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Supplemental methods:

Measurements of cardiovascular risk factors and vascular function.

The homeostasis model assessment of insulin resistance (HOMA-IR) index = fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5) was used to estimate insulin resistance (1). Overnight fasting lipid profiles were obtained at the NIH Clinical Center Central Laboratories. Lipoprotein particle concentration and diameters were measured using automated Nuclear Magnetic Resonance Spectroscopy (NMR) using the LP4.20 algorithm. The HDL cholesterol efflux capacity was measured using published methods(2). Briefly, 3x10^5 J774 cells/well were seeded in 24-well plate and radiolabeled with 2 μCi of 3H-cholesterol/mL in RPMI-1640 media containing 1% FBS for 24-hours. Cells were incubated for 16-hours in RPMI/2% BSA in the presence or absence of 0.3 mmol/L 8-(4-chlorophenylthio)-cAMP to upregulate ATP-binding cassette transporter A1. This was followed by addition of 2.8% apoB-depleted plasma to the efflux medium for 4 hours. A liquid scintillation counter was used to quantify the efflux of radioactive cholesterol from cells using the formula: (μCi of 3H-cholesterol in media containing 2.8% apoB-depleted subject plasma-μCi of 3H-cholesterol in plasma-free media /μCi of 3H-cholesterol in media containing 2.8% apoB-depleted pooled control plasma-μCi of 3H-cholesterol in pooled control plasma-plasma-free media). Pooled plasma was obtained from five healthy adult volunteers. All assays were performed in duplicate. LCAT concentration was quantified by ELISA (BioVendor; Ashville, NC).

Non-invasive vascular function studies:

These studies included the cardio-ankle vascular index (CAVI), peripheral arterial tonometry (PAT; reactive hyperemia index (RHI), and pulse wave velocity (PWV) (3). Subjects were asked to fast for at least 6 hours prior to these tests and to refrain from smoking or drinking caffeinated beverages for 24 hours prior to the studies. Subjects were asked to hold vasodilators,
anti-hypertensives and statins on the morning of the test. During testing, subjects were placed in a temperature-controlled quiet room in the supine position.

1) CAVI. CAVI was measured using VaSera-1500A (Fukuda Denshi Co. Redmond, WA). After placing blood pressure (BP) cuffs around both arms and ankles and attaching electrocardiogram electrodes to the upper arms, a microphone was placed on the sternal angle to record heart sounds. Measurements were automatically calculated using the VaSera VS-1000 software. The principle underlying CAVI has been discussed previously.(4)

2) PAT. Microvascular endothelial function was evaluated using PAT with an EndoPAT 2000 device (Itamar Medical Ltd. Caesarea, Israel) as previously described.(5) Finger probes were placed on symmetric fingers bilaterally, and a BP cuff was placed on one arm, with the other arm serving as control. PAT was continuously measured for 20 minutes. In between, for 5 minutes, BP cuff was inflated to supra systolic pressure in the test arm. At the end of the occlusion and dilatation periods, reactive hyperemia was captured as an increase in the PAT signal amplitude and compared with the control arm. A postocclusion to preocclusion ratio was calculated by EndoPAT software, providing RHI. Augmentation index (AI) was calculated from PAT pulses at the baseline period. The result was further normalized to heart rate of 75 bpm (AI@75), as previously described.(5)

3) SphygmoCor PWV and velocity system: Central aortic BP and stiffness were quantified using SphygmoCor CP system (AtCor Medical Pty Ltd.; New South Wales, Australia). The central aortic pressure PWV was determined by using the pressure tonometer and an EKG signal was used simultaneously to visualize ventricular-vascular interactions. Standard algorithm and procedures, as described elsewhere, were used to quantify results.(6)
Quantification of LDGs:
PBMCs were isolated by Ficoll-Paque density gradient and red blood cells were lysed with hypertonic solution. PBMCs were resuspended in 2% FBS/PBS, blocked for 15 minutes with Human TruStain Fc Receptor Blocking Solution (BioLegend; San Diego, CA), then resuspended in FACS buffer and incubated with fluorochrome-conjugated mouse anti-human-CD10 (clone H10A, catalog 312209), –CD15 (clone H198, catalog 301906), and –CD14 (clone HCD14, catalog 325610) antibodies (BioLegend; San Diego, CA) or isotype controls for 15 minutes in the dark. Cells were fixed with 2% PFA. Data was collected using a BD FACSCanto RUO and analyzed using FlowJo Software Version 10. Cutoff values for positive staining were determined using compensation controls for each fluorophore. LDGs were classified as CD10⁺, CD15⁺, CD14lo. (7)

NETs ELISA:
HNE-DNA NET complexes were measured in plasma, as described. (8) In brief, 96-well ELISA plates were coated overnight at 4°C with rabbit anti-human neutrophil elastase (HNE; Calbiochem; San Diego, CA). Plates were blocked in 1% BSA and incubated overnight with plasma in blocking buffer. After washing, plates were incubated for 1 hour at room temperature with anti-dsDNA (clone BV16-13, MilliporeSigma; Burlington, MA). Plates were washed and incubated for 1 hour with anti–mouse IgG-HRP conjugate (Bio-Rad), followed by a wash and the addition of TMB substrate and stop reagent (MilliporeSigma; Burlington, MA). Absorbance was measured at 450 nm, and values were calculated as an OD Index.

ELISAs for soluble markers of endothelial cell activation:
Serum sICAM-1, sVCAM-1, and sL-selectin levels were detected using commercially available ELISA kits (Invitrogen, BMS201, BMS232, BMS206) following manufacturer protocols.
**18F-FDG–PET/CT:**

A subset of 30 subjects underwent this test, which was performed following an overnight fast. Images were obtained approximately 60 minutes after administration of 10 mCi of \(^{18}\)F-FDG. All scans were completed using a 64-slice scanner (Siemens Biograph) acquiring 1.5 mm axial slices of the aorta. Standard bed positions of 3 minutes each were applied, and whole body scans were obtained for each patient from the vertex of the skull to the toes. The extent of \(^{18}\)F-FDG uptake within the aortic wall was measured with dedicated software (OsiriX MD, Pixmeo SARL). Each arterial region of interest produced 2 measures of metabolic activity: a mean standardized uptake value (SUV\(_{\text{mean}}\)) and a maximal SUV (SUV\(_{\text{max}}\)), which were obtained in the aorta from the aortic outflow tract to the abdominal aorta. Regions of interest were also placed on 10 contiguous slices over the superior vena cava to obtain a single average background blood activity. The SUV\(_{\text{mean}}\) from each of the superior vena cava slices were then averaged to produce 1 venous value. To account for background blood activity, SUV\(_{\text{max}}\) values from each aortic slice were divided by the average venous SUV\(_{\text{mean}}\) value to yield target/background ratio (TBR), a measure of vascular inflammation as previously described (9).

