Supplementary Material

Trial design: Randomized controlled trial including a total of 96 patients with 1:1:1 allocation to adalimumab injections, placebo injections, or narrow band ultraviolet B phototherapy at baseline (NCT01553058). At week 12 eligible patients entered an open label extension in which they were treated with adalimumab for a total of 40 (if initially assigned to adalimumab) weeks or 52 weeks (if initially assigned to placebo injections or phototherapy) (NCT01866592).

Participants: To be included in the study participants had to be 18 years of age or older with a diagnosis of psoriasis for at least 6 months and that of stable moderate-to-severe plaque psoriasis for at least 2 months. Moderate to severe psoriasis skin disease severity was defined as body surface area ≥10% and psoriasis area severity index score ≥12 at baseline visit. Women of child bearing potential were required to use contraception and subjects were required to be in good health based on medical history, screening labs, physical exam, and electrocardiogram results. Patients were excluded if they had a previous adverse event or lack of response to a TNF-alpha antagonist and/or UV phototherapy that led to discontinuation of either of these therapies; had diagnoses of other forms of psoriasis or other active skin conditions that may interfere with evaluation of psoriasis; used any of the following psoriasis treatments: UVB phototherapy within 14 days of baseline, psoralen-UVA phototherapy within 30 days of baseline, oral psoriasis treatments within 30 days of baseline, biologics within 90 days of baseline (or 180 days for ustekinumab); investigational agents within 30 days or 5 half-lives (whichever is longer) of baseline; subjects requiring oral or injectable steroids, or with a poorly controlled medical condition, history of diabetes mellitus (unless the duration of type 2 diabetes is <10 years and HbA1c is <7.0%); uncontrolled hypertension, with measured systolic blood pressure >180 mmHg or diastolic blood pressure >90 mmHg; history of demyelinating diseases or

photosensitivity, or lupus; active infection or risk factors for severe infection; has history of hematological or solid malignancy within the past five years other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical carcinoma in situ; female subject who is pregnant or breast-feeding or considering becoming pregnant during the study; Hemoglobin (Hgb) < 10 g/dL in females or <12 g/dL in males; white blood cell (WBC) count <2.5 x 10^9/L or > 15 x 10^9/L; platelet count < 100 x 10^9/L; serum aspartate transaminase (AST) or alanine transaminase (ALT) >2.5 upper limits of normal; serum total bilirubin ≥2 mg/dL; serum creatinine >1.6 mg/dL; recent history of substance abuse or psychiatric illness that could preclude compliance with the protocol; history of any substance abuse within 365 days of screening visit; alcohol use >14 drinks per week at the screening visit or within 30 days of the screening period; if subject is on cholesterol-lowering medication (e.g. statin), dose and form of medication must be stable for 90 days prior to week 0 and remain stable throughout the duration of the study. The study was conducted at 8 centers across the United States.

Interventions: Adalimumab (or corresponding placebo) therapy was administered in a double-blind manner as subcutaneous injection with an initial 80mg dose at week 0, followed by maintenance doses of 40mg every other week, starting from week 1 and then continued throughout the study. These doses were consistent with those reported in previous randomized trials that have demonstrated efficacy of adalimumab in treating psoriasis skin disease.[1, 2] During the placebo-controlled period, adalimumab was administered at the study site and during the extension phase, subjects were given the option of home dosing of adalimumab therapy. NB-UVB phototherapy dosing was based on estimated minimal erythema dose (MED) and Fitzpatrick skin type using a standardized protocol published by Zanolli and Feldman.[3] Subjects with skin types 1-2, 3-4, and 5-6 respectively received 300, 500, and 800 mJ/cm^2 as initial doses.

Thereafter, dosing was adjusted at each treatment visit allowing for increases as a percentage of MED based on patient reaction to the previous treatment. Patients presenting with 1) transient erythema lasting <24 hours following treatment had a 20% dose increase; 2) persistent erythema for 24-48 hours had the same dose held until the erythema lasts <24 hours; 3) persistent erythema for >48 resulted in no treatment on that day and a return to the last lower dose that did not cause persistent erythema.

