

Original Research**Randomized Double-Blinded Pilot Study of Doxycycline for HIV-Associated COPD and Emphysema**

Robert J. Kaner, MD^{1,2} Sarah L. O’Beirne^{1,2*} Amy Krambrink³ Cathie Spino³ He Sarina Yang⁴
Yuan-Shan Zhu^{5,6} Ronald G. Crystal^{1,2} Marshall J. Glesby⁷

¹Division of Pulmonary and Critical Care Medicine, Weill Cornell Medicine, New York, New York, United States

²Department of Genetic Medicine, Weill Cornell Medicine, New York, New York, United States

³Statistical Analysis of Biomedical and Educational Research Group, Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, United States

⁴Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, New York, United States

⁵Clinical and Translational Science Center, Weill Cornell Medicine, New York, New York, United States

⁶Division of Endocrinology, Diabetes and Metabolism, Weill Cornell Medicine, New York, New York, United States

⁷Division of Infectious Diseases, Weill Cornell Medicine, New York, New York, United States

**Current affiliation: University College, Dublin, Ireland*

Address correspondence to:

Robert J. Kaner, MD
1300 York Avenue, Box 164
Weill Cornell Medicine
New York, NY 10065
Email: rkaner@med.cornell.edu

Running Head: Doxycycline for HIV-Associated COPD and Emphysema

Keywords: COPD; emphysema; treatment protocols; immunodeficiency

Abbreviations:

Funding Support: Research reported in this publication was supported by the National Heart, Lung, and Blood Institute and National Center for Advancing Translational Sciences of the National Institutes of Health under awards R34HL117352 and UL1TR002384 (Weill Cornell Medicine Clinical and Translational Science Center). Pfizer, Inc (New York, NY) provided doxycycline (Vibramycin®). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Date of Acceptance: September 3, 2026 | **Published Online Date:** September 30, 2026

Citation: Kaner RJ, O'Beirne SL, Krambrink A, et al. Randomized double-blinded pilot study of doxycycline for HIV-associated COPD and emphysema. *Chronic Obstr Pulm Dis*. 2026; Published online September 30, 2026.

<https://doi.org/10.15326/jcopdf.2026.0796>

This article has an online supplement.

Abstract

Rationale: Emphysema is prevalent in smoke-exposed people living with HIV. Matrix metalloproteinases are increased in bronchoalveolar lavage (BAL) fluid in People Living with HIV (PLWH) with emphysema. Doxycycline is an FDA-approved MMP-9 inhibitor, in addition to its antimicrobial properties.

Objectives: To test the safety and tolerability of doxycycline in PLWH.

Methods: Single center double blind randomized placebo-controlled (2:1) pilot study of doxycycline 100 mg po twice daily in 27 PLWH who have COPD and/or emphysema (NCT01744093).

Measurements and Main Results: Doxycycline was safe and well-tolerated. There were robust serum and BAL fluid levels of doxycycline in individuals assigned to the doxycycline arm. Preliminary evidence of potential biologic effects of doxycycline in the lung included a reduction in BAL lung lymphocytes and a trend toward decreased MMP-9 activity.

Conclusions: These data provide a rationale for a Phase II 72-week randomized placebo-controlled trial of doxycycline to slow the progression of emphysema in PLWH (NCT05382208).

Introduction

With the success of antiretroviral therapies in treating people living with HIV (PLWH), co-morbidities are assuming increasing importance¹. In a recent systematic review and meta-analysis, the overall prevalence of chronic obstructive pulmonary disease (COPD) in six studies of PLWH was estimated to be 10.6%. After adjusting for tobacco use, the risk of COPD remained higher in PLWH compared to persons without HIV². A subsequent meta-analysis reported associations between HIV and obstructive lung disease, impaired gas exchange, emphysema and more rapid decline in lung function. Furthermore, in an umbrella review of meta-analyses of observational studies of physical health outcomes, higher COPD prevalence was one of five of 55 health outcomes that showed suggestive evidence of being associated with HIV. HIV infection may accelerate the onset of emphysema in PLWH³ and both the prevalence and severity of emphysema were greater in veterans with HIV compared to controls⁴. COPD/emphysema contributes to excess mortality, more rapid lung function decline, frailty, poorer functional status, hospitalizations, in-hospital mortality and greater healthcare utilization in PLWH⁵⁻¹³. The GOLD Guidelines recognize HIV as a risk factor for the development of COPD¹⁴.

The extracellular matrix, including basement membranes, is the scaffolding that provides the structure of organs, including the lung. Matrix metalloproteinases are a family of enzymes with the capacity to degrade the lung extracellular matrix. Matrix degradation is a key component of emphysema pathogenesis. Degradative enzymes are released by leukocytes, particularly neutrophils and macrophages. The paradigm disease for this process is alpha-1 antitrypsin deficiency leading to unopposed enzymatic activity and increased risk of emphysema. We previously observed that PLWH with early emphysema have increased matrix metalloproteinases (MMP-2, -7, -9, -12; each implicated in emphysema pathogenesis¹⁵) in

bronchoalveolar lavage (BAL) fluid samples relative to controls and HIV-negative individuals with emphysema¹⁶. MMPs are therefore potential targets for intervention aimed at modifying progression of emphysema specifically in PLWH. In addition to its antimicrobial effects, doxycycline is FDA-approved as an MMP inhibitor (by binding to the active site in MMP-9) to prevent tissue breakdown in periodontal disease. Based on this background, doxycycline is a candidate drug to test in slowing the progression of emphysema in PLWH¹⁷.

There are prior studies evaluating the efficacy of doxycycline in COPD. A retrospective analysis showed that short-term doxycycline added to steroids in the treatment of acute exacerbation of COPD reduced treatment failures in individuals 75 years or older¹⁸. In a small randomized, placebo-controlled trial, a 3-week course of doxycycline did not reduce sputum or systemic markers of inflammation in people with COPD¹⁹. Once daily doxycycline over 12 months did not reduce the overall incidence of acute exacerbations of COPD but did demonstrate benefit in individuals with severe COPD or blood eosinophils < 300/ml²⁰.

As the initial step towards testing the hypothesis that doxycycline will favorably affect the natural history of emphysema in PLWH and given the paucity of safety and tolerability data in this population, we conducted a proof of concept, randomized, double-blinded placebo-controlled pilot study of doxycycline for COPD/emphysema in PLWH to assess short-term safety and biological effects. We also report BAL fluid concentrations of doxycycline, which have not been systematically studied in humans.

Methods

Design

This was a single center, randomized, placebo-controlled trial of oral doxycycline 100 mg twice daily for 24 weeks (NCT01744093). Eligible participants were randomized by the investigational

pharmacy in a 2:1 ratio to doxycycline or placebo using permuted blocks of size 3. Lists of treatment assignments were generated by the research pharmacist based on a random numbers table. Only the research pharmacist was aware of treatment assignments until the study was completed and unblinded. The randomization occurred prior to the first research bronchoscopy. Participants were instructed to initiate study drug on the day after the bronchoscopy. The study was approved by the Weill Cornell Medical College Institutional Review Board, and all participants provided written informed consent.

Entry Criteria

Eligible participants had documented HIV infection with current CD4 cell count >200 cells/mm³, HIV RNA level <400 copies/ml on stable antiretroviral therapy for ≥ 12 weeks. They were current or former smokers (minimum 3 pack-year history³) and met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition for COPD (post-bronchodilator forced expiratory volume in 1 sec/forced vital capacity (FEV₁/FVC) <0.7)²¹ Grade I or II and/or had radiographic evidence of emphysema ($\geq 5\%$ of voxels <-910 Hounsfield units on chest CT). We chose the more lenient cutoff for Hounsfield units (vs <-950 HU) in order to be inclusive of individuals with early emphysema. We chose a minimum of 3 pack-years to maximize inclusivity, based on the concept of increased susceptibility to emphysema in the original description by Diaz et al³, where the average pack-years was 7. Those on therapy for COPD must have been on stable doses for at least 4 weeks. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were less than 3 x upper limit of normal. Exclusion criteria included: pulmonary infection, COPD exacerbation, or acute opportunistic infection within 30 days of entry; conditions with increased sedation risk, including but not limited to GOLD Class 3/4 COPD, requirement for home oxygen, hypercapneic respiratory failure, or poorly controlled hypertension; known allergy/intolerance to doxycycline or any local anesthetic; inability to

provide informed consent; pregnant or lactating persons; receipt of any investigational drug within 28 days; end stage renal disease; cirrhosis; international normalized ratio (INR) >1.4, platelets <80,000/ μ L; any condition including active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements or increase the risk of bronchoscopy.

Study Drug

Doxycycline hyclate 100 mg (Vibramycin[®]) capsules were provided by Pfizer Inc and emptied and re-encapsulated to match placebo capsules with lactose filler (Rockwell Compounding Associates, Inc., Rye, NY).

Key Assessments

Eligibility was assessed after a screening visit with baseline laboratory tests, pulmonary function tests and a high-resolution chest CT (multiple helical CT images acquired at a slice thickness of 1.25 mm) at a pre-entry visit unless CT data were available within the preceding 12 months. Percent emphysema, defined as the percent of lung voxels less than -910 Hounsfield units, was quantified by Slicer density mask software (<https://chestimagingplatform.org>)²². Pulmonary function tests were performed according to ATS guidelines^{23, 24}. Spirometry pre- and post-bronchodilator was repeated at study entry and used as the baseline values. The diffusing capacity (DLCO) was adjusted for carboxyHb (COHb) and percent predicted calculated using Global Lung Function Initiative (GLI) race-neutral equations²⁵. Participants underwent bronchoscopy with bronchoalveolar lavage and brushings at study entry and week 12²⁶. Adverse event assessments including safety laboratory testing were done at weeks 2, 6, 12, 18 and 24 and graded using the NIH Division of AIDS Toxicity Grading Table²⁷. Follow-up spirometry was done at weeks 12 and 24 and DLCO at week 24. The COPD Assessment Test (CAT)²⁸ and smoking questionnaires were administered at entry and weeks 6, 12, and 24. Bronchoalveolar

lavage (BAL) fluid MMP-9 activity was semi-quantified by gelatinase assays and normalized to total protein (BCA assay). Doxycycline levels were quantified in BAL fluid and plasma by High-Performance Liquid Chromatography-Mass Spectrometry (HPLC/MS). Serum inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6), interferon- γ (IFN- γ), and tumor necrosis factor- α (TNF- α) were determined by an electrochemiluminescent method (Meso Scale Diagnostics, Rockville, MD), procalcitonin (PCT, BioVendor, Asheville, NC) and soluble CD14 (sCD14, Abcam, Waltham, MA) were assayed by ELISA in the Clinical Translational Science Center Core Laboratory, Weill Cornell Medicine. Study personnel were blinded to the treatment assignments during the assessment of all clinical and laboratory parameters.