**RNA Isolation and IFN Gene Signature (ISG) quantification by Nanostring:**

Total RNA was extracted from whole blood using Paxgene blood RNA isolation kit (PreAnalytiX, Switzerland). RNA concentration was measured by NanoDrop (Thermo Fisher Scientific). The nCounter Element prep kit (NanoString Technologies) was used for Nanostring assay. A NanoString TagSet consisting of fluorescently labeled specific Reporter Tags and a biotinylated universal Capture Tag were supplied by NanoString. There were 6 spike-in positive controls used to determine the hybridization efficiency, and 6 negative controls used to check non-specific background. A target-specific oligonucleotide probe pairs (synthesized by IDT, Coralville, IA) contained 37 ISGs, previously identified as discriminative of the IFN signature,
and 4 housekeeping genes (*ALAS1, HPRT1, TBP, TUBB*). A total of 100ng of RNA was used for hybridization at 67°C for 16-21 hour on thermocycler. The hybridized samples were inserted into the nCounter Prep Station, where they were purified and immobilized onto the internal surface of a sample cartridge for 2-3 h. The sample cartridge was transferred to the nCounter Digital Analyzer where color codes were counted and tabulated for each target molecule. The resulting data were processed with nSolver software (NanoString Technologies), which included assessment of quality of the runs. Data were combined, normalized, and analyzed in Excel (Microsoft Corporation). Synthetic DNA oligonucleotides of each of the 37 ISGs and 4 housekeeping genes were used in each run as a calibration standard to check run and reagent lot consistency.

**High dimensional transcriptional, and flow cytometry analysis.**

Sample collection and selection for high dimensional analysis:
Peripheral blood was stored in PAXgene Blood RNA tubes for transcriptional analysis and viable PBMC were isolated and cryopreserved for flow cytometry according to Center for Human Immunology (CHI) protocols ([https://chi.niaid.nih.gov/web/new/our-research/sop.html](https://chi.niaid.nih.gov/web/new/our-research/sop.html)).

A subgroup of 24 subjects were selected for high dimensional phenotyping, which comprised the 12 individuals from each study arm that demonstrated the greatest decreases in CAVI when treated with pioglitazone.

**Transcriptomics:**
RNA extraction was performed on a QIAsymphony SP instrument, using QIAsymphony PAXgene Blood RNA Kits, with RNA yields determined on the Biotek Synergy H1 plate reader using Quant-IT Ribo Green Assay Kit, and RNA quality assessed on the Agilent 4200 TapeStation using RNA Screen Tape. RNA-seq libraries were prepared from 500 ng of total RNA on the Biomek FXp robot using Universal Plus mRNA-Seq kit with Human
Globin AnyDeplete. Library concentration was determined on the Biotek Synergy H1 plate reader using Quant-IT Pico Green dsDNA Assay Kit. Library size distribution was determined using D1000 ScreenTape on the 4200 TapeStation System. All libraries were diluted to the same molar concentration with a QIAgility liquid handling robot, equal volumes of normalized samples were pooled, and plate pools quantified by qPCR using KAPA Library Quantification Kit. One lane of a NovaSeq 6000 S4 run (200 cycles) was then used for sequencing at NHLBI Sequencing Core. Sequencing reads were adapter and quality trimmed then aligned to the human genome using STAR software, with read counts determined using HTSeqCount software, before normalization using the LIMMA packages and R software.

Flow Cytometry: Cytometry used a Cytek Aurora with broad immune lineages assessed in unstimulated cells using a 27-color panel and manual quantification of 58 populations (Supplemental Table 1A,B). For more comprehensive characterization of T cell focused phenotypes a 34-color panel and manual quantification of 83 populations was performed (Supplemental Table 2 A,B), after in vitro stimulation with PMA (10 ng/mL) and ionomycin (500 ng/mL) in combination with protein transport inhibitors (Monensin 2uM, Brefeldin A 1 ug/mL) for 4 hours in a 37°C tissue culture incubator.

Data analysis: Longitudinal changes in either gene expression or flow cytometry populations were evaluated by paired test, with $P$ values corrected for multiple comparisons using the Benjamini-Hochberg method when described, using R-Shiny web tools developed in-house but similar to those previously described (10). For transcriptomic responses differentially expressed genes were used for gene set enrichment analyses performed using tmod and BTM that reflect biologically responding pathways (11, 12).
Statistical Analysis:

Sample size was calculated based on previous publications for arterial stiffness and vascular dysfunction in SLE and RA (5, 13-16). Based on our previous experience with the CV lupus cohort and on published literature on cross-over designs using PGZ to measure CV markers in other populations, dropout rate was estimated between 3-20%. Bring a proof of concept study, at least moderate differences in outcome were considered to be clinically meaningful. The actual analysis used data on all subjects including those who provided partial information. This sample was considered to provide power to detect moderate standardized differences for the other variables measured in this study.

Most of the outcome variables were measured at Day 1 (prior to randomization), month 3 (end of period 1), month 5 (start of period 2) and month 8 (end of period 2). Change score in these continuous outcomes was summarized by mean and standard deviation (SD): M3 – D1 for period 1 and M8 – M5 for period 2, for each sequence respectively. Linear mixed models were used to analyze the change scores in mean CAVI, PWI, and the log-transformed RHI. The models included the fixed effects of baseline value (D1 for period 1, M3 for period 2), treatment group (PGZ or placebo), period (1 or 2), and sequence (AB or BA). The random effect was “subject”. Residual plots were used to assess model normality assumptions. For the treatment group difference (assessed by the difference in change scores between PGZ and placebo), the estimate, its associated confidence interval (CI), and p-values were reported from the mixed effects models. Other secondary efficacy endpoints were analyzed in a similar manner. The Wilcoxon rank sum test was used to analyze NETs when normality assumption was violated (43). For continuous variables only measured in period 1, analysis of covariance was used to analyze the data. Efficacy analyses were based on the intention to treat population, which includes all the subjects who were randomized. For the primary endpoints, 0.05/3 was set as the cutoff for statistical significance.
all secondary efficacy endpoints, p-values and 95% confidence intervals were provided to examine the statistical evidence. All statistical analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC).

**Supplemental Results**

As the targeted analysis of inflammation-related genes showed no effect when subjects were treated with pioglitazone, we performed unbiased screening to detect potentially other effects of this drug on immune phenotype. For this we focused on analyzing a subgroup of 24 subjects, which comprised the 12 individuals from each study arm that demonstrated the greatest decreases in CAVI when treated with pioglitazone. Whole blood transcriptomic analysis was performed with changes between consecutive study timepoints used to rank genes for enrichment analyses of blood transcriptional modules (BTM). The number of significantly enriched pathways (FDR<0.05) was no higher in the study arms receiving pioglitazone than placebo for both of 0-3- and 5-8-month treatment periods (Supplemental Table 6A). Further, the pathways that did change with pioglitazone treatment showed no overlap between the two study arms (Supplemental Table 6 B, C). Next, PBMC were analyzed by high-dimensional flow cytometry, using a 27-color panel to quantify 58 populations spanning broad immune lineages in unstimulated cells, and a 34-color panel to quantify 83 populations that more comprehensively characterized T cell populations revealed by transcription factor or cytokine expression after in vitro stimulation with PMA. For both panels no significant changes in any population frequencies were observed between study timepoints after correction for multiple testing. The numbers of populations changing with nominal significance are reported (Supplemental Table 7 A, D), with those populations corresponding to the periods of drug treatment in each study arm also shown (Supplemental Table 7 B, C,E,F). Together this broad immune phenotyping analysis
indicated that although some longitudinal changes were observed in these 24 subjects, no changes in either peripheral blood transcriptional profiles or cell population frequencies could be attributed to treatment with pioglitazone.
Supplemental Figures:

