Supplementary Table S1. Key study design features including patient population

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Treatments** | **Prior RA treatments** | **Concomitant** **therapies** | **Rescue (from week)** | **Study length (weeks)** | **Nuclear magnetic resonance** | **Adjudicated MACE** |
| **PHASE II** |  |  |  |  |  |  |  |
| NCT01185353JADAa | PlaceboBari 8 mgBari 4 mgBari 2 mgBari 1 mg | MTX-IRbDMARD naïve | Optional csDMARDsno bDMARDs |  | 12: double blind12: blinded extension (no placebo104: open-label extension | Yes | - |
| NCT00902486JADCa | PlaceboBari 10 mgBari 7 mgBari 4 mg | DMARD-IRprior bDMARD allowed | no bDMARDs |  | 12: double blind12: blinded extension (no placebo) | - | - |
| NCT01469013(Japan, JADN) a,b | PlaceboBari 8 mgBari 4 mgBari 2 mgBari 1 mg | MTX-IRprior bDMARD alloweda | Optional csDMARDsno bDMARDs |  | 12: double blind52: blinded extension (no placebo) | - | - |
| **PHASE III** |  |  |  |  |  |  |  |
| RA-BEGINNCT01711359 | MTX aloneBari 4 mg alone Bari 4 mg + MTX | DMARD naive |  | 24 | 52: double blind |  | Yes |
| RA-BEAMNCT01710358a | PlaceboBari 4 mgAdalimumab | MTX-IRbDMARD naive | Background MTX | 16 | 24: double blind placebo control28: double blind active control | Yes | Yes |
| RA-BUILDNCT01721057a | PlaceboBari 4 mgBari 2 mg | csDMARD-IRbDMARD naive | Optional csDMARDsno bDMARDs | 16 | 24: double blind |  | Yes |
| RA-BEACONNCT01721044a | PlaceboBari 4 mgBari 2 mg | TNFi-IR | BackgroundcsDMARD | 16 | 24: double blind |  | Yes |
| **Long-term Extension** |  |  |  |  |  |  |
| RA-BEYONDNCT01885078 | Bari 4 mgBari 2 mg | Depends on originator study |  | As needed | Ongoing long-term extensionc |  | Yes |

aIncluded in the six-study, placebo-controlled set.
bPrior bDMARDs allowable; however, patients could not have stopped treatment due to insufficient response.
cData as of January 1, 2016.
Bari=baricitinib, bDMARD=biologic disease-modifying antirheumatic drugs; csDMARD=conventional synthetic disease-modifying antirheumatic drugs; IR=inadequate responder; MACE=major adverse cardiovascular events; MTX=methotrexate; TNFi=tumor necrosis factor inhibitor.

Supplementary Table S2. Correlation analysis between lipid changes and clinical endpoints from baseline to week 12 in the baricitinib 2 mg/4 mg analysis set

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| --- | --- | --- | --- | --- |
|  | **HDL-C** | **LDL-C** | **Triglycerides** | **Total cholesterol** |
|  | Partial Pearson correlation coefficient (r)a |
| DAS28-CRP | -0.15 | -0.19 | -0.03 | -0.18 |
| DAS28-ESR | -0.15 | -0.15 | -0.00 | -0.13 |
| SDAI | -0.08 | -0.16 | -0.01 | -0.13 |
| CDAI | -0.05 | -0.13 | 0.01 | -0.09 |

aPartial Pearson correlation coefficients were calculated adjusting for treatment group.

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

Supplementary Table S3. Treatment-emergent highest value through week 24 with data censored at rescue

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| --- | --- | --- | --- |
| **Increased by maximum (and minimum for HDL-C) category, n (%)** | **Placebo****(N=1070)** | **Baricitinib 2 mg****(N=479)** | **Baricitinib 4 mg****(N=997)** |
| LDL-C | n=797 | n=369 | n=836 |
|  Borderline high (3.36-4.11 mmol/L) | 56 (7) | 61 (17) | 174 (21) |
|  High (4.14-4.89 mmol/L) | 45 (6) | 45 (12) | 132 (16) |
|  Very high (≥4.91 mmol/L) | 19 (2) | 17 (5) | 63 (8) |
| HDL-C | n=635 | n=285 | n=672 |
|  Low (<1.03 mmol/L for men; <1.29 mmol/L for women) | 80 (13) | 20 (7) | 37 (6) |
| Triglycerides | n=982 | n=445 | n=945 |
|  Borderline high (1.69-2.25 mmol/L) | 82 (8) | 46 (10) | 121 (13) |
|  High (2.26-5.63 mmol/L) | 71 (7) | 49 (11) | 116 (12) |
|  Very high (≥5.64 mmol/L) | 7 (1) | 5 (1) | 5 (1) |

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.