Primary and Secondary Endpoints

The primary endpoint was safety and tolerability of the study drug, as measured by the number of participants with any treatment-related or dose-limiting adverse events. Secondary outcomes included: levels of MMP-9 activity in BAL fluid before and after study drug administration; change in FEV₁, FEV₁/FVC, and diffusing capacity (DL_{co}); change in respiratory symptoms by CAT; change in serum inflammatory markers; change in BAL absolute cell number; change in BAL fluid MMP-9 activity; and incidence of acute exacerbations of COPD.

Statistical Analysis

The study was powered on an expected rate of grade 2 or higher toxicity of 20-30%. With an overall sample size of 30 (20 doxycycline recipients) provided approximately 80% power (one-sided alpha = 0.05) to detect a true proportion of 20% (grade 2 or higher toxicity) while rejecting the null hypothesis of 45.5% or higher (in other words, ruling out the possibility of the event rate being any higher than 45.5%).

Secondary analyses.

The change in continuous outcomes were compared between the doxycycline and placebo

arms using two-sample independent t-tests. Non-parametric Wilcoxon Rank Sum tests were used when normality assumptions were not met. Given the potential for imbalance in baseline values, ANCOVA was also utilized, adjusting for baseline values as a covariate.

The difference in MMP9 (defined as Week 12 MMP9*1000/protein minus Week 0 MMP9*1000/protein) was also dichotomized as an increase vs decrease and the association with treatment was explored using Fisher's Exact test.

Among those in the doxycycline arm, relationships between serum doxycycline levels and each of the inflammatory markers (CRP, IFNG, IL6, TNF, sCD14) at Week 24 were examined using scatterplots. Due to non-normal data, Spearman rho was used to measure the monotonic relationship between drug concentration at Week 24 and each inflammatory marker. The relationship between the change in cell differentials (neutrophils, lymphocytes, and eosinophils) from baseline to Week 12 and the Week 12 doxycycline concentration levels were explored in similar fashion.

Data are expressed as mean $\pm$ standard deviation or median (Q1, Q3). Mean differences between treatment groups are reported as mean values of those in the doxycycline arm minus the mean of those in the placebo arm. Data were analyzed with SAS version 9.4. Due to the exploratory nature of many of the endpoints, p-values were not adjusted for multiple comparisons.

Results

Participant Disposition

We screened 61 and enrolled 27 participants of a planned 30 prior to closing due to slow accrual. The first and last participants were randomized on 2/5/2015 and 2/17/2017, respectively. Figure 1 summarizes the disposition of participants. Two participants in the doxycycline arm and

one in the placebo arm withdrew consent prior to the baseline bronchoscopy and did not initiate study drug. Paired BAL fluid samples from baseline and week 12 were available on 10 participants in the doxycycline arm and 7 in the placebo arm.

Characteristics

Table 1 summarizes the baseline characteristics of the study participants. The majority of participants were male, African American, and current smokers with well-controlled HIV infection. Twelve of 27 (44%) with available data were hepatitis C virus seropositive. Two of 27 (7%) were hepatitis B surface antigen (HBsAg) positive, one of whom had documented HBV viremia. An additional participant had an indeterminant HbsAg result. Thirty percent were taking inhaled bronchodilators and 7.4% were on inhaled corticosteroids. Twelve participants had protocol-defined emphysema ($\geq 5\%$ of voxels < -910 Hounsfield units). Of those with emphysema, % emphysema was similar in the 2 arms: 13% (10, 23) in the doxycycline arm and 14% (11, 24) in the placebo arm.

Safety and Tolerability

There were no serious or treatment-limiting adverse events. One participant in the placebo arm had a mild reversible creatinine elevation. Table 2 lists the adverse events by study arm. Adverse events were not concentrated in a single category and were mild in intensity.

There were no significant changes in COPD symptoms as assessed by the CAT (data not shown). No COPD acute exacerbations were observed during the study.

Pulmonary Function

There were a total of 22 subjects (13 doxycycline and 9 placebo) with FEV₁, FVC, and FEV₁/FVC measurements at both weeks 0 and 12, and 19 subjects (11 doxycycline and 8 placebo) at both weeks 0 and 24. Change from Week 0 was defined as Week 12/24 measurements minus Week 0. Supplemental Figure 1-3 show the distributions of FEV₁, FVC,

and FEV1/FVC, respectively, at baseline, Week 12 and Week 24. There were no significant differences in the change in any of the pulmonary measures between the doxycycline and placebo arms at either Week 12 or Week 24, after adjusting for baseline values ($p>0.14$, ANCOVA).

There were a total of 19 participants (11 doxycycline and 8 placebo) with DLCO measurements at both weeks 0 and 24. The change from Week 0 was defined as Week 24 %predicted DLCO minus Week 0 %predicted DLCO. There was a numerically larger mean decrease in %predicted DLCO from Week 0 to Week 24 in the placebo group compared to the doxycycline group (-2.6 vs -0.4, Figure 2), although this difference between treatment groups was not statistically significant after adjusting for baseline DLCO (-0.094; 95% CI = -5.59 to 5.41; $p=0.972$; ANCOVA).

Doxycycline Levels

Doxycycline levels (ng/ml) were quantifiable in serum (3950 ± 2062) and BAL fluid (20.0 ± 12.8) in 11 of the 12 individuals with measurable levels assigned to the doxycycline arm at week 12 (Figure 3). Serum and BAL concentrations were closely correlated (Spearman's $\rho=0.72$; $p=0.013$).

Effects on BAL Cell Differentials

There were a total of 20 participants (12 doxycycline and 8 placebo) with absolute cell differentials normalized to BAL fluid at both Week 0 and Week 12; change was defined as Week 12 values minus Week 0 values. There were no statistically significant differences in the change from baseline to Week 12 for BAL fluid neutrophils, eosinophils or lymphocytes between the doxycycline and placebo arms ($p>0.27$, ANCOVA, Supplemental Figures 4, 5 and 6). Higher BAL concentrations of doxycycline were associated with larger decreases in lymphocytes

(Spearman's $\rho = -0.63$, $p = 0.028$, Supplemental Figure 7) and eosinophils (Spearman's $\rho = -0.58$, $p = 0.050$, Supplemental Figure 8).

Effects on MMPs

There were 18 total participants (11 doxycycline and 7 placebo) with MMP9 measurements at both Week 0 and Week 12. Among participants with paired bronchoscopy data, a higher proportion of participants in the doxycycline arm had decreases in MMP-9 activity in BAL fluid at week 12 vs baseline (8 of 11 participants on doxycycline versus 3 of 7 participants on placebo ($p = 0.22$, Fisher's exact test). The median % change in MMP-9 activity compared to baseline (ng/mg protein) was -38.4 (IQR: -61.8; 46.7) for the doxycycline arm and +20.9 (IQR: -23.1; 93.2; $p = 0.09$, Wilcoxon Rank Sum test) for the placebo arm (Figure 4).

Cytokines/Inflammatory Markers

There were no significant monotonic relationships between serum levels of doxycycline and any of the inflammatory markers, CRP, IL-6, IFN- γ , TNF- α , and sCD14 at Week 24 ($p > .44$, Spearman's ρ , Supplemental Figures 9-13).

Discussion

In this small pilot study of PLWH with COPD and/or emphysema and tobacco smoke exposure, doxycycline at full treatment doses of 100 mg po bid was safe and well-tolerated over 24 weeks. It is interesting to note that the participants had significant respiratory symptoms (CAT scores 14-17), but only 30% were using inhaled bronchodilators at study entry. Of note, symptom burden due to COPD is higher in PWH²⁹. This is concordant with our anecdotal experience of undertreatment of COPD in PWH. While the study was not powered to detect physiologic or biomarker endpoints, there was relative stabilization of the DLCO from baseline to week 24 in the doxycycline arm, although this was not statistically significant. Quantitative

changes in emphysema were not assessed, as we opted not to repeat the CT scan at 24 weeks given the expected slow rate of progression of emphysema in this relatively short time frame³⁰.

The doxycycline drug concentrations observed at week 12 indicate good adherence to the protocol. The levels also suggest robust drug concentrations in both serum and epithelial lining fluid, allowing for the ~50-fold dilution of epithelial lining fluid by infused saline in the BAL technique²⁶. This study adds to our understanding of lung penetration of doxycycline as assessed by BAL fluid concentrations, which have not previously been reported in humans. Prior human data are limited to sputum/plasma concentration ratios in people with cystic fibrosis dosed with doxycycline, which suggested moderate lung penetration³¹. The BAL fluid concentrations of doxycycline are relevant to the site of action of destruction of alveolar walls in emphysema. These alveolar drug levels also comport with the proven clinical efficacy of doxycycline in successfully treating mild to moderate community acquired pneumonia³².