**Supplemental Figure 1.** Flow diagram of clinical trial. Subjects were randomized to either sequence AB (PGZ=3 months, washout=2 months and placebo=3 months) or sequence BA (placebo=3 months, washout=2 months and PGZ=3 months).
Supplemental Figure 2. Effect of pioglitazone on IFN gene signature. RNA was assessed for a ISGs by NanoString, generating an “IFN score” for each patient at each time point. Change in IFN score over the allocation period was not significantly different between patients receiving PGZ and patients receiving placebo.
Supplemental Figure 3. Effect of PGZ on levels of circulating LDGs and NETs. (A) LDGs were quantified by flow cytometry for each patient before and after each allocation period. Change in levels of LDGs was not significantly different for patients when comparing the levels over the period on placebo to those over the period on PGZ. (B) Levels of NETs were assessed in plasma by quantifying HNE:DNA complexes. On PGZ, median level of NETs was lower compared to median level of NETs on placebo (p = 0.026).* = p ≤ 0.05;
Supplemental Tables:

**Supplemental Table 1.** Twenty-seven-color panel for flow cytometry analysis of broad lineage populations in unstimulated PBMC.

1A) Antibody clones and fluoros are detailed for the 27-color panel.

|   | Specificity | Fluorochrome | Clone | vendor | cat#          |
|---|-------------|--------------|-------|--------|--------------|
| 1 | CD197       | BUV395       | 150503| BD     | CUSTOM       |
| 2 | Dead cells  | Live/Dead Blue|       |        | ThermoFisher | L23105       |
| 3 | CD16        | BUV496       | 3G8   | BD     | 612944       |
| 4 | HLA-DR      | BUV661       | G46-6 | BD     | 612980       |
| 5 | CD196       | BUV737       | 11A9  | BD     | 564377       |
| 6 | CD183(CXCR3)| BUV805       | IC6/CXCR3 | BD | 742048       |
| 7 | IgD         | BV421        | IA6-2 | BD     | 562518       |
| 8 | CD4         | eFluor450    | SK3   | BD     | 560345       |
| 9 | CD127       | BV480        | HIL-7R-M21 | BD | 566101       |
|10 | CD19        | BV570        | HIB19 | BD     | CUSTOM       |
|11 | CD194(CCR4) | BV605        | 1G1   | Biolegend | 359418       |
|12 | CD123       | BV650        | 7G3   | BD     | 563405       |
|13 | CD25        | BV711        | 2A3   | BD     | 563159       |
|14 | CD14        | BV750        | M5E2  | BD     | 746920       |
|15 | CD27        | BV786        | L128  | BD     | 563327       |
|16 | CD45RA      | BB515        | H100  | BD     | 564552       |
|17 | CD38        | PerCP-Cy5.5  | HIT2  | BD     | 551400       |
|18 | CD24        | BB700        | ML5   | BD     | 566524       |
|19 | CD45        | BB790        | HI30  | BD     | CUSTOM       |
|20 | CD8         | PE           | RPA-T8| BD     | 555367       |
|21 | CD45RO      | PE-Texas Red | UCHL1 | Beckman Coulter | IM2712U |
|22 | CD11c       | PE-Cy5       | B-Ly6 | BD     | 551077       |
|23 | CD20        | PE-Cy5.5     | HI47  | ThermoFisher | MHCD2018 |
|24 | CD185(CXCR5)| PE-Cy7       | RF8B2 | Biolegend | 356924       |
|25 | CCR10       | AlexaFluor 647(APC)| 314305 | R&D Systems | FAB3478A |
|26 | CD56        | APC-R700     | NCAM 16.2 | BD | 565139       |
|27 | CD3         | APC-H7       | SK7   | BD     | 560176       |
1B) Panel of 58 subsets of PBMCs which were quantified are shown with the manual gates by which they were defined.

| Pop # | Gate 1 | Gate 2 | Gate 3 | Gate 4 | Gate 5 | Gate 6 | Gate 7 | Subset name I | Subset name II |
|-------|--------|--------|--------|--------|--------|--------|--------|---------------|---------------|
| 1     | single t Live CD45 + |         |         |         |        |        |        | Leukocytes    | Leukocytes    |
| 2     | single t Live CD45 + | CD3+CD19- |         |         |        |        |        | Total T cells | Total T cells |
| 3     | single t Live CD45 + | CD3+CD19- | CD4+CD8- |         |        |        |        | T helper cells (CD4+ T cells) | Th |
| 4     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD38+ |        |        |        | CD38+ activated T helper cells | CD38+ actTh |
| 5     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD38+HLA-DR+ |        |        |        | CD38+HLA-DR+ activated T helper cells | CD38+HLA-DR+actTh |
| 6     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- |        |        |        | CD45RA- T helper cells | CD45RA- |
| 7     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5+CCR10- |        |        | CXCR5+ T helper cells (T follicular helper) | Th |
| 8     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- |        |        | CXCR5- T helper cell subsets | Th subsets |
| 9     | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR6- |        | CXCR5-CCR6- T helper cell subsets | Th1_Th2_ThGM |
| 10 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR6- | CXCR3+CCR10-CCR6- | Th1 |
| 11 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR6- | CXCR3-CCR10-CCR6- | Th2 |
| 12 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR6- | CXCR3-CCR10+CCR6- | Th_GM_CS |
| 13 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR4-CCR6+ | CCR4+CCR6+T helper cells | Th9 |
| 14 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR4+CCR6+ | CCR4+CCR6+T helper cells | Th22_Th17 |
| 15 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR4+CCR6+ | CCR10-CCR4+CCR6+CCR10-T helper cells | Th17 |
| 16 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD45RA- | CXCR5- | CCR4+CCR6+ | CCR10+CCR4+CCR6+CCR10-T helper cells | Th22 |
| 17 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD127lowCD25 high | CXCR5- | CCR4+CCR6+ | CD127lowCD25high T helper cells | CD127lowCD25high_Th |
| 18 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD127lowCD25 high | CCR4+ | T regulatory cells | Treg |
| 19 | single t Live CD45 + | CD3+CD19- | CD4+CD8- | CD127lowCD25 high | CCR4+ | HLA-DR+ | Activated T regulatory cells (HLA-DR+) | actTreg |
| Table | Description |
|-------|-------------|
| 20    | Memory T regulatory cells | Memory Treg |
| 21    | Naïve T regulatory cells | Naive Treg |
| 22    | Central memory T helper cells | CM_Th |
| 23    | Effector T helper cells | Eff_Th |
| 24    | Effector memory T helper cells | EM_Th |
| 25    | HLA-DR+ activated T helper cells | HLA-DR+actTh |
| 26    | Naïve T helper cells | Naive Th |
| 27    | Cytotoxic T cells (CD8+ T cells) | Tc |
| 28    | CD38+ activated cytotoxic T cells | CD38+ actTc |
| 29    | CD38+ HLA-DR+ activated cytotoxic T cells | CD38+HLA-DR+Tc |
| #  | Name                        | 19 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 |
|----|-----------------------------|----|----|----|----|----|----|----|----|----|----|----|
| 30 | single t Live CD3+CD45-     | CD3+CD19- | CD4-CD8+ | CCR7+CD45RA- | CD45RA - | Central memory cytotoxic T cells | CM Tc |
| 31 | single t Live CD3+CD45+     | CD3+CD19- | CD4-CD8+ | CCR7-CD45RA+ | CD45RA+ | Effector cytotoxic T cells | Eff Tc |
| 32 | single t Live CD3+CD45+     | CD3+CD19- | CD4-CD8+ | CCR7-CD45RA- | CD45RA- | Effector memory cytotoxic T cells | EM Tc |
| 33 | single t Live CD3+CD45+     | CD3+CD19- | CD4-CD8+ | HLA-DR+ | CD45RA- | HLA-DR+ activated cytotoxic T cells | HLA-DR+actTc |
| 34 | single t Live CD3+CD45+     | CD3+CD19- | CD4-CD8+ | CCR7+CD45RA+ | CD45RA+ | Naive cytotoxic T cells | Naive Tc |
| 35 | single t Live CD3+CD45+     | CD3+CD19- | CD4-CD8- | CD4-CD8- | CD45RA- | CD4-CD8- T cells | DNT |
| 36 | single t Live CD3+CD45+     | CD3+CD19- | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ T cells | DPT |
| 37 | single t Live CD3+CD19+     | CD3-CD19- | CD4-CD8+ | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ T cells | DPT |
| 38 | single t Live CD3+CD19+     | CD3-CD19- | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ T cells | DPT |
| 39 | single t Live CD3+CD19+     | CD3-CD19- | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ | CD4+CD8+ T cells | DPT |