Supplementary Table S4. Change in lipid and GlycA levels from baseline to week 12 according to baseline statin use in the phase III RA-BEAM study

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Baseline statin use** | **Placebo****(N=488)** | **Baricitinib 4 mg****(N=487)** | **Adalimumab****(N=330)** | **Baricitinib 4 mg vs Placebo** | **Adalimumab vs Placebo** |
|  | LSM (SE) | LSMD (95% CI) |
| GlycA, µmol/L |  |  |  |  |  |
|  No (n=389) | -13.5 (4.0) | -109.5 (4.0) | -99.5 (4.9) | -96.0 (-107, -85)\*\*\* | -86.0 (-98, -74)\*\*\* |
|  Yes (n=37) | -14.3 (14.1) | -131.0 (14.3) | -94.2 (16.3) | -116.7 (-157, -77)\*\*\* | -79.9 (-123, -37)\*\*\* |
| Total cholesterol, mmol/L |  |  |  |  |  |
|  No (n=412) | -0.0 (0.03) | 0.7 (0.03) | 0.3 (0.04) | 0.7 (0.6, 0.8)\*\*\* | 0.3 (0.2, 0.4)\*\*\* |
|  Yes (n=37) | -0.1 (0.17) | 0.9 (0.17) | 0.3 (0.20) | 1.0 (0.6, 1.5)\*\*\* | 0.4 (-0.1, 0.9) |
| LDL cholesterol, mmol/L |  |  |  |  |  |
|  No (n=404) | -0.1 (0.03) | 0.4 (0.03) | 0.2 (0.03) | 0.5 (0.4, 0.5)\*\*\* | 0.3 (0.2, 0.3)\*\*\* |
|  Yes (n=37) | -0.1 (0.14) | 0.5 (0.13) | 0.2 (0.16) | 0.6 (0.3, 1.0)\*\* | 0.3 (-0.1, 0.7) |

\*\*p≤0.01, \*\*\*p≤0.001 vs placebo

CI=confidence interval; LDL=low-density lipoprotein; LSM=least squares mean; LSMD=least squares mean difference; SE=standard error.

Supplementary Figure S1. Long-term lipid profile for LDL-C and HDL-C in all patients who received baricitinib 4 mg. Data are least squares mean absolute values (mmol/L) from baseline to week 104 with SE depicted by error bars (though the SEs were very tight, and therefore some error bars are not very visible). HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; SE=standard error.

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Supplementary Figure S2. Correlation analysis of the changes in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels from baseline to week 12 versus changes in high sensitivity C-reactive protein level (hsCRP) and GlycA from baseline to week 12. Patients were divided into tertiles of increase in LDL-C (first tertile: ≤-0.08, second tertile: >-0.08 but ≤0.41, and third tertile: >0.41 mmol/L) and HDL-C (first tertile: ≤0.0, second tertile: >0.0 but ≤0.21, and third tertile: >0.21 mmol/L) and in reduction of hsCRP (lowest tertile of reduction: <1.76, second tertile: ≥1.76 but <11.08 and, highest tertile: ≥11.08 mg/L) and glycA (lowest tertile of reduction: <24, second tertile: ≥24 but <104, and highest tertile: ≥104 umol/L). Higher peaks along the east–west diagonal represent an increased relationship between changes in LDL-C/HDL-C levels and changes in hsCRP/glycA.



Supplementary Figure S3. Relationship between MACE and change in LDL-C. Plot shows MACE from the all-baricitinib set in phase III studies (N=2890) plotted against change from baseline in LDL-C. Occurrences of positively adjudicated MACE were evenly distributed among patients with increased LDL-C and included some occurrences in patients with decreased LDL-C. Post-baseline LDL was censored at statin initiation, when statin dose increased, or with statin type change. Graph shows all MACEs from the all BARI RA analysis set except 3 MACEs for which the patients did not have any post-baseline LDL data available. LDL-C=low-density lipoprotein cholesterol; MACE=major adverse cardiovascular events.