Interestingly, there was a statistically significant association of BAL doxycycline levels with reduction of BAL fluid lymphocytes, which have been implicated in the pathogenesis of emphysema¹⁸, particularly in PLWH³. There was also a trend toward reduction in BAL MMP-9 activity levels in the doxycycline arm. These observations are evidence of potentially favorable biologic effects of doxycycline in the alveolar space in PLWH.

There are significant limitations to our study. As a pilot study, it was not adequately powered to identify infrequent side effects, demonstrate significant effects on diffusing capacity, BAL fluid cell differentials, or MMP-9 activity. Furthermore, we had a significant amount of missing data from the bronchoscopies due to premature discontinuations from the study. The duration of study drug administration was likely too short to observe any potential effects on radiographic emphysema progression. As a single center study, the results may not be generalizable. While doxycycline was well tolerated, we did not assess for effects on the

microbiota and for the acquisition of tetracycline resistance due to budgetary constraints. Despite these limitations, our results support feasibility and proof of concept for a phase II randomized, double-blind placebo-controlled trial of doxycycline to evaluate its ability to slow emphysema progression over 72 weeks in PLWH (NCT05382208).

Pre-proof

Acknowledgments. The authors acknowledge the dedicated work of Ms. Sandra Hyde in facilitating all aspects of participant scheduling and interactions during the entire study. The authors thank N. Mohamed for editorial assistance.

Author Contributions: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: All; Statistical analysis: AK, CS
Drafting the work or reviewing it critically for important intellectual content: RJK, AK, CS, RGC, MJG; Final approval of the version to be published: All

References

1. Wong C, Gange SJ, Moore RD, Justice AC, Buchacz K, Abraham AG, et al. Multimorbidity Among Persons Living with Human Immunodeficiency Virus in the United States. *Clin Infect Dis*. 2018;66(8):1230–8. Epub 2017/11/18. doi: 10.1093/cid/cix998. PubMed PMID: 29149237; PubMed Central PMCID: PMC5889007.
2. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. *Lancet Glob Health*. 2018;6(2):e193–e202. Epub 2017/12/20. doi: 10.1016/s2214-109x(17)30451-5. PubMed PMID: 29254748.
3. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Nagaraja HN, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med*. 2000;132(5):369–72.
4. Attia EF, Akgun KM, Wongtrakool C, Goetz MB, Rodriguez-Barradas MC, Rimland D, et al. Increased risk of radiographic emphysema in HIV is associated with elevated soluble CD14 and nadir CD4. *Chest*. 2014;146(6):1543–53. Epub 2014/08/01. doi: 10.1378/chest.14-0543. PubMed PMID: 25080158; PubMed Central PMCID: PMC4251616.
5. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. *Am J Respir Crit Care Med*. 1995;152(5 Pt 2):S77–121. Epub 1995/11/01. PubMed PMID: 7582322.
6. Triplette M, Justice A, Attia EF, Tate J, Brown ST, Goetz MB, et al. Markers of chronic obstructive pulmonary disease are associated with mortality in people living with HIV. *Aids*. 2018;32(4):487–93. Epub 2017/11/15. doi: 10.1097/qad.0000000000001701. PubMed PMID: 29135579; PubMed Central PMCID: PMC6366454.
7. Akgun KM, Tate JP, Oursler KK, Crystal S, Leaf DA, Womack JA, et al. Association of chronic obstructive pulmonary disease with frailty measurements in HIV-infected and uninfected Veterans. *Aids*. 2016;30(14):2185–93. Epub 2016/05/19. doi: 10.1097/qad.0000000000001162. PubMed PMID: 27191979.
8. Attia EF, McGinnis KA, Feemster LC, Akgun KM, Butt AA, Graber CJ, et al. Association of COPD With Risk for Pulmonary Infections Requiring Hospitalization in HIV-Infected Veterans. *J Acquir Immune Defic Syndr*. 2015;70(3):280–8. Epub 2015/07/17. doi: 10.1097/qai.0000000000000751. PubMed PMID: 26181820; PubMed Central PMCID: PMC4607625.
9. de Miguel-Diez J, Lopez-de-Andres A, Jimenez-Garcia R, Puente-Maestu L, Jimenez-Trujillo I, Hernandez-Barrera V, et al. Trends in Epidemiology of COPD in HIV-Infected Patients in Spain (1997-2012). *PLoS One*. 2016;11(11):e0166421. Epub 2016/11/16. doi: 10.1371/journal.pone.0166421. PubMed PMID: 27846297; PubMed Central PMCID: PMC5112896 manuscript have the following competing interests: This study was partly funded by URJC-Banco Santander to the Grupo de Excelencia Investigadora ITPSE (Grant N degrees 30VCPIGI03). There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials, as detailed online in the guide for authors.
10. Drummond MB, Merlo CA, Astemborski J, Kalmin MM, Kisalu A, McDyer JF, et al. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS*. 2013;27(8):1303–11. doi: 10.1097/QAD.0b013e32835e395d. PubMed PMID: 23299176; PubMed Central PMCID: PMC3953568.

11. Samperiz G, Fanjul F, Valera JL, Lopez M, Rios A, Penaranda M, et al. Increased rate of FEV1 decline in HIV patients despite effective treatment with HAART. *PLoS One*. 2019;14(10):e0224510. Epub 20191029. doi: 10.1371/journal.pone.0224510. PubMed PMID: 31661533; PubMed Central PMCID: PMC6818778.
12. Konstantinidis I, Zou RH, Papageorgiou SN, Ronit A, Drummond MB, Kunisaki KM, et al. Effect of Human Immunodeficiency Virus on Lung Function and Structure: A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc*. 2025;22(2):274–84. doi: 10.1513/AnnalsATS.202404-384OC. PubMed PMID: 39417747; PubMed Central PMCID: PMC11808551.
13. Grabovac I, Veronese N, Stefanac S, Haider S, Jackson SE, Koyanagi A, et al. Human Immunodeficiency Virus Infection and Diverse Physical Health Outcomes: An Umbrella Review of Meta-analyses of Observational Studies. *Clin Infect Dis*. 2020;70(9):1809–15. doi: 10.1093/cid/ciz539. PubMed PMID: 31401650; PubMed Central PMCID: PMC7156772.
14. Disease GfCOL. Pocket guide to COPD diagnosis, management, and prevention: 2026 report. 2025.
15. Gharib SA, Manicone AM, Parks WC. Matrix metalloproteinases in emphysema. *Matrix Biol*. 2018;73:34–51. Epub 2018/02/07. doi: 10.1016/j.matbio.2018.01.018. PubMed PMID: 29406250; PubMed Central PMCID: PMC6377072.
16. Kaner RJ, Santiago F, Crystal RG. Up-regulation of alveolar macrophage matrix metalloproteinases in HIV1(+) smokers with early emphysema. *J Leukoc Biol*. 2009;86(4):913–22. doi: jlb.0408240 [pii];10.1189/jlb.0408240 [doi].
17. Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol*. 2000;71(4):521–32. Epub 2000/05/12. doi: 10.1902/jop.2000.71.4.521. PubMed PMID: 10807113.
18. Wang Y, Bos JH, Boezen HM, Aiffenaar JC, van Boven JFM, Schuiling-Veninga CCM, et al. Influence of age on real-life effects of doxycycline for acute exacerbations among COPD outpatients: a population-based cohort study. *BMJ Open Respir Res*. 2020;7(1). doi: 10.1136/bmjresp-2019-000535. PubMed PMID: 32075781; PubMed Central PMCID: PMC7047485.
19. Prins HJ, Daniels JM, Lindeman JH, Lutter R, Boersma WG. Effects of doxycycline on local and systemic inflammation in stable COPD patients, a randomized clinical trial. *Respir Med*. 2016;110:46–52. Epub 2015/12/01. doi: 10.1016/j.rmed.2015.10.009. PubMed PMID: 26616678.
20. Allinson JP, Vlies BH, Brill SE, Law M, Burnside G, Finney LJ, et al. A Double-Blind, Randomized, Placebo-controlled Trial of Long-Term Doxycycline Therapy on Exacerbation Rate in Patients with Stable Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2023;208(5):549–58. doi: 10.1164/rccm.202212-2287OC. PubMed PMID: 37450935; PubMed Central PMCID: PMC10492249.
21. Venkatesan P. GOLD COPD report: 2025 update. *Lancet Respir Med*. 2025;13(1):e7–e8. Epub 20241205. doi: 10.1016/s2213-2600(24)00413-2. PubMed PMID: 39647487.
22. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging*. 2012;30(9):1323–41. Epub 20120706. doi: 10.1016/j.mri.2012.05.001. PubMed PMID: 22770690; PubMed Central PMCID: PMC3466397.

23. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. 2017;49(1). Epub 2017/01/04. doi: 10.1183/13993003.00016-2016. PubMed PMID: 28049168.
24. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am J Respir Crit Care Med*. 2019;200(8):e70–e88. Epub 2019/10/16. doi: 10.1164/rccm.201908-1590ST. PubMed PMID: 31613151; PubMed Central PMCID: PMC6794117.
25. Stanojevic S, Kaminsky DA, Miller MR, Thompson B, Aliverti A, Barjaktarevic I, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1). Epub 20220713. doi: 10.1183/13993003.01499-2021. PubMed PMID: 34949706.
26. Kaner RJ, Crystal RG. Compartmentalization of vascular endothelial growth factor to the epithelial surface of the human lung. *Mol Med*. 2001;7(4):240–6. PubMed PMID: 11471568; PubMed Central PMCID: PMC1950032.
27. Services USDoHaH. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. In: National Institutes of Health NIAID, Division of AIDS, editor. <https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf>2017.
28. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648–54. doi: 10.1183/09031936.00102509. PubMed PMID: 19720809.
29. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. *PLoS One*. 2009;4(7):e6328. Epub 20090721. doi: 10.1371/journal.pone.0006328. PubMed PMID: 19621086; PubMed Central PMCID: PMC2709444.
30. Pompe E, Moore CM, Mohamed Hoesein FAA, de Jong PA, Charbonnier JP, Han MK, et al. Progression of Emphysema and Small Airways Disease in Cigarette Smokers. *Chronic Obstr Pulm Dis*. 2021;8(2):198–212. doi: 10.15326/jcopdf.2020.0140. PubMed PMID: 33290645; PubMed Central PMCID: PMC8237975.
31. Beringer PM, Owens H, Nguyen A, Benitez D, Rao A, D'Argenio DZ. Pharmacokinetics of doxycycline in adults with cystic fibrosis. *Antimicrob Agents Chemother*. 2012;56(1):70–4. Epub 2011/10/26. doi: 10.1128/aac.05710-11. PubMed PMID: 22024822; PubMed Central PMCID: PMC3256044.
32. Choi SH, Cesar A, Snow TAC, Saleem N, Arulkumaran N, Singer M. Efficacy of Doxycycline for Mild-to-Moderate Community-Acquired Pneumonia in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clin Infect Dis*. 2023;76(4):683–91. doi: 10.1093/cid/ciac615. PubMed PMID: 35903011.