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| #  | Name       | Antibody Targets | Phenotypic Markers | Description                                      |
|----|------------|------------------|-------------------|--------------------------------------------------|
| 40 | Plasmacytoid Dendritic cells (pDC) | CD3-CD19-CD45+, CD14-HLA-DR+, CD11c-CD123+ |                  |                                                   |
| 41 | Granulocytes and NK cells (Gr_NK) | CD3-CD19-CD45+, CD14-HLA-DR-, CD123+CD56- |                  |                                                   |
| 42 | Basophils   | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56- |                  |                                                   |
| 43 | Granulocytes (Gr) | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56- |                  |                                                   |
| 44 | NK cells    | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56+ |                  |                                                   |
| 45 | CD16+ NK cells (CD16+NKs) | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56+ | CD16+ |                                                   |
| 46 | CD56highCD16low NK cells (CD56highCD16low NKS) | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56+ | CD56highCD16low |                                                   |
| 47 | CD56lowCD16low NK cells (CD56lowCD16low NKS) | CD3-CD19-CD45+, CD14-HLA-DR-, CD123-CD56+ | CD56lowCD16low |                                                   |
| 48 | Monocytes   | CD3-CD19-CD45+, CD14+ |                  |                                                   |
| 49 | Classical Monocytes | CD3-CD19-CD45+, CD14+ | CD16- |                                                   |
|   |   |   |   |   |
|---|---|---|---|---|
| 50 | single t Live | CD3-CD19+ | CD14+ | CD16-HLA-DR- |
|   | CD45+ |   |   | containing MDSCs subsets |
|   |   |   |   | containing MDSCs subsets |
| 51 | single t Live | CD3-CD19- | CD14+ | CD16+ |
|   | CD45+ |   |   | Non-classical Monocytes |
|   |   |   |   | Non-classical Mono |
| 52 | single t Live | CD3-CD19+ | CD20+ |
|   | CD45+ |   |   | CD19+ B cells |
|   |   |   |   | CD19+ B cells |
| 53 | single t Live | CD3-CD19+ | CD20+ |
|   | CD45+ |   |   | CD19+CD20+ transitional B cells |
|   |   |   |   | transitional B cells |
| 54 | single t Live | CD3-CD19+ | CD20+ | CD24+CD38+ |
|   | CD45+ |   |   | CD24+CD38+ transitional B cells |
|   |   |   |   | CD24+CD38+ transitional B |
| 55 | single t Live | CD3-CD19+ | CD20+ | IgD-CD27- |
|   | CD45+ |   |   | IgD-CD27- B cells |
|   |   |   |   | IgD-CD27- B cells |
| 56 | single t Live | CD3-CD19+ | CD20+ | IgD+CD27+ |
|   | CD45+ |   |   | Memory IgD+ B cells |
|   |   |   |   | memory IgD+ B |
| 57 | single t Live | CD3-CD19+ | CD20+ | IgD-CD27+ |
|   | CD45+ |   |   | Memory IgD-B cells |
|   |   |   |   | memory IgD-B |
| 58 | single t Live | CD3-CD19+ | CD20+ | IgD+CD27- |
|   | CD45+ |   |   | Naive B cells |
|   |   |   |   | Naive B cells |
**Supplemental Table 2.** A 34-color panel for flow cytometry analysis of T cell focused populations in PMA-stimulated PBMC.

2A) Antibody clones and fluoros are detailed for the 34 color panel.

| Target          | Fluorochrome | clone    | company      | cat#      |
|-----------------|--------------|----------|--------------|-----------|
| 1 CD197 (CCR7)  | BUV395       | 150503   | BD           | CUSTOM   |
| 2 CD26          | BUV496       | M-A261   | BD           | 50667     |
| 3 Dead cells    | Live/Dead Blue |         | ThermoFisher | L23105    |
| 4 CD161         | BUV363       | HP-3G10  | BD           | 749223    |
| 5 CD25          | BUV615       | 2A3      | BD           | 612996    |
| 6 HLA-DR        | BUV661       | G46-6    | BD           | 612980    |
| 7 CD56          | BUV373       | NCAM16-2 | BD           | 612766    |
| 8 CD3           | BUV805       | UCHT1    | BD           | 612895    |
| 9 IL-2          | BV421        | MQ1-17H12| BD           | 564164    |
| 10 Tbet         | V450         | O4-46    | BD           | 561312    |
| 11 IFNg          | BV480        | B27      | BD           | 566100    |
| 12 CD14         | BV510 (Dump channel) |         | BD           | 740163    |
| CD19           | BV510 (Dump channel) |         | BD           | 562947    |
| CD41a          | BV510 (Dump channel) |         | BD           | 563250    |
| 13 CD45         | Pacific Orange | H30    | ThermoFisher | MHCD4530  |
| 14 TCRVa7.2     | BV605        | OF-5A12  | BD           | 749491    |
| 15 CD4          | Qdot 605     | S3.5     | ThermoFisher | Q10008    |
| 16 Ki67         | BV650        | B56      | BD           | 563757    |
| 17 CD69         | BV711        | FN50     | BD           | 563836    |
| 18 TNF          | BV750        | MAb11    | BD           | 566359    |
| 19 CD196(CCR6)  | BV785        | G034E3   | Biolegend    | 353422    |
| 20 CD8          | Qdot 500     | JB5      | ThermoFisher | Q22157    |
| 21 IL-5         | BI515        | JES1-39D10 | BD          | CUSTOM    |
| 22 Granzyme B   | FITC         | G811     | Biolegend    | 515403    |
| 23 IL-13        | BB680        | JES10-5A2 | BD          | CUSTOM    |
| 24 CD45RA       | PerCP-Cy5.5  | HI100    | BD           | 563429    |
| 25 GATA3        | PerCP-eFluor710 |       | ThermoFisher | 46-9966-42 |
| 26 MR1          | PE           | NIH Tetramer Core Facility | hu MR1 5-OP-RU PE labeled tetramer |
| 27 GM-CSF       | PE/Dazzle 594 |         | Biolegend    | 502318    |
| 28 TCRgd        | PE-Cy5       | B1       | BD           | CUSTOM    |
| 29 FOXp3        | PE-Cy5.5     | PCH101   | ThermoFisher | 35-4776-42 |
| 30 IL-22        | PE-Cy7       | 22UR1I   | ThermoFisher | 25-7229-42 |
| 31 IL-4         | APC          | MPS-25D2 | BD           | 554486    |
| 32 RORgt        | Alexa Fluor 647 | Q21-559 | BD           | 563620    |
| 33 IL-17A       | APC-R700     | N49-653  | BD           | 565163    |
| 34 Perforin     | APC/Fire750  | B-D48    | Biolegend    | 353318    |
2B) A panel of 83 subsets of PBMCs which were quantified are shown with the manual gates by which they were defined.

