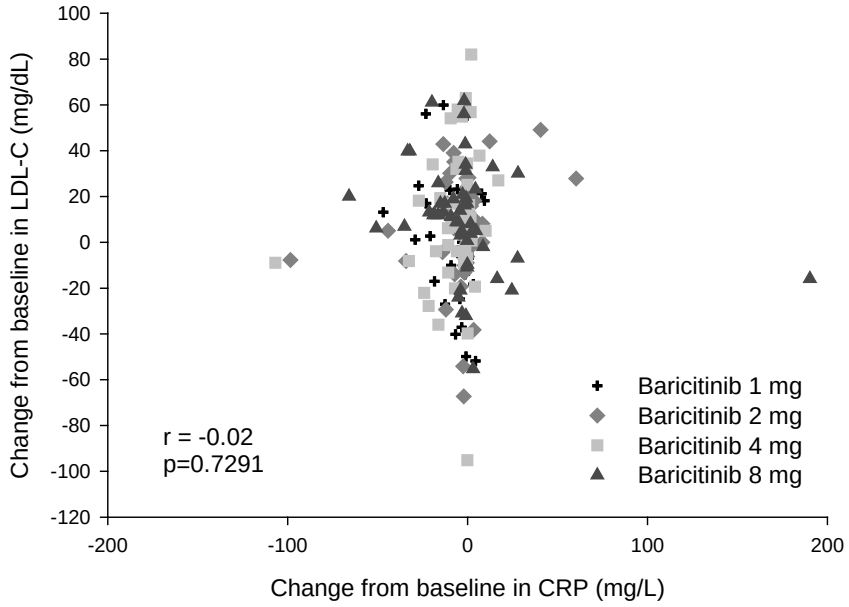
†$p<0.05$ (within treatment)

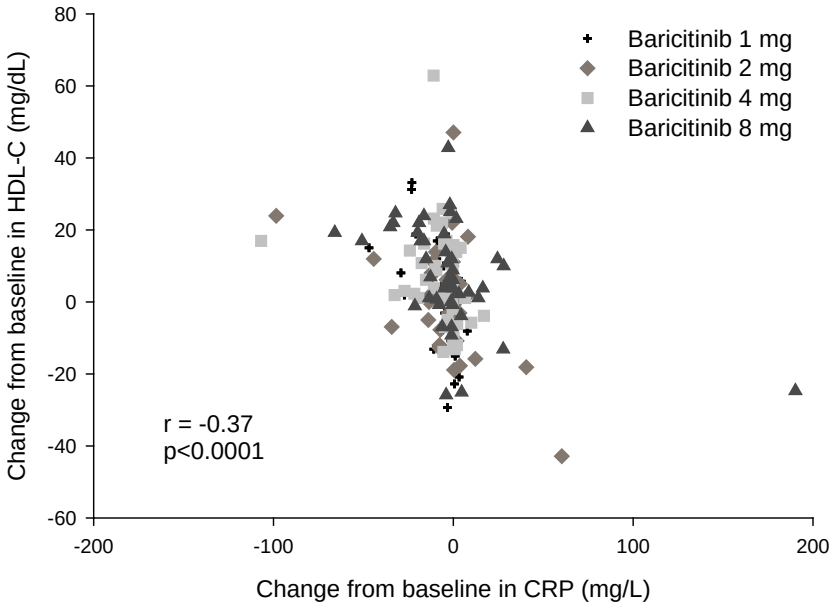
††$p<0.001$ (within treatment)

*$p<0.05$ vs. placebo (only conducted at week 12)

**$p<0.001$ vs. placebo (only conducted at week 12)

Supplementary Figure 1. Correlation analysis of change from baseline to week 12 in low-density lipoprotein cholesterol (LDL-C) or high-density lipoprotein cholesterol (HDL-C) versus change from baseline to week 12 in C-reactive protein (CRP).





Supplementary Figure 2. Correlation analysis of change from baseline to week 12 in high-density lipoprotein cholesterol (HDL-C) versus change from baseline to week 12 in DAS28-CRP.