Table 1. Baseline Characteristics

	Doxycycline (n = 18)	Placebo (n = 9)
Male sex	13 (72.2)	8 (88.9)
Race:		
American Indian/Alaskan Native	2 (11.1)	0
Black	10 (56.6)	7 (77.8)
White	4 (22.2)	2 (22.2)
> 1 race	2 (11.1)	0
Ethnicity:		
Hispanic/Latino	2 (11.1)	0
Not reported	16 (88.9)	9 (100)
Age	56.5 (49, 61.3)	55 (48, 59.4)
Body mass index (kg/m ²)	24.8 ± 3.2	23.8 ± 3.6
Current smoker	13 (72.2)	5 (55.6)
Pack-years smoking	23.3 ± 14.6	30.9 ± 19.7
CD4 count (cells/μL)	556 (464, 946)	539 (346, 584)
History of injection drug use	1 (5.6)	2 (22.2)
History of inhalational drug use	9 (50.0)	5 (55.6)
HIV-1 RNA < 20 copies/ml	15 (83.3)	7 (77.8)
On inhaled bronchodilator	6 (33)	2 (22.2)
On inhaled corticosteroid	1 (5.6)	1 (11.1)
FEV ₁ (% predicted)	87.7 ± 17.9	87.8 ± 19.1
FVC (% predicted)	103.8 ± 14.8	99.3 ± 14.9
FEV ₁ /FVC (%)	67.6 ± 9.5	69.7 ± 8.4
DLCO (% predicted)	66.8 ± 18.7	73.6 ± 17.7
GOLD stage (I/II/NA)	6/5/7	2/2/5
CAT score*	14.4 ± 6.5	17.3 ± 7.9
% emphysema on high resolution CT	13 (10, 23.3)**	14 (11, 24)***

Normal data are presented as n (%) or mean ± standard deviation with non-normally distributed data (by Shapiro-Wilk test) presented as median (Q1, Q3)

*Chronic obstructive pulmonary disease (COPD) Assessment Test

**Of n = 7 with emphysema

***Of n = 5 with emphysema

Table 2. Adverse Events in the Safety Population*

Event	Doxycycline (n=16)	Placebo (n=8)
Any	13 (81.2%)	6 (75.0%)
Blood and lymphatic system disorders		
Hemoglobin decrease	1 (6.2%)	0
Low absolute neutrophil count	1 (6.2%)	0
Gastrointestinal disorders		
Mouth lesions	1 (6.2%)	0
Diarrhea	1 (6.2%) ¹	0
Vomiting	1 (6.2%)	0
General disorders		
Fatigue	1 (6.2%)	3 (37.5%)
Infections and infestations		
Oral thrush	1 (6.2%)	0
Musculoskeletal and connective tissue disorders		
Right-sided pain	1 (6.2%)	0
Nervous system disorders		
Headache	1 (6.2%)	0
Renal and urinary disorders		
Creatinine elevation	0	1 (12.5%)
Respiratory, thoracic, and mediastinal disorders		
Cough	1 (6.2%)	2 (25.0%)
Hemoptysis	1 (6.2%) ²	1 (12.5%) ²
Skin and subcutaneous disorders		
Excoriated lesions on arms	1 (6.2%)	0
Maculopapular rash	1 (6.2%)	0

*Events include those of any grade regardless of attribution to study drug

¹ Intermittent diarrhea for 4 weeks

² Mild hemoptysis attributed to bronchoscopy

Figure Legends

Figure 1. CONSORT Diagram of Enrollment and Analysis of the Study Population

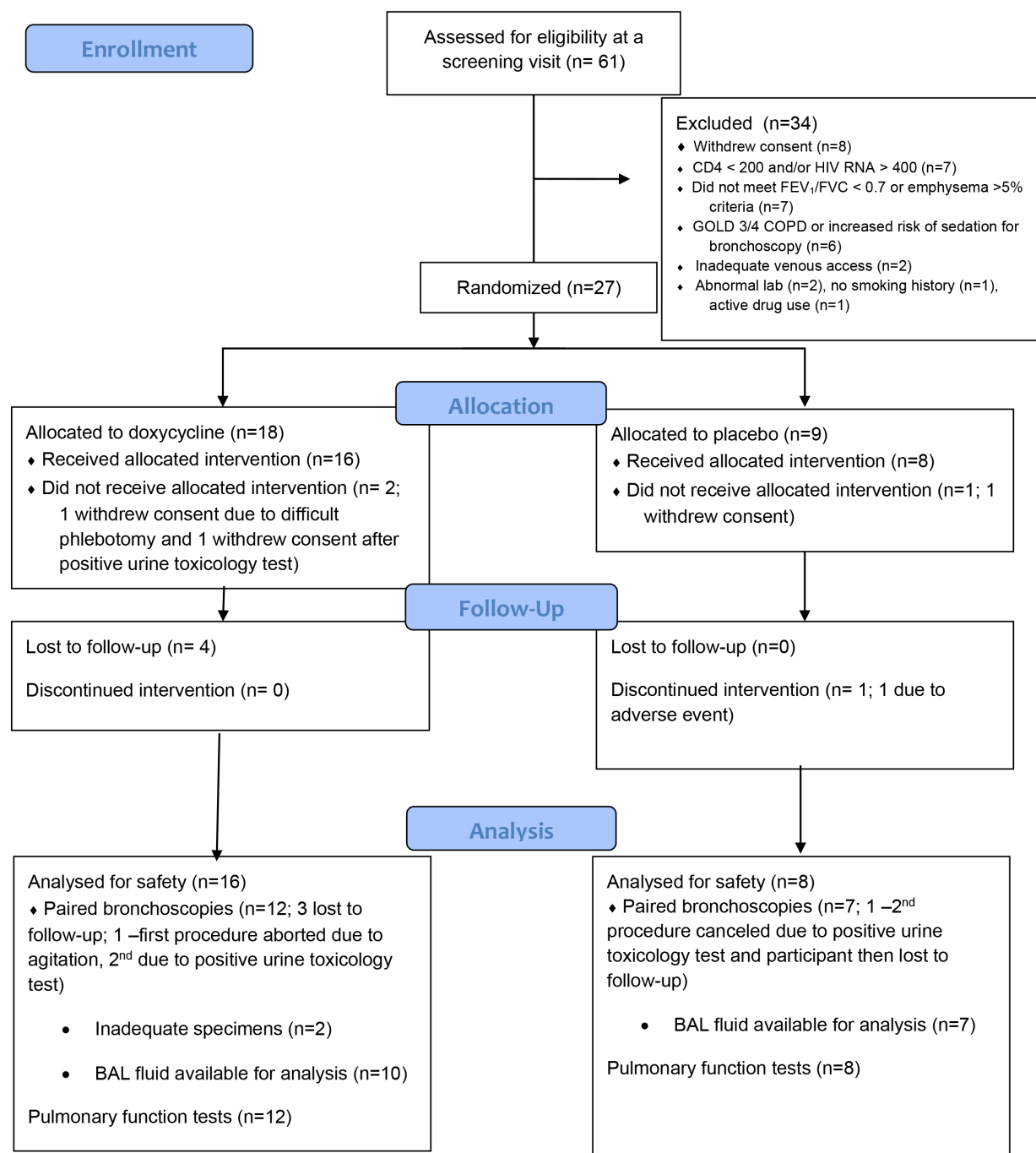
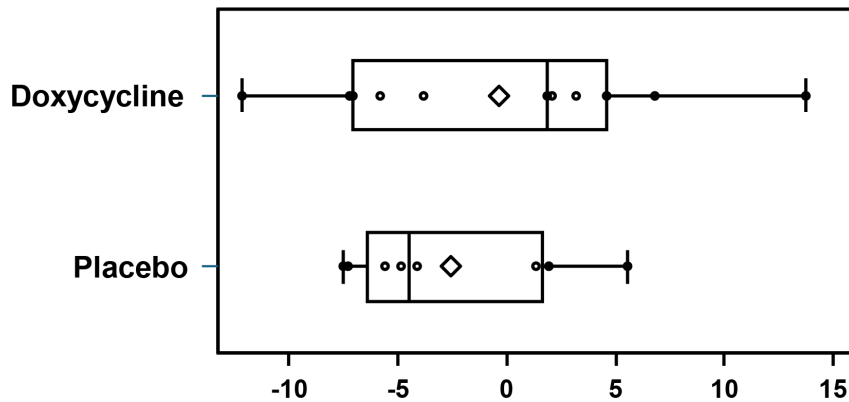
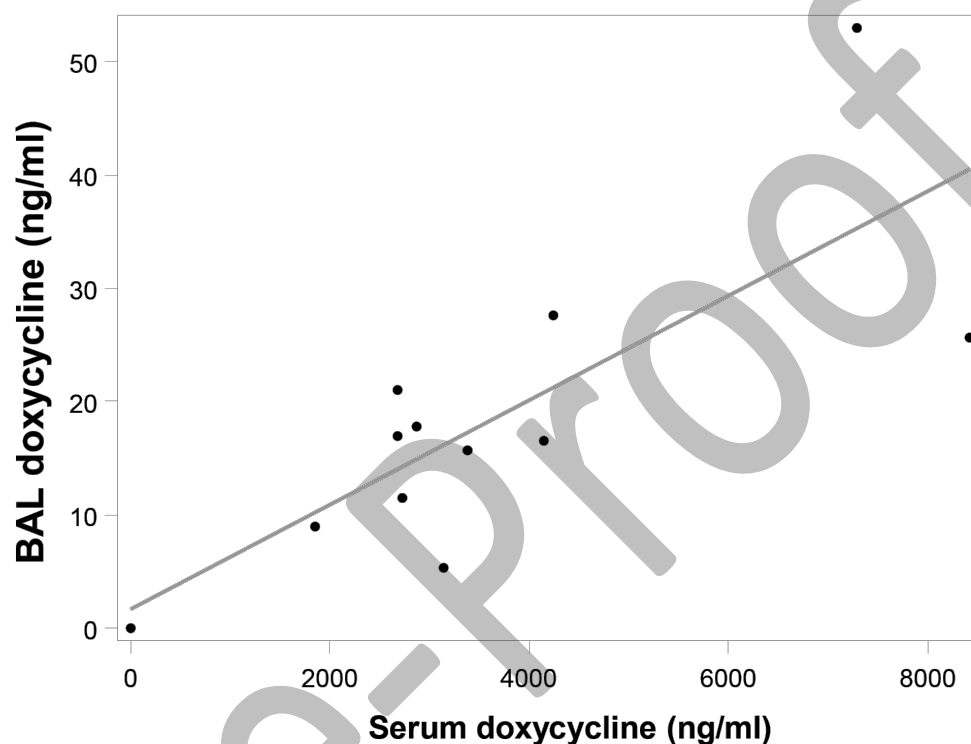