| Pop # | Gate 1 | Gate 2 | Gate 3 | Gate 4 | Gate 5 | Gate 6 | Subset name |
|-------|--------|--------|--------|--------|--------|--------|-------------|
| 1     | singlet Live CD45+ |        |        |        |        |        | Leukocytes(CD45+) |
| 2     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD161+CD26+ |        |        | CD3+ T cells |
| 3     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD161+CD26+ |        |        | CD161+CD26+ T cells |
| 4     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD161+CD26+ | TCRValpha 7.2+MR1+ |        | MAIT cells |
| 5     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3+C D56+ |        |        | NKT cells |
| 6     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3+C D56+ | GranzymeB+Perforin+ |        | GranzymeB+Perforin+ NKT cells |
| 7     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3+C D56+ | IFNg+ |        | IFNg+ NKT cells |
| 8     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3+C D56+ | IFNg+TNF+ |        | IFNg+TNF+ NKT cells |
| 9     | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3+C D56+ | TNF+ |        | TNF+ NKT cells |
| 10    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- |        | T cells |
| 11    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-2+IFNg+ | T helper cells (Th) |
| 12    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-2+TNF+ | IL-2+TNF+ Th cells |
| 13    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-2+IFNg+ | IL-2+IFNg+ Th cells |
| 14    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD25+Foxp3+ | CD25+Foxp3+ Treg cells |
| 15    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD25+Foxp3+ | CD69+ Activated Foxp3+ Treg cells |
| 16    | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD69+ | CD69+ Th cells |
| No. | Singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD69+Ki67+ | CD69+Ki67+ Th cells |
|-----|---------|------|-------|----------------------|--------|----------|-----------|-------------------|
| 17  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD69+Ki67+ | CD69+Ki67+ Th cells |
| 18  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | CD4+FoxP3+ | Foxp3+ Treg cells |
| 19  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | GATA3+IL-4+ | GATA3+IL-4+ Th cells |
| 20  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | GATA3+IL-5+ | GATA3+IL-5+ Th cells |
| 21  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | GATA3+IL-13+ | GATA3+IL-13+ Th cells |
| 22  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | GM-CSF+ | GM-CSF+ Th cells |
| 23  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | GM-CSF+IL-17A+ | GM-CSF+IL-17A+ Th cells |
| 24  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IFNγ+ | IFNγ+ Th cells |
| 25  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IFNγ+TNF+ | IFNγ+TNF+ Th cells |
| 26  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-2+ | IL-2+ Th cells |
| 27  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-4+ | IL-4+ Th cells |
| 28  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-4+IL-5+ | IL-4+IL-5+ Th cells |
| 29  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-4+IL-13+ | IL-4+IL-13+ Th cells |
| 30  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-5+ | IL-5+ Th cells |
| 31  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-13+ | IL-13+ Th cells |
| 32  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-13+IL-5+ | IL-13+IL-5+ Th cells |
| 33  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-17A+ | IL-17A+ Th cells |
| 34  | singlet | Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4+CD8- | IL-17A+IL-22+ | IL-17A+IL-22+ Th cells |
| No. | Singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | IL-22+ | IL-22+Th cells |
|-----|---------|------|-------|-----------|-------------|--------|----------|--------|----------------|
| 35  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | IL-22+ | IL-22+Th cells |
| 36  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | IL-22+ | IL-22+GM-CSF+ Th cells |
| 37  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | Ki67+ | Ki67+ Th cells |
| 38  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | RORgT+ | RORgT+ Th cells |
| 39  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | RORgT+ | RORgT+IL-17A+ Th cells |
| 40  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | Tbet+IFNg+ | Tbet+IFNg+ Th cells |
| 41  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | Tbet+IL-2+ | Tbet+IL-2+ Th cells |
| 42  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | Tbet+TNF+ | Tbet+TNF+ Th cells |
| 43  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | TNF+ | TNF+ Th cells |
| 44  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | CCR7+/CD45RA- | Central Memory Th cells (CM Th) |
| 45  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | CCR7-/CD45RA+ | Effector Th cells (Eff Th) |
| 46  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | CCR7-/CD45RA- | Effector Memory Th cells (EM Th) |
| 47  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | GATA3+ | GATA3+Th2 cells |
| 48  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | CCR7+/CD45RA+ | Naive Th cells |
| 49  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | CD25-/Foxp3- | non-Treg cells |
| 50  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | RORgT+IL-22+ | RORgT+IL-22+ Th cells |
| 51  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8- | Tbet+ | Tbet+ Th1 cells |
| 52  | singlet | Live | CD45+ | CD3+/CD19- | CD14-/CD41a- | TCRgd- | CD4+/CD8+ | | Cytotoxic T cell (Tc) |
|   | singlet Live | CD45+ | CD3+CD19-CD14-CD41a- | TCRgd- | CD4-CD8+ | CD69+ | CD69+Tc |
|---|-------------|-------|------------------------|--------|----------|-------|---------|
| 53 |             |       |                        |        |          |       |         |
| 54 |             |       |                        |        |          |       |         |
| 55 |             |       |                        |        |          | IFNg+ | IFNg+Tc |
| 56 |             |       |                        |        |          | IFNg+IL-2+ | IFNg+IL-2+Tc |
| 57 |             |       |                        |        |          | IFNg+TNF+ | IFNg+TNF+Tc |
| 58 |             |       |                        |        |          | IFNg+ | IFNg+Tc |
| 59 |             |       |                        |        |          | IL-2+ | IL-2+Tc |
| 60 |             |       |                        |        |          | Ki67+ | Ki67+Tc |
| 61 |             |       |                        |        |          | Ki67+ | Ki67+CD69+Tc |
| 62 |             |       |                        |        |          | Perforin+ | Perforin+Tc |
| 63 |             |       |                        |        |          | Perforin+ | Perforin+GranzyneB+ |
| 64 |             |       |                        |        |          | TNF+ | TNF+Tc |
| 65 |             |       |                        |        |          | CCR7+CD45RA- | CCR7+CD45RA- Central Memory Tc (CM Tc) |
| 66 |             |       |                        |        |          | CCR7-CD45RA+ | Effector Tc (Eff Tc) |
| 67 |             |       |                        |        |          | CCR7-CD45RA- | Effector Memory Tc (EM Tc) |
| 68 |             |       |                        |        |          | Naive Tc |
| 69 |             |       |                        |        |          | gd T cells (Tgd) |
| 70 |             |       |                        |        |          | GranzyneB+ |
|    |             |       |                        |        |          | GranzyneB+ gd T cells |
| No. | Description | Expression 1 | Expression 2 | Expression 3 |
|-----|-------------|--------------|--------------|--------------|
| 71  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | IFNg+ | IFNg+ gd T cells |
| 72  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | IFNg+Perforin+ | IFNg+Perforin+ gdT cells |
| 73  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | IFNg+TNF+ | IFNg+TNF+ gdT cells |
| 74  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | Perforin+ | Perforin+ gdT cells |
| 75  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | Perforin+GranzymeB+ | Perforin+GranzymeB+ gdT cells |
| 76  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | TNF+ | TNF+ gdT cells |
| 77  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | TNF+Perforin+ | TNF+Perforin+ gdT cells |
| 78  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | TCRgd+ | CD3-CD19-CD14-CD41a- | CD3-CD19-CD14-CD41a- gd T cells |
| 79  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3-CD56+ | CD56+ NK cells |
| 80  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3-CD56+ | CCR6+CD69+ | CCR6+CD69+ NK cells |
| 81  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3-CD56+ | CD69+TNF+ | CD69+TNF+ NK cells |
| 82  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3-CD56+ | IFNg+CD69+ | IFNg+CD69+ NK cells |
| 83  | singlet Live CD45+ | CD3+CD19-CD14-CD41a- | CD3-CD56+ | Perforin+GranzymeB+ | Perforin+GranzymeB+ NK cells |
Supplemental Table 3.
SLE disease activity and patient reported outcomes by sequence and period