Primary Outcomes: The primary imaging outcome for our study was the change in total vascular inflammation estimated as target to background ratio (TBR) ^{18}F-FDG PET/CT at week 12 compared to baseline in adalimumab and phototherapy groups compared to placebo. ^{18}F-FDG PET/CT scans were analyzed to derive TBR values to quantify vascular inflammation by previously published, and validated methods[4]. Patients underwent ^{18}F-FDG PET/CT scans using the standard protocol [5, 6] following overnight fast. Serum glucose levels were checked to ensure a glucose level <200 mg/dL prior to FDG administration. Standard bed positions of three minutes each, scanning whole body were obtained for each patient from the vertex of the skull to the toes. All scans were completed and images obtained using (Gemini TF; Philips Medical Systems, Bothell, Washington, USA, and Siemens Biograph mCT PET/CT 64 slice scanner, Malvern, PA, USA) about 60 minutes after IV administration of 15 mCi of ^{18}F-FDG with 1.5-4mm axial slices of the aorta obtained. After qualitative review of PET and CT images, the extent of ^{18}F-FDG uptake within the aorta was directly measured by using a dedicated image analysis software (OsiriX MD, Pixmeo SARL, Bernex, Switzerland) to measure vascular inflammation calculated as TBR. Each region of interest produced two measures of metabolic activity: a mean standardized uptake value (SUV_{mean}) and maximal standardized uptake value (SUV_{max}), and these were obtained in the entire aorta from the aortic outflow tract to the abdominal aorta.

Moreover, 1 cm^2 regions of interest were also placed on 6 contiguous slices over the superior vena cava to obtain background activity of the FDG tracer. The SUV_{mean} from each of the superior vena cava slices were then averaged to produce one venous value. To account for background blood activity, SUV_{max} values from each aortic slice were divided by the average venous SUV_{mean} value yielding TBR_{max} values, the primary outcome measure[4, 7-9]. Image analysis was completed at NIH with a random sample of analyses confirmed at PENN for quality assurance.

We also conducted a series of analyses of biomarkers of cholesterol, glucose metabolism, and inflammation selected based on their known association with psoriasis and/or cardiovascular disease at baseline, week 4, and 12.

Secondary outcomes: Change in vascular inflammation and cholesterol/metabolic/inflammatory biomarkers at week 52 (for those originally assigned to adalimumab) or 64 (for those originally assigned to placebo or phototherapy) compared to baseline or week 12. We also evaluated clinical measures of psoriasis such as the psoriasis area and severity index (PASI) and physician's global assessment (PGA) at week 4, 8, 12, and week 52 or 64 and report a dichotomized 75% reduction in PASI (called PASI75) which is a standard endpoint for this measure[10]. We used a 6 point PGA (0=clear, 1=minimal, 2=mild, 3=moderate, 4=marked, 5=severe, individually scored for erythema, induration, and scaling and then averaged), dichotomized as clear or almost clear disease (0–1), which is a standard endpoint for this measure[11]. We evaluated change in patient-reported outcomes (i.e. EQ-5D (a generic measure of health related quality of life), DLQI (a skin specific measure of quality of life), MEDFICTS[12] (a measure of diet), and IPAQ[13] (a measure of physical activity)) from baseline to week 4, 8, 12, and week 52 or 64 (EQ-5D and DLQI to be reported separately).

Sample size: Sample size calculations were based on the primary outcome on changes in standard uptake value (SUV) of the tracer measured by FDG-PET/CT. Using a two-sided test with significance level of α=0.017 (applying a Bonferroni correction), we determined that 32 patients per arm would provide 82% power to detect the clinically significant change in SUV of 0.1 between groups assuming an anticipated standard deviation (SD) of the change in SUV of 0.11 and a drop-out rate of 15%.

Randomization: Study group assignment was performed via block randomization (of 3 and 6), stratified by center, using a computerized system at the Investigational Drug Services (IDS), University of Pennsylvania.

Blinding: Study investigators, staff, and patients were blinded to adalimumab or placebo status during the placebo-controlled period. No blinding was provided for the phototherapy group as this was not feasible. All scans were read in a blinded fashion to patient characteristics, treatment allocation and visit dates. (i.e., baseline, week 12, or end of study).