Figure 2. Box and Whisker Plot of DLCO Change from Baseline to Week 24.



Circles represent change for each individual, defined as week 24 DLCO percent predicted minus week 0 DLCO percent predicted. Diamonds indicate the mean; the right-most vertical bar of the box represents the 75th percentile; the middle vertical bar represents the 50th percentile; the left-most vertical bar represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values.

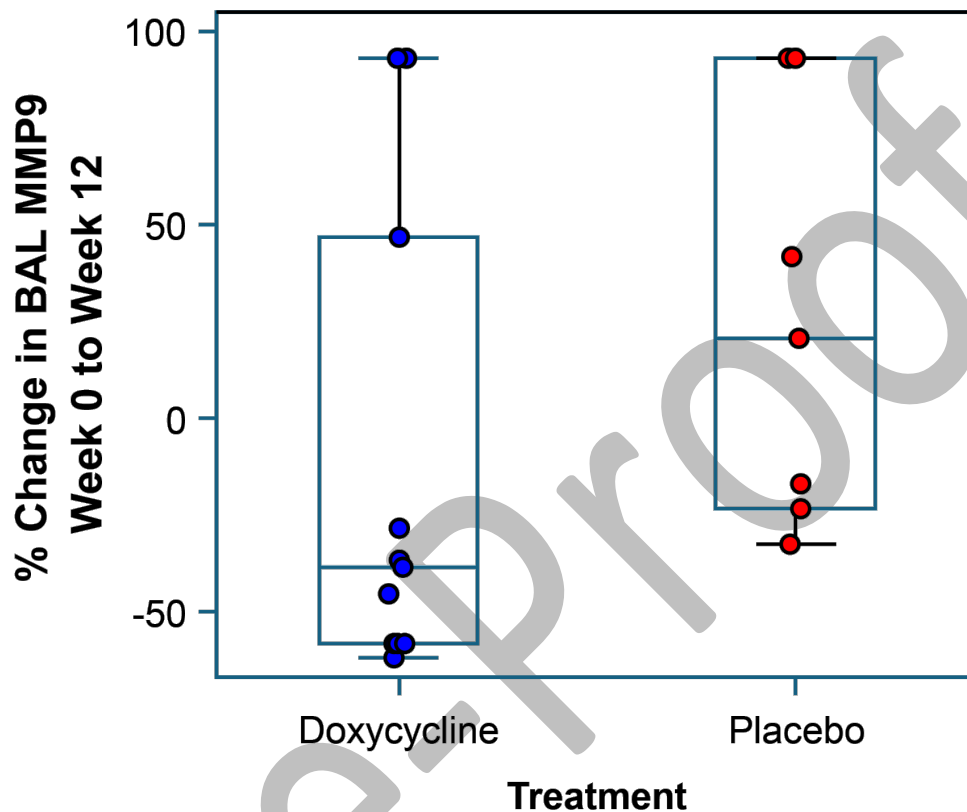
Figure 3. Quantification of Doxycycline Levels in the Doxycycline Arm.



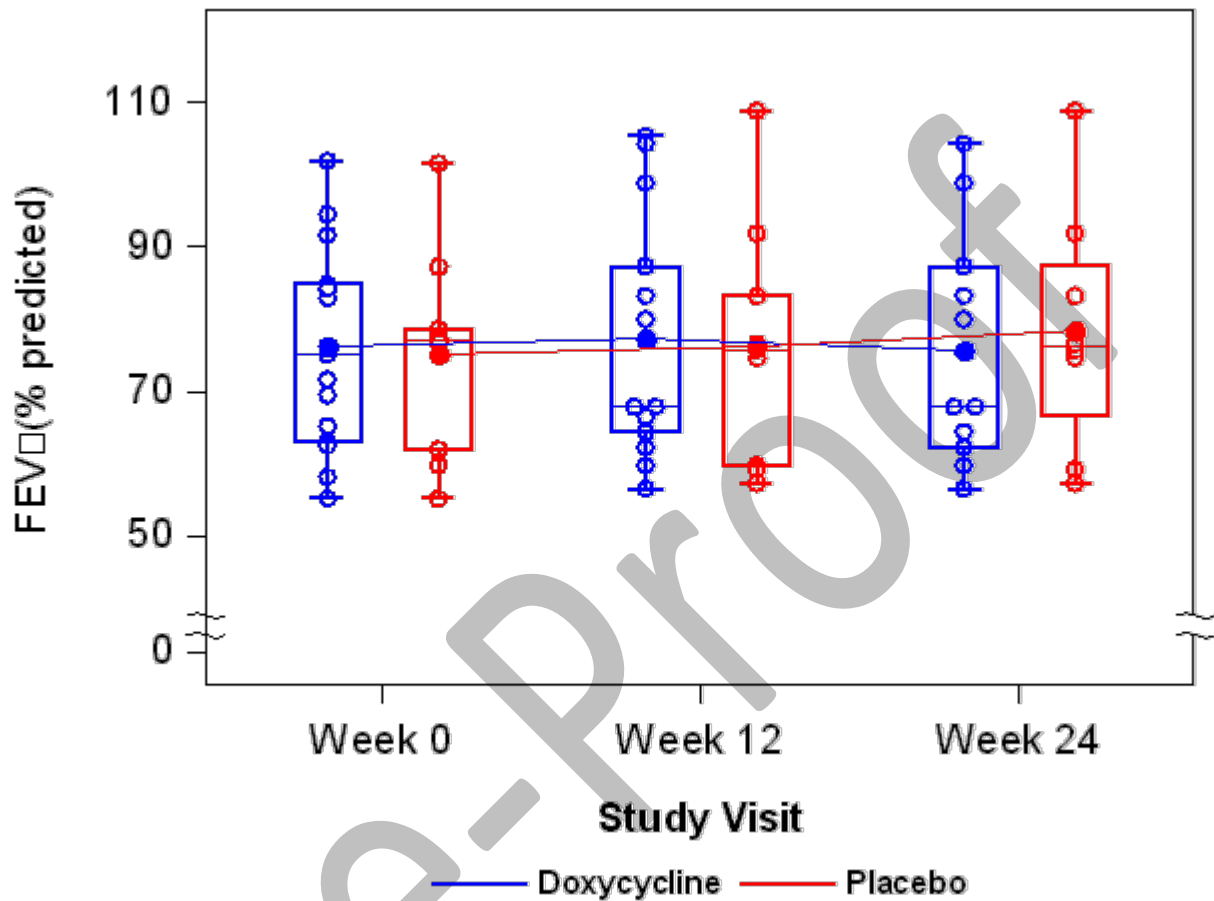
Doxycycline levels were quantified (ng/ml) by HPLC/MS. Y-axis: BAL fluid; X-axis: serum.

Correlation was assessed by Spearman's Rho among the 11 subjects with quantifiable doxycycline levels ($\rho = 0.72$; $p = 0.013$).

Figure 4. Boxplots of percent change in BAL fluid MMP9/mg protein (Week 12-Week 0) by treatment group.