| Variable         | Period1 (pioglitazone) | Period2 (placebo) | Period1 (placebo) | Period2 (pioglitazone) | Treatment Effect* |
|------------------|------------------------|-------------------|-------------------|------------------------|-------------------|
|                  | Baseline               | Change            | Baseline          | Change                 | Estimate (95%CI)  | P-value          |
| SLEDAI-2K        | 5.13±2.75              | -0.78±1.46        | 4.06±2.14         | 0.22±1.99              | 5.07±3.04         | -1.03±2.66       | -0.72±2.11       | -0.42 (-1.00, 0.16) | 0.15              |
| C3 mg/dL         | 98.5±23.8              | -1.01±13.08       | 99.0±23.73        | 2.77±9.88              | 105.6±25.9        | 0.76±13.44       | -0.84±12.86      | -2.55 (-6.26, 1.17) | 0.18              |
| C4 mg/dL         | 17.0±7.49              | 0.17±4.74         | 16.8±7.13         | 0.72±2.69              | 19.22±10.08       | 0.54±3.16        | -1.38±3.66       | -1.22 (-2.37, -0.07) | 0.04              |
| SF36 Total       | 111.6±9.13             | 0.94±7.29         | 111.47±8.23       | 0.67±6.47              | 112.12±7.88       | -0.2±6.43        | 1.33±6.54        | 1.59 (-0.21, 3.38) | 0.08              |
| PGA              | 0.42±0.2               | -0.06±0.18        | 0.32±0.12         | 0.02±0.26              | 0.38±0.21         | -0.01±0.25       | 0.32±0.18        | -0.06±0.15        | -0.05 (-0.12, 0.01) | 0.12              |

Anti-dsDNA data analysis results: 59 subjects had their anti-dsDNA status unchanged (stayed negative or positive) in both periods, 7 showed improvement (DNA status changed from positive to negative) under PGZ and 3 showed improvement under placebo. All other subjects had mixed results.

Data are mean±SD. Change is defined as the post baseline value minus the baseline value during the period: i.e., M3 – D1 for period 1, M8 – M5 for period 2.
SLEDAI 2K = Systemic Lupus Erythematosus Disease Activity Index 2000; Anti-ds-DNA IU/mL= Anti double-stranded DNA antibody international unit/milliliter; C3 mg/dL= Complement protein C3 milligram/deciliter; C4 mg/dL= Complement protein C4 milligram/deciliter; SF36= Short Form 36; PGA= Physician global assessment

*: Linear mixed effects models were used to calculate the estimated treatment effect (the treatment group difference in the change score between pioglitazone and the placebo), its 95% CI, and the p-value.
Supplemental Table 4. Adverse events by severity

| Body System Preferred Term                      | Mild n (%) | Moderate n (%) | Severe n (%) | Life-Threatening n (%) | Overall n (%) |
|------------------------------------------------|------------|----------------|--------------|-------------------------|---------------|
| Blood and lymphatic system disorders           | 3 (1.2)    | 3 (1.2)        | 0 (0)        | 0 (0)                   | 6 (2.4)       |
| Cardiac disorders                              | 5 (2.01)   | 0 (0)          | 0 (0)        | 0 (0)                   | 5 (2.0)       |
| Eye disorders                                  | 3 (1.2)    | 1 (0.4)        | 0 (0)        | 0 (0)                   | 4 (1.6)       |
| Gastrointestinal disorders                     | 26 (10.4)  | 6 (2.4)        | 1 (0.4)      | 0 (0)                   | 33 (13.3)     |
| General disorders                              | 15 (6.0)   | 2 (0.8)        | 0 (0)        | 0 (0)                   | 17 (6.8)      |
| Immune system disorders                        | 1 (0.4)    | 0 (0)          | 0 (0)        | 0 (0)                   | 1 (0.4)       |
| Infections and infestations                    | 19 (7.6)   | 28 (11.2)      | 5 (2.0)      | 1 (0.4)                 | 53 (21.3)     |
| Injury poisoning and procedural complications   | 0 (0)      | 1 (0.4)        | 0 (0)        | 0 (0)                   | 1 (0.4)       |
| Investigations                                 | 22 (8.8)   | 11 (4.4)       | 4 (1.6)      | 0 (0)                   | 37 (14.9)     |
| Metabolism and nutrition disorders             | 7 (2.8)    | 1 (0.4)        | 0 (0)        | 0 (0)                   | 8 (3.2)       |
| Musculoskeletal and connective tissue disorders| 5 (2.0)    | 4 (1.6)        | 0 (0)        | 0 (0)                   | 9 (3.6)       |
| Nervous system disorders                       | 31 (12.5)  | 3 (1.2)        | 0 (0)        | 0 (0)                   | 34 (13.7)     |
| Psychiatric disorders                          | 4 (1.6)    | 0 (0)          | 0 (0)        | 0 (0)                   | 4 (1.6)       |
| Renal and urinary disorders                    | 7 (2.81)   | 0 (0)          | 0 (0)        | 0 (0)                   | 7 (2.8)       |
| Reproductive system and breast disorders       | 2 (0.8)    | 0 (0)          | 0 (0)        | 0 (0)                   | 2 (0.8)       |
| Respiratory thoracic and mediastinal disorders | 12 (4.8)   | 7 (2.8)        | 0 (0)        | 0 (0)                   | 19 (7.6)      |
| Skin and subcutaneous tissue disorders         | 4 (1.6)    | 1 (0.4)        | 0 (0)        | 0 (0)                   | 5 (2.0)       |
| Surgical and medical procedures                | 0 (0)      | 0 (0)          | 1 (0.4)      | 0 (0)                   | 1 (0.4)       |
| Vascular disorders                             | 2 (0.8)    | 0 (0)          | 1 (0.4)      | 0 (0)                   | 3 (1.2)       |
| Total                                          | 168 (67.5) | 68 (27.3)      | 12 (4.82)    | 1 (0.4)                 | 249 (100)     |
### Supplemental Table 5. Summary of safety laboratory values by sequence and period