Statistical methods: Stata 14 (StataCorp, College Station, TX) was used for analysis. All data were summarized using descriptive statistics (mean, SD, range for continuous variables; frequencies for categorical variables) and graphical techniques (histograms, scatterplots); missing data were summarized using frequencies for each outcome measure.

An intention-to-treat approach was used for the primary analyses. The primary analyses were the comparisons of the treatment effects of adalimumab, phototherapy and placebo, on the outcome measures. The changes in TBR_{max} and biomarker values were calculated for each subject and compared across groups using linear regressions. The primary analyses were restricted to subjects who completed the trial (i.e. had primary outcome measures assessed at baseline and week 12). For TBR_{max}, additional multivariate linear regression models were fitted

to assess sensitivity to potential imbalance of covariates, adjusting for clinical and demographic covariates using a backward model building approach (age, sex, major CVD risk factors (serum glucose, systolic and diastolic blood pressure, tobacco use, serum LDL, HDL, and total cholesterol, BMI, and psoriasis activity)). Analyses were performed on the natural log scale for the concentrations of triglycerides, VLDL triglycerides, insulin, leptin, adiponectin, high-reactive CRP, TNF-alpha, GlycA, and IL-6. For binary outcomes, the treatment group comparisons were assessed using logistic regression models.

The secondary analyses were the changes in outcome measures from baseline to the end of open label extension period, and were restricted to subjects whose outcome measures were assessed at the end of study or at early termination. The final analytic sample sizes were also within the target sample size for the extension study. The mean changes and proportions were calculated along with their respective 95% confidence intervals (CIs). Additional analyses included longitudinal random effects models, restricting to adalimumab treatment period only (i.e. from baseline to end of extension trial for patients randomized to adalimumab group and extension trial period only for patients randomized to placebo and phototherapy), and various sensitivity analyses. Group-level summary measures of clinical disease severity and patient-reported outcomes were also plotted longitudinally along with their respective 95% CIs.

Study ethics: Study approval was obtained from the Institutional Review Board (IRB) of the University of Pennsylvania or respective local IRB when indicated in accordance with the principles of Declaration of Helsinki. All guidelines for good clinical practice and those set forth by the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research) were followed. All study participants in the study

provided written informed consent. The randomized placebo controlled trial was overseen by an independent data monitoring committee.

Role of the sponsors: The sponsors (NHLBI and Abbvie) had no role in the analysis or reporting of the results. Abbvie reviewed the manuscript for compliance purposes.

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Supplemental Table 1. Changes in clinical measures by treatment group during RCT period

	Placebo	Adalimumab		Phototherapy		
			Compared to Placebo[1,2]		Compared to Placebo[1,2]	F-test p-value
PASI75 N (%)	2 (6.67)	15 (46.88)	12.35[2] (0.002)	14 (46.67)	12.25[2] (0.002)	0.005
PGA Clear/ Almost clear N (%)	2 (6.67)	14 (43.75)	10.89[2] (0.003)	8 (26.67)	5.09[2] (0.053)	0.011

[1] Difference of differences (p-value)

[2] Odds Ratio (p-value)

Supplemental Table 2. Changes in clinical measures from RCT baseline to end of open label extension

	End of study (N=67)
PASI 75 N, Proportion (95% CI)	40, 0.61 (0.48, 0.72)
PGA clear/almost clear N, Proportion (95% CI)	35, 0.53 (0.40, 0.65)

Supplemental Table 3: Mean SUVmax and TBRmax values from each group of the study at specified time-points

	Placebo			Adalimumab			Phototherapy		
	Baseline	Week 12	Week 52	Baseline	Week 12	Week 52	Baseline	Week 12	Week 52
N	31	30	24	33	32	21	32	30	22
SUV max (SD)	2.497 (0.640)	2.493 (0.640)	2.589 (0.585)	2.500 (0.517)	2.488 (0.553)	2.480 (0.497)	2.581 (0.914)	2.621 (0.825)	2.468 (0.551)
TBR max (SD)	1.620 (0.267)	1.579 (0.227)	1.564 (0.234)	1.610 (0.336)	1.547 (0.176)	1.558 (0.158)	1.636 (0.226)	1.567 (0.190)	1.587 (0.178)