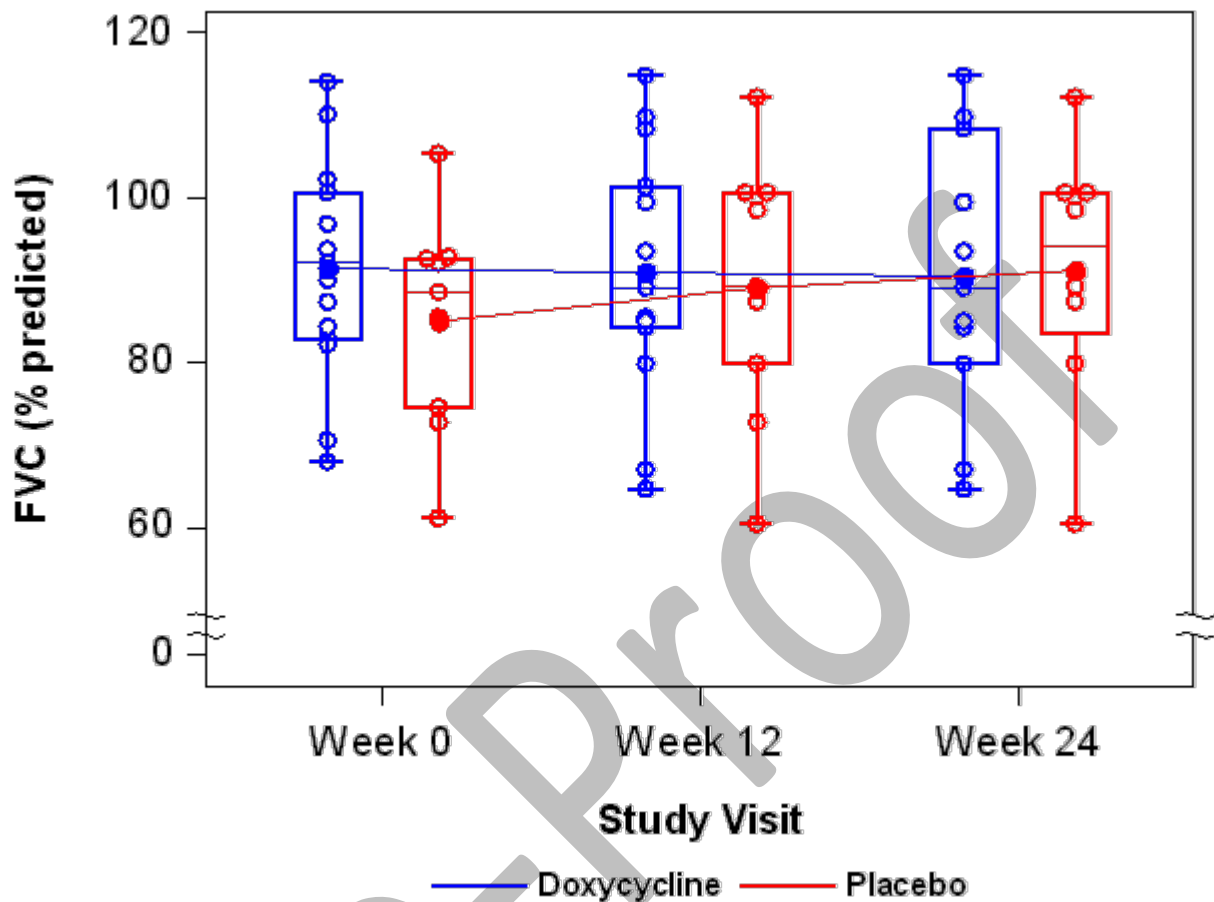


Data shown are 15% winsorized by removing the three most extreme upper and lower values (this is for ease of illustration only and was not done for the actual analysis of the data). The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values.

Supplemental Figure Legends**Supplemental Figure 1.**

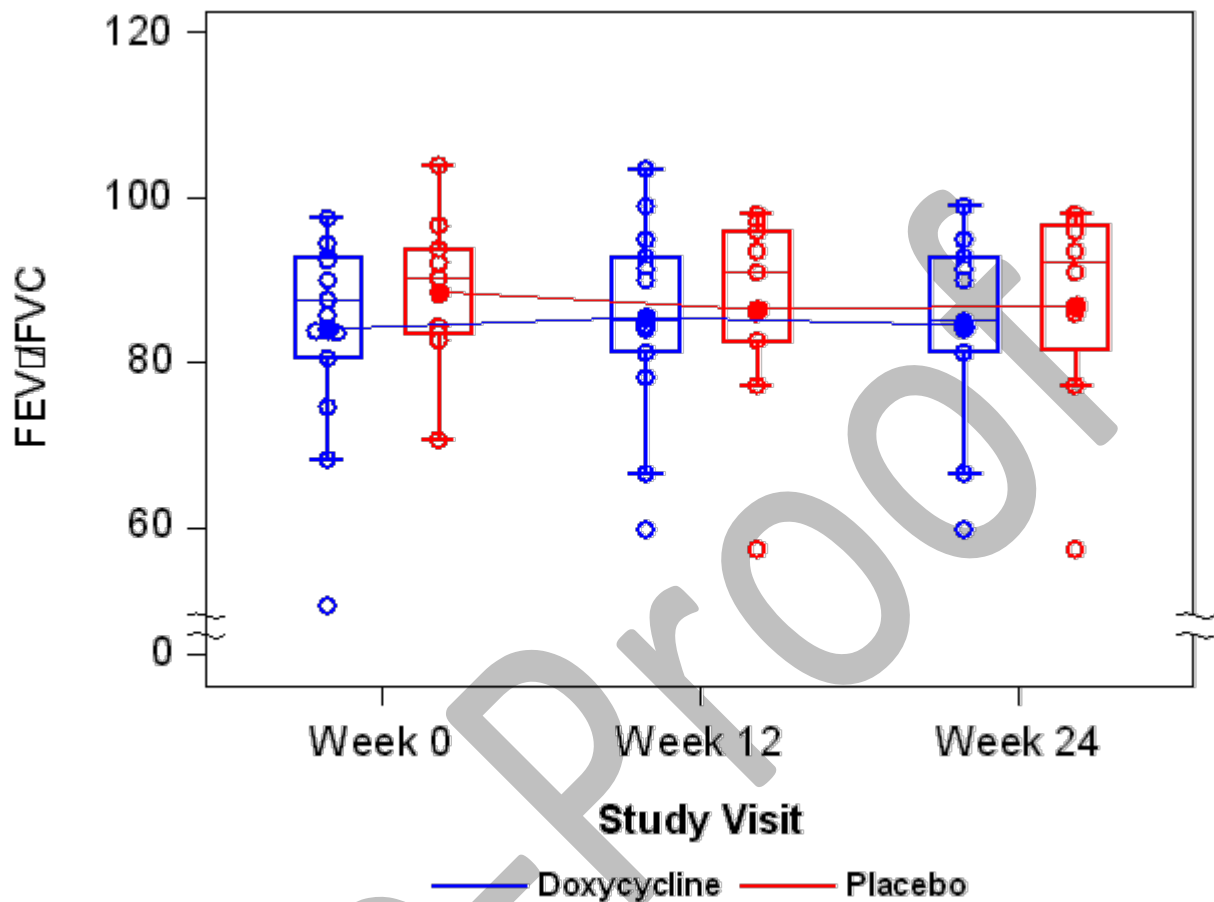
Boxplots of FEV₁ percent predicted by treatment at weeks 0, 12, and 24. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values.

Supplemental Figure 2.



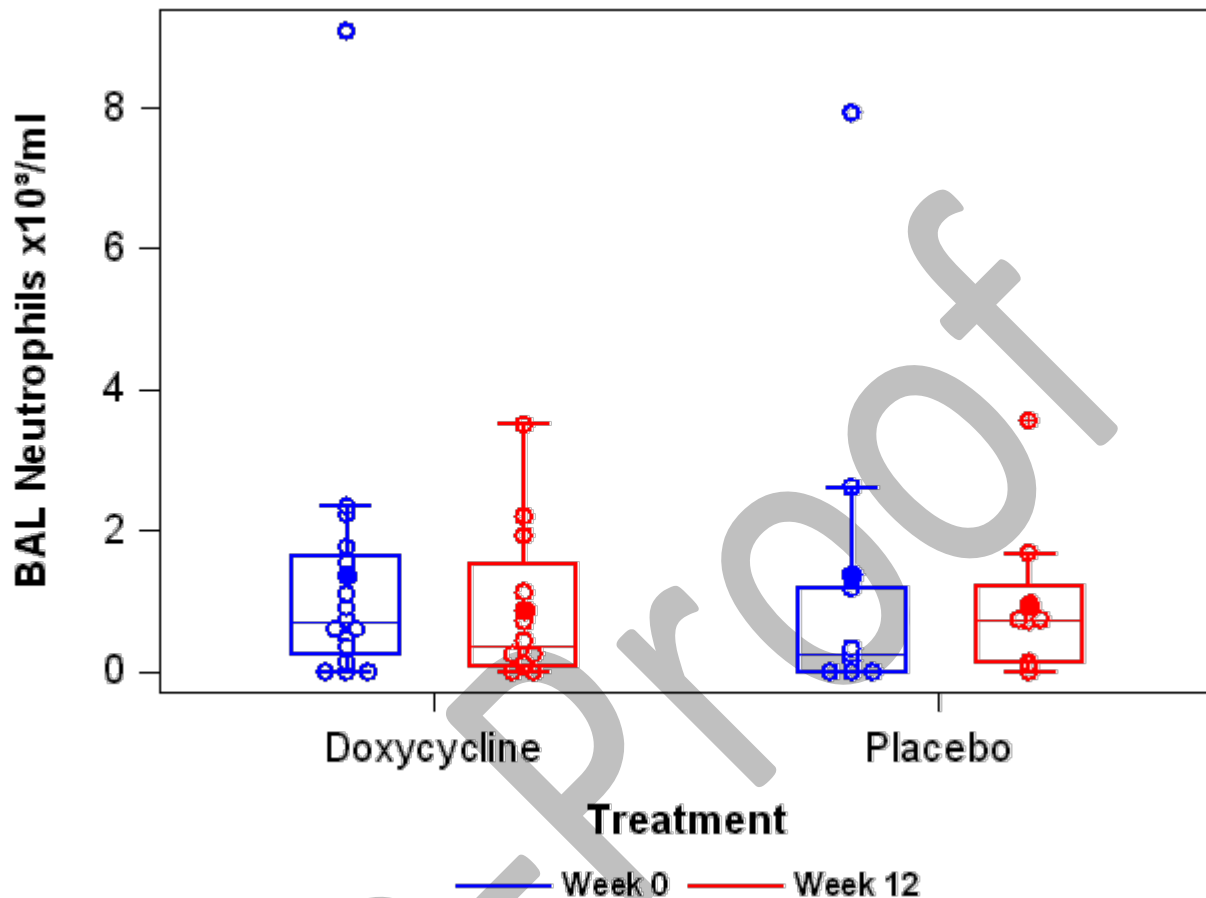
Boxplots of FVC percent predicted by treatment at weeks 0, 12, and 24. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values.