| Variable (Mean±SD) | Sequence AB (pioglitazone/placebo) | Sequence BA (placebo/pioglitazone) | Treatment Effect* |
|-------------------|-------------------------------------|-------------------------------------|-------------------|
|                   | Period1(pioglitazone) Period2(placebo) | Period1(placebo) Period2(pioglitazone) |                  |
| AST u/L           | Baseline Change Baseline Change    | Baseline Change Baseline Change    | Estimate (95%CI)  |
|                   | 22.13±7.98 -0.28±4.74 24.61±16.92 -2.31±10.11 | 24.88±13.71 -1.05±13.15 26.42±13.22 -2.19±13.52 | -0.75(-2.39,3.9) 0.64 |
| ALT u/L           | 18.56±8.31 -0.72±8.09 22.42±22.51 -3.08±13.9 | 22.2±18.4 -0.5±16.14 26.34±24.53 -6.86±23.3 | -1.58(-6.01,2.84) 0.48 |
| CRP mg/L          | 3.46±5.07 -1.84±4.31 2.66±5.12 0.35±5.85 | 4.35±6.38 -0.94±7.08 2.67±2.61 1.16±9.5 | -0.04(-2.31,2.23) 0.97 |
| ESR mm/hr         | 24.26±22.55 -2.33±10.25 20.61±21.35 1.56±7.73 | 20.76±14.7 -1.43±10.3 20.37±15.11 1.92±10.8 | -0.28(-3.29,2.74) 0.85 |
| WBC K/mcL         | 5.11±2.04 -0.75±1.33 5.27±2.12 -0.27±1.51 | 5.02±1.33 -0.03±1.49 4.91±1.29 -0.72±1.29 | -0.58(-1.03,0.14) 0.01 |
| RBC M/μL          | 4.32±0.58 -0.21±0.26 4.29±0.55 0.05±0.23 | 4.3±0.49 0.02±0.28 4.31±0.47 -0.19±0.25 | -0.24(-0.32,0.15) <.0001 |
| Hemoglobin g/dL   | 12.66±1.48 -0.46±0.94 12.71±1.36 0.04±0.8 | 12.51±1.51 -0.02±0.76 12.49±1.43 -0.47±0.68 | -0.48(-0.74,0.22) 0.0004 |
| Hematocrit %      | 38.74±3.98 -1.2±2.58 38.7±3.4 0.24±2.19 | 38.07±4.15 0.03±2.33 38.22±3.76 -1.26±2.36 | -1.36(-2.11,0.61) 0.0005 |
| Platelet K/mcL    | 234.74±67.97 -22.42±35.34 220.97±52.42 11.36±30.39 | 225.9±62.22 7.95±50.46 223.5±63.1 -18.19±29.98 | -30.1(-42.32,17.89) <.0001 |
| BUN mg/dL         | 13.18±4.89 2±3.49 13.33±5.13 -0.58±3.47 | 12.59±3.54 1.05±3.21 13.11±4.78 1.75±4.46 | 1.64(0.51,2.77) 0.005 |
| Creatinine mg/dL  | 0.74±0.14 0.04±0.07 0.73±0.15 0.01±0.08 | 0.74±0.2 0.01±0.06 0.73±0.17 0.03±0.07 | 0.02(0.002,0.05) 0.03 |

Data are mean±SD. Change is defined as the post baseline value minus the baseline value during the period: i.e., M3 – D1 for period 1, M8 – M5 for period 2.

AST u/L = Aspartate aminotransferase units/liter; ALT u/L = Alanine aminotransferase units/liter; CRP mg/L = C-Reactive protein milligram/liter; ESR mm/hr = Erythrocyte sedimentation rate millimeters/hour; WBC K/mcL = White blood cell count thousands/cubic milliliter; RBC M/μL = Red blood cells count million/microliter; g/dL = grams/deciliter; BUN mg/dL = Blood urea nitrogen; milligrams/deciliter

*: Linear mixed effects models were used to calculate the estimated treatment effect (the treatment group difference in the change score between pioglitazone and the placebo), its 95% CI, and the p-value.
Supplemental Table 6. Longitudinal transcriptomic profiling of whole blood from 24 subjects.

6A) For 12 subjects from each study arm, comparing between consecutive study timepoints, changes in expression of all genes were used for enrichment analyses of BTM. The number of significantly enriched pathways are reported (FDR<0.05) and periods of pioglitazone treatment highlighted in red.

|         | 0 vs 3 months | 3 vs 5 months | 5 vs 8 months |
|---------|---------------|---------------|---------------|
| **AB arm** | 44            | 30            | 10            |
| **BA arm** | 69            | 28            | 7             |

6B) In the AB arm gene expression changes spanning the pioglitazone treatment period from months 0 to 3 were enriched for 44 pathways shown.

| Pathway name | padj   | NES       |
|--------------|--------|-----------|
| platelet activation (I) (M32.0) | 0.004531 | 2.386684 |
| platelet activation (II) (M32.1) | 0.004531 | 2.570327 |
| CORO1A-DEF6 network (I) (M32.2) | 0.004531 | 2.227201 |
| CORO1A-DEF6 network (II) (M32.4) | 0.004531 | 2.193038 |
| cytoskeletal remodeling (M32.8) | 0.004531 | 2.416415 |
| BCR signaling (M54) | 0.004531 | 2.242604 |
| regulation of localization (GO) (M63) | 0.004531 | 2.375884 |
| enriched in cell cycle (M167) | 0.004531 | 2.461214 |
| chaperonin mediated protein folding (I) (M204.0) | 0.004531 | -2.38958 |
| proteasome (M226) | 0.004531 | -2.39559 |
| translation initiation (M227) | 0.004531 | -2.27608 |
| Term                                                   | p-value  | Log2 Fold Change |
|--------------------------------------------------------|----------|-----------------|
| spliceosome (M250)                                     | 0.004531 | -2.41079        |
| transcription regulation in cell development (M49)     | 0.004535 | 2.214802        |
| enriched in T cells (I) (M7.0)                         | 0.005438 | -1.89505        |
| enriched in NK cells (I) (M7.2)                        | 0.005438 | -1.94443        |
| mismatch repair (I) (M22.0)                            | 0.005438 | -1.99312        |
| KLF12 targets network (M32.3)                          | 0.005438 | 2.126701        |
| MAPK, RAS signaling (M100)                             | 0.005438 | 2.000217        |
| cell cycle, ATP binding (M144)                         | 0.005438 | -2.12247        |
| mitosis (TF motif CCAATNNNSNNNGCG) (M169)              | 0.005438 | -2.21195        |
| heme biosynthesis (I) (M171)                           | 0.005438 | 2.127342        |
| erythrocyte differentiation (M173)                     | 0.005438 | 1.975573        |
| chaperonin mediated protein folding (II) (M204.1)      | 0.005438 | -2.20546        |
| respiratory electron transport chain (mitochondrion)   | 0.005438 | -2.10727        |
| (M216)                                                 |          |                 |
| respiratory electron transport chain (mitochondrion)   | 0.005438 | -2.36719        |
| (M219)                                                 |          |                 |
| respiratory electron transport chain (mitochondrion)   | 0.005438 | -2.10437        |
| (M238)                                                 |          |                 |
| intracellular transport (M147)                         | 0.006423 | -2.09795        |
| respiratory electron transport chain (mitochondrion)   | 0.006423 | -2.02438        |
| (M231)                                                 |          |                 |
| enriched for ubiquitination (M138)                     | 0.015695 | -1.9272         |
| Enrichment Description                                                                 | FDR   | Log2FoldChange |
|--------------------------------------------------------------------------------------|-------|----------------|
| nuclear pore, transport; mRNA splicing, processing (M143)                            | 0.021452 | -1.89463      |
| enriched in membrane proteins (M124)                                                 | 0.022968 | 1.895463      |
| regulation of transcription, transcription factors (M213)                            | 0.024864 | -1.93951      |
| golgi membrane (II) (M237)                                                           | 0.024864 | -1.93583      |
| enriched for TF motif PAX3 (M179)                                                    | 0.025604 | -1.86712      |
| mitochondrial cluster (M235)                                                         | 0.025858 | -1.88417      |
| nuclear pore complex (M106.0)                                                        | 0.031756 | -1.82812      |
| phosphatidylinositol signaling system (M101)                                          | 0.032571 | -1.83433      |
| T cell activation (I) (M7.1)                                                         | 0.035241 | -1.68189      |
| heme biosynthesis (II) (M222)                                                        | 0.035241 | 1.807254      |
| enriched in T cells (II) (M223)                                                      | 0.035241 | -1.82317      |
| Resting dendritic cell surface signature (S10)                                        | 0.03856  | 1.634133      |
| cell cycle, mitotic phase (M230)                                                     | 0.03897  | -1.80618      |
| translation initiation factor 3 complex (M245)                                        | 0.043798 | -1.77373      |
| CD4 T cell surface signature Th2-stimulated (S7)                                     | 0.043798 | -1.78455      |
6C) In the BA gene expression changes spanning the pioglitazone treatment period from months 5 to 8 were enriched for 7 pathways shown. For each pathway adjusted p values (padj) and normalized enrichment scores (NES) are reported.

| Pathway name                                      | padj    | NES      |
|---------------------------------------------------|---------|----------|
| enriched in monocytes (II) (M11.0)                | 0.016859| 1.777754 |
| intracellular transport (M147)                    | 0.016859| 2.060838 |
| DC surface signature (S5)                         | 0.016859| 2.121322 |
| cell cycle, ATP binding (M144)                    | 0.019504| 1.994704 |
| cell division - E2F transcription network (M4.8)  | 0.025238| 1.974083 |
| platelet activation (II) (M32.1)                  | 0.037629| -1.84243 |
| endoplasmic reticulum (M37.2)                     | 0.037629| 1.906045 |
### Supplemental Table 7. Longitudinal high-dimensional cytometry phenotyping of 24 subjects.

7A) Broad immune lineages were assessed in unstimulated PBMC using a 27-color panel quantifying 58 populations. For 12 subjects from each study arm, comparing between consecutive study timepoints, changes in frequency for each population were assessed by paired t test. The number of populations changing with nominal significance are reported (p<0.05) with periods of pioglitazone treatment highlighted in red.

|          | 0 vs 3 months | 3 vs 5 months | 5 vs 8 months |
|----------|---------------|---------------|---------------|
| **AB arm** | 6             | 4             | 1             |
| **BA arm** | 0             | 3             | 4             |

7B) In the AB arm 6 populations which showed nominally significant changes between months 0 and 3 when treated with pioglitazone are reported.

| Population name                              | p value     | p adj         | change |
|----------------------------------------------|-------------|---------------|--------|
| IgD-CD27- B cells                            | 0.003499328 | 0.199461694   | up     |
| CD38+ HLA-DR+ activated cytotoxic T cells    | 0.013402901 | 0.311747941   | up     |
| CXCR3+CCR10-CCR6- T helper cells (Th1)       | 0.018423396 | 0.311747941   | down   |
| CD38+ activated cytotoxic T cells (actTe)    | 0.021877048 | 0.311747941   | up     |
| CXCR3-CCR10-CCR6- T helper cells (Th2)       | 0.031399249 | 0.357951437   | up     |
| Memory IgD+ B cells                          | 0.047990365 | 0.455908466   | down   |
7C) In the BA arm 4 populations which showed nominally significant changes between months 5 and 8 when treated with pioglitazone are reported.

| Population name                        | p value       | p adj            | change |
|----------------------------------------|--------------|------------------|--------|
| Central memory T helper cells          | 0.003078447  | 0.175471491      | down   |
| CCR4+CCR6+ T helper cells (TH22_Th17)  | 0.008299668  | 0.236540551      | down   |
| Myeloid Dendritic cells                | 0.02680646   | 0.457905801      | up     |
| CXCR5-CCR6-T helper cell subsets       | 0.03213374   | 0.457905801      | down   |

7D) A more comprehensive analysis of T cell phenotypes was assessed in PBMC stimulated with PMA using a 34-color panel quantifying 83 populations. Again for 12 subjects from each study arm, comparing between consecutive study timepoints, changes in frequency for each population were assessed by paired t test and the number of populations changing with nominal significance are reported (p<0.05), with periods of pioglitazone treatment highlighted in red.

|       | 0 vs 3 months | 3 vs 5 months | 5 vs 8 months |
|-------|---------------|---------------|---------------|
| AB arm | 2             | 12            | 2             |
| BA arm | 5             | 7             | 8             |
7E) In the AB arm 2 populations which showed nominally significant changes between months 0 and 3 when treated with pioglitazone are reported.

| Population name            | p value       | p adj           | change |
|----------------------------|---------------|-----------------|--------|
| IL-17A+IL-22+ Th cells    | 0.029328693   | 0.871776657     | down   |
| RORgT+IL-22+ Th cells     | 0.040843106   | 0.871776657     | down   |

7F) In the BA arm 8 populations which showed nominally significant changes between months 5 and 8 when treated with pioglitazone are reported.

| Population name            | p value       | p adj           | change |
|----------------------------|---------------|-----------------|--------|
| GATA3+Th2 cells           | 0.003899897   | 0.283905385     | down   |
| Tbet+ Th1 cells            | 0.00959779    | 0.283905385     | up     |
| Tbet+TNF+ Th cells         | 0.015756715   | 0.283905385     | up     |
| Naive Tc                   | 0.016004047   | 0.283905385     | down   |
| Perforin+ Tc               | 0.019028108   | 0.283905385     | up     |
| Perforin+GranzymeB+Tc      | 0.020773565   | 0.283905385     | up     |
| Effector Tc                | 0.038717688   | 0.435032839     | up     |
| GranzymeB+Tc               | 0.049714765   | 0.435032839     | up     |
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