Supplemental Figure 3.



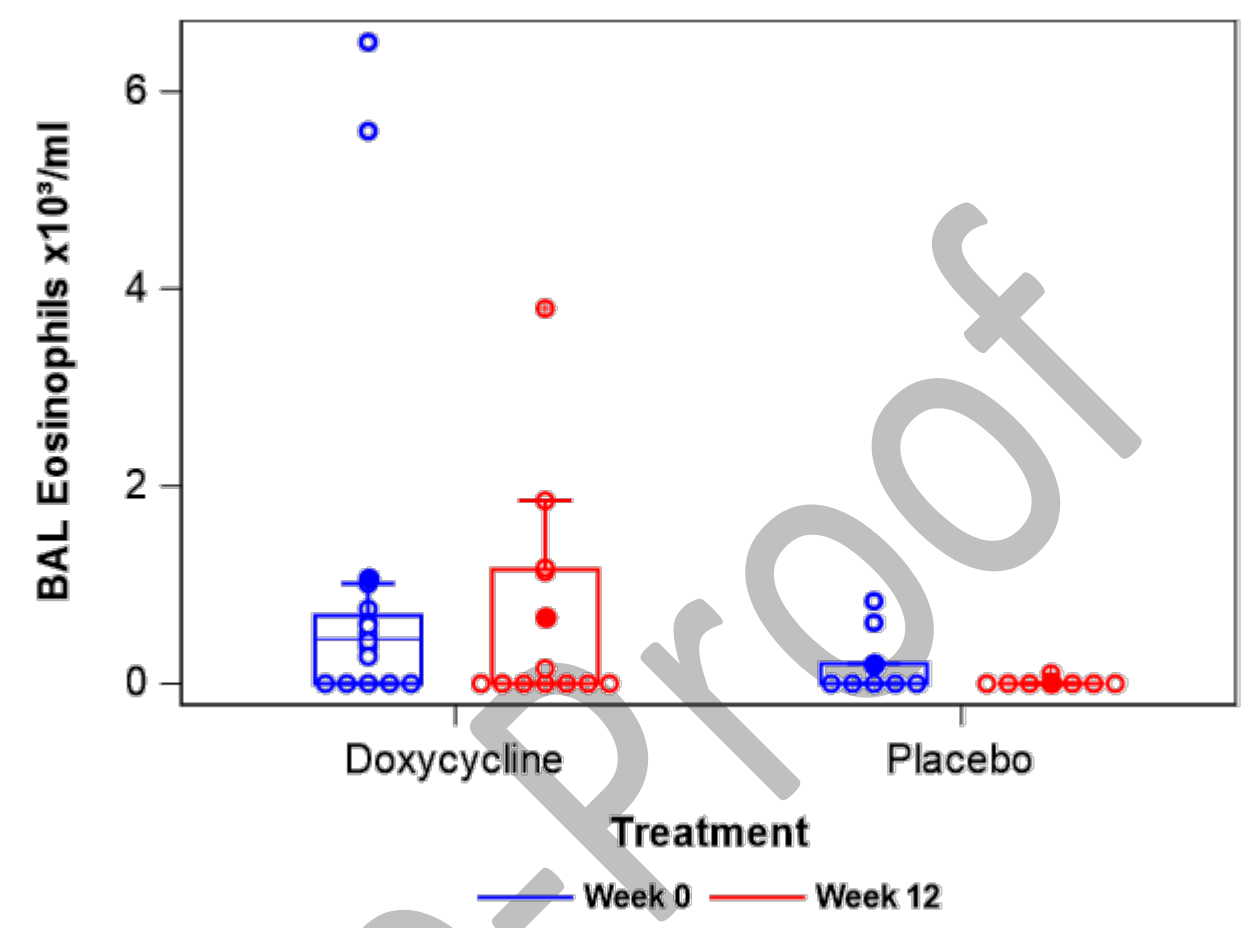
Boxplots of FEV/FVC ratio by treatment at weeks 0, 12, and 24. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values, excluding outliers. Outliers are denoted by single data points (circles) beyond the whiskers.

Supplemental Figure 4.



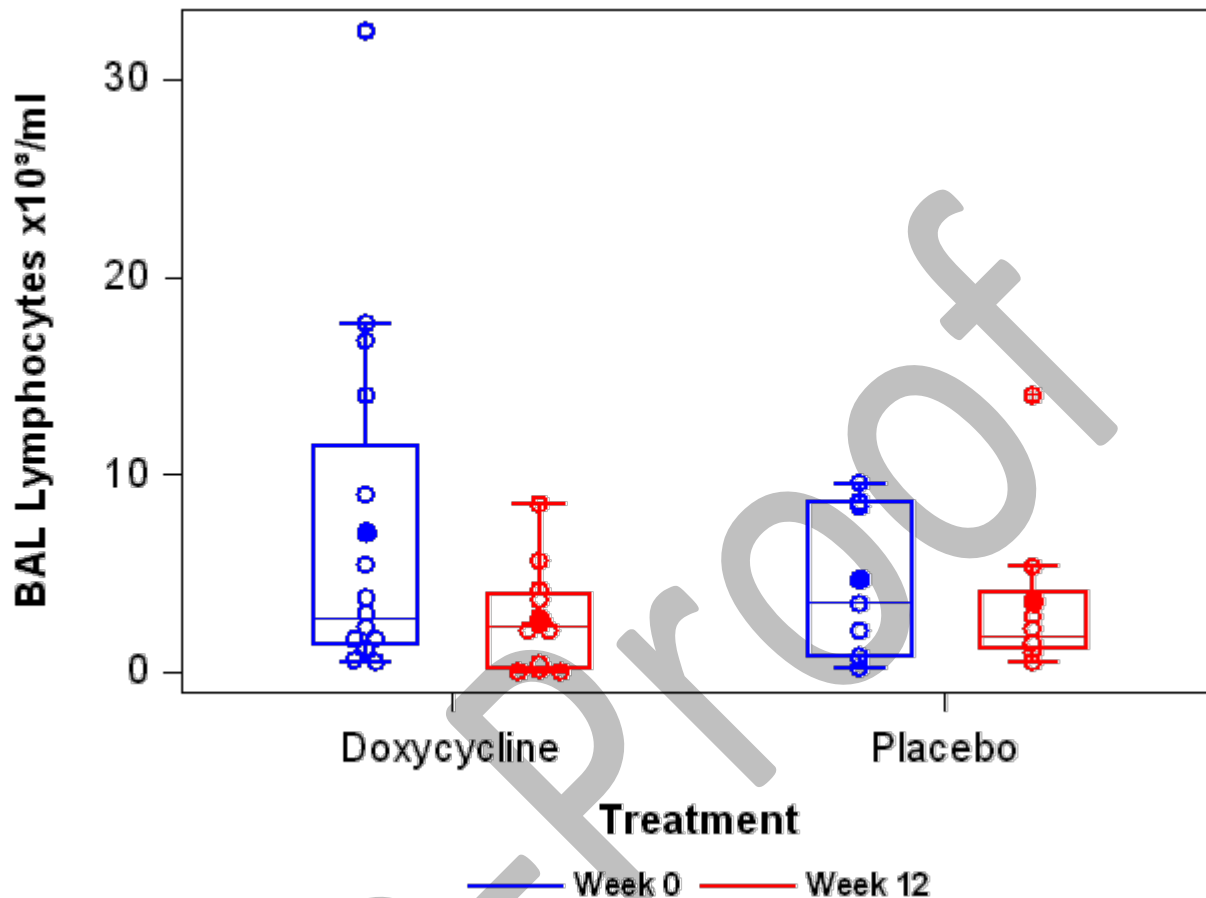
BAL neutrophil count (x10³/ml) at Weeks 0 and 12 by treatment. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values, excluding outliers. Outliers are denoted by single data points (circles) beyond the whiskers.

Supplemental Figure 5.



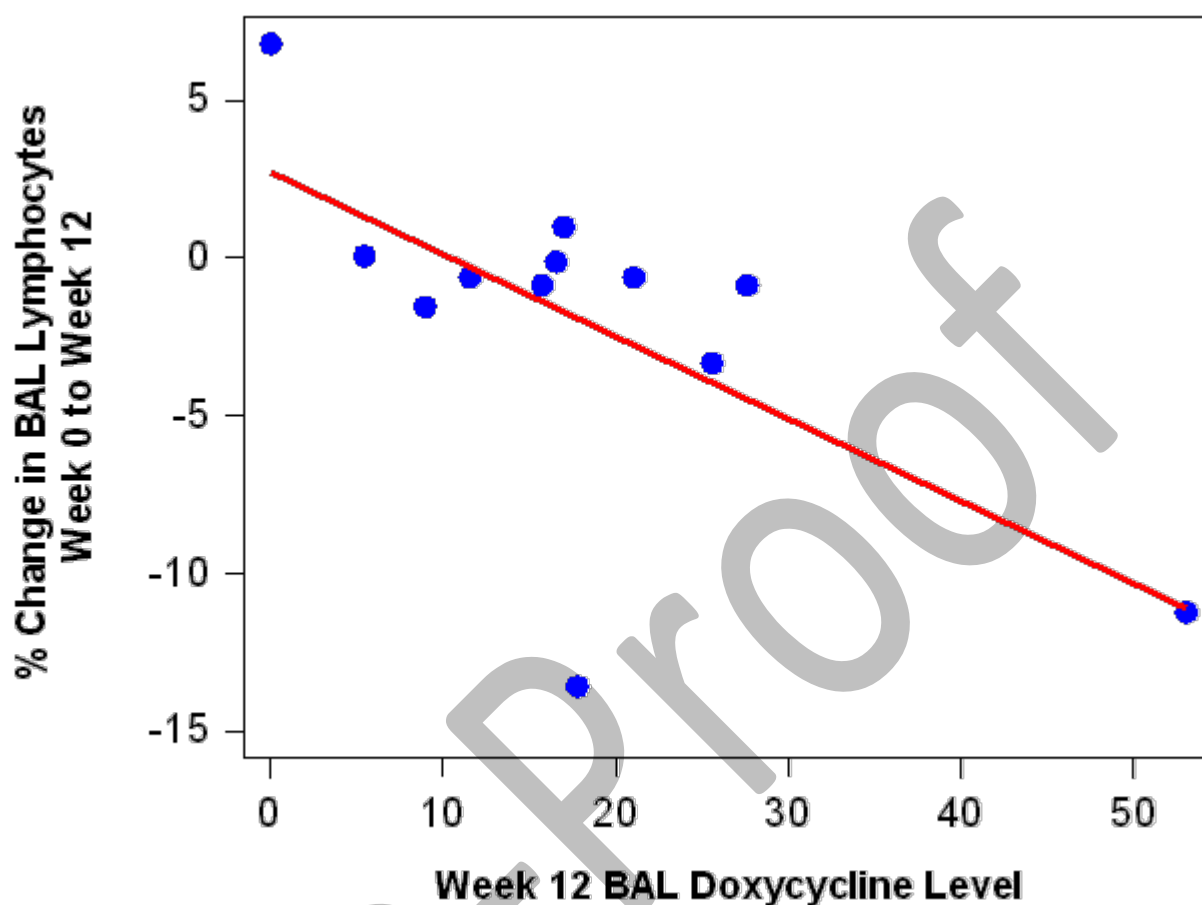
BAL eosinophil count (x10³/ml) at Weeks 0 and 12 by treatment. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values, excluding outliers. Outliers are denoted by single data points (circles) beyond the whiskers.

Supplemental Figure 6.



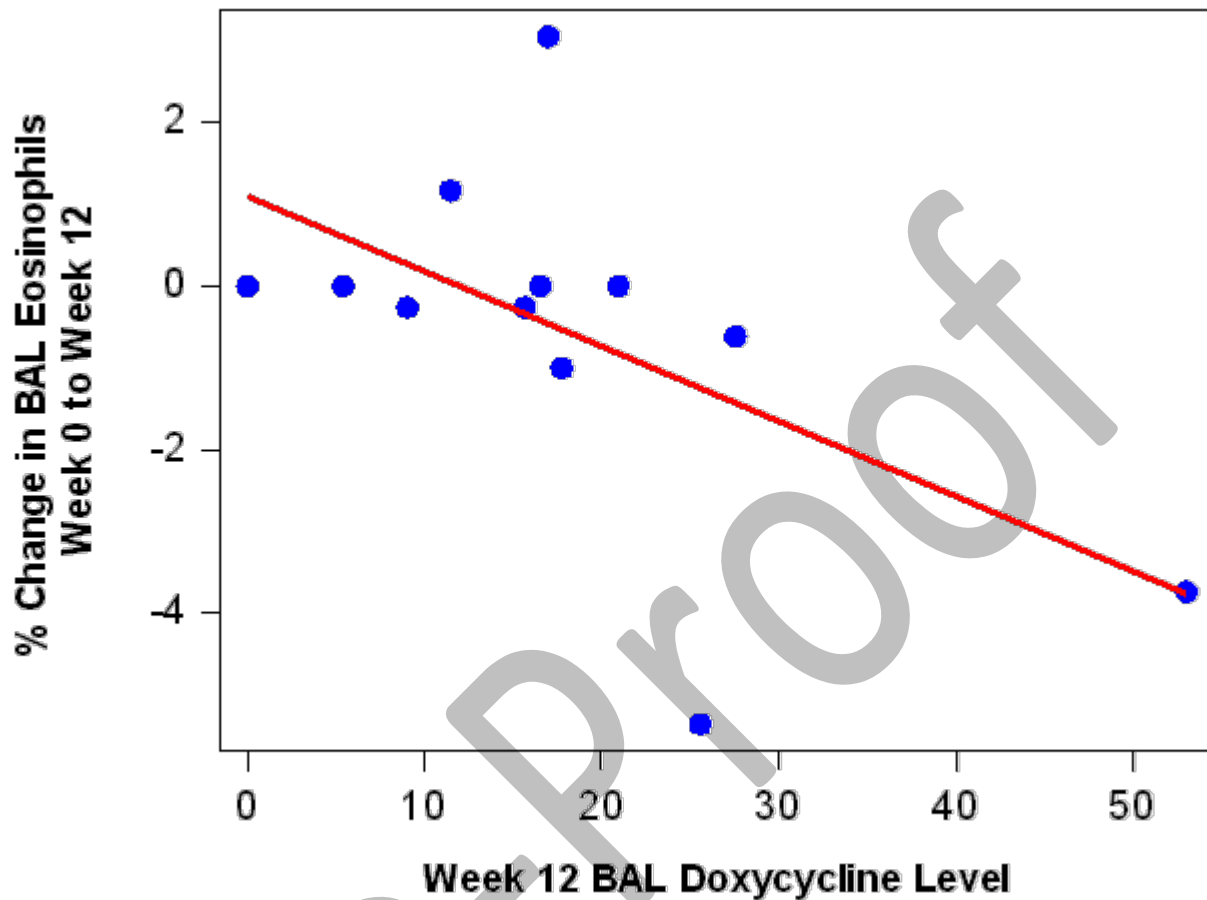
BAL lymphocyte count (x10³/ml) at Weeks 0 and 12 by treatment. The upper horizontal line of the box represents the 75th percentile; the middle line represents the 50th percentile; the lower line represents the 25th percentile. Whiskers extend from the box to the minimum and maximum values, excluding outliers. Outliers are denoted by single data points (circles) beyond the whiskers.

Supplemental Figure 7.



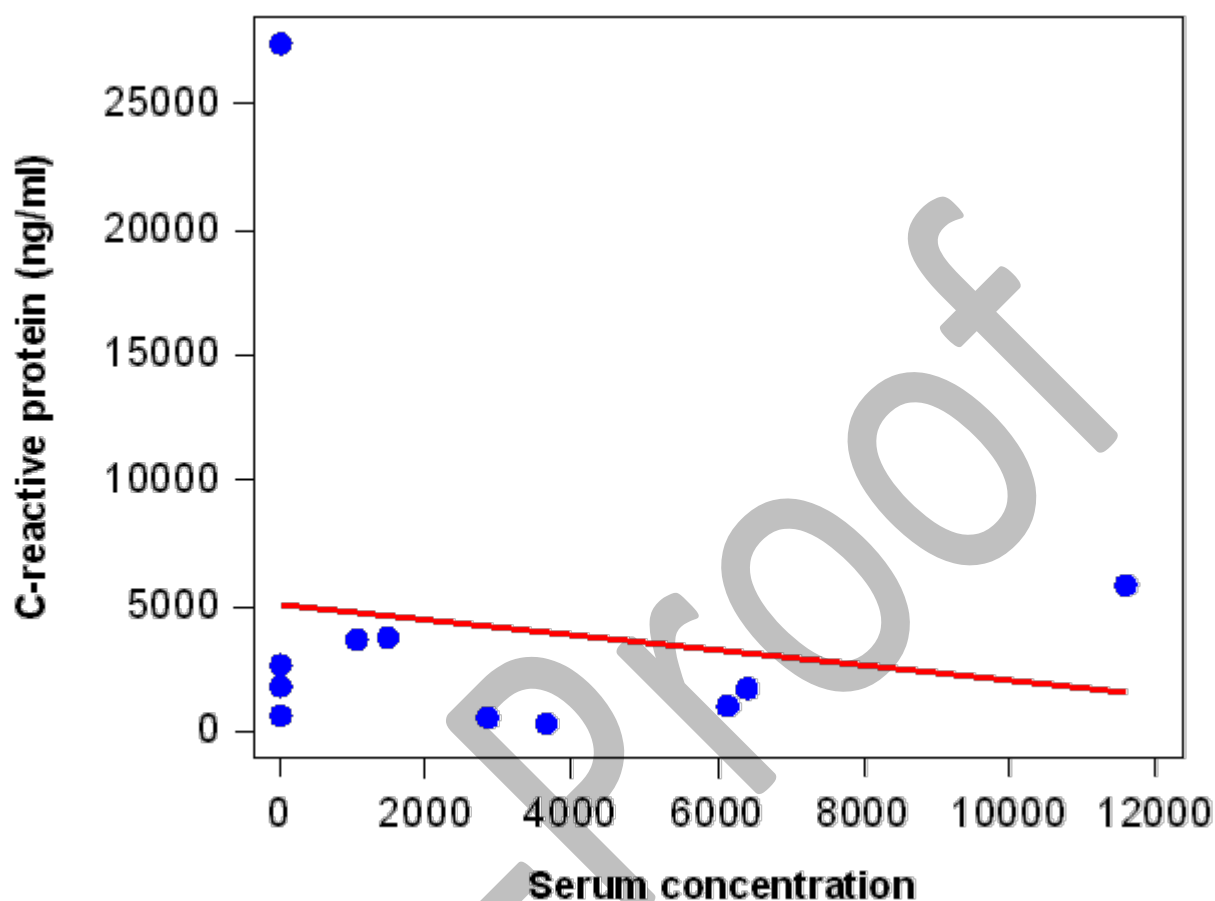
Change in BAL lymphocytes (absolute lymphocyte count at week 12 minus absolute lymphocyte count at week 0) vs Week 12 BAL doxycycline concentration. A regression line showing the linear relationship between the change in lymphocyte count and week 12 BAL doxycycline level is shown in red.

Supplemental Figure 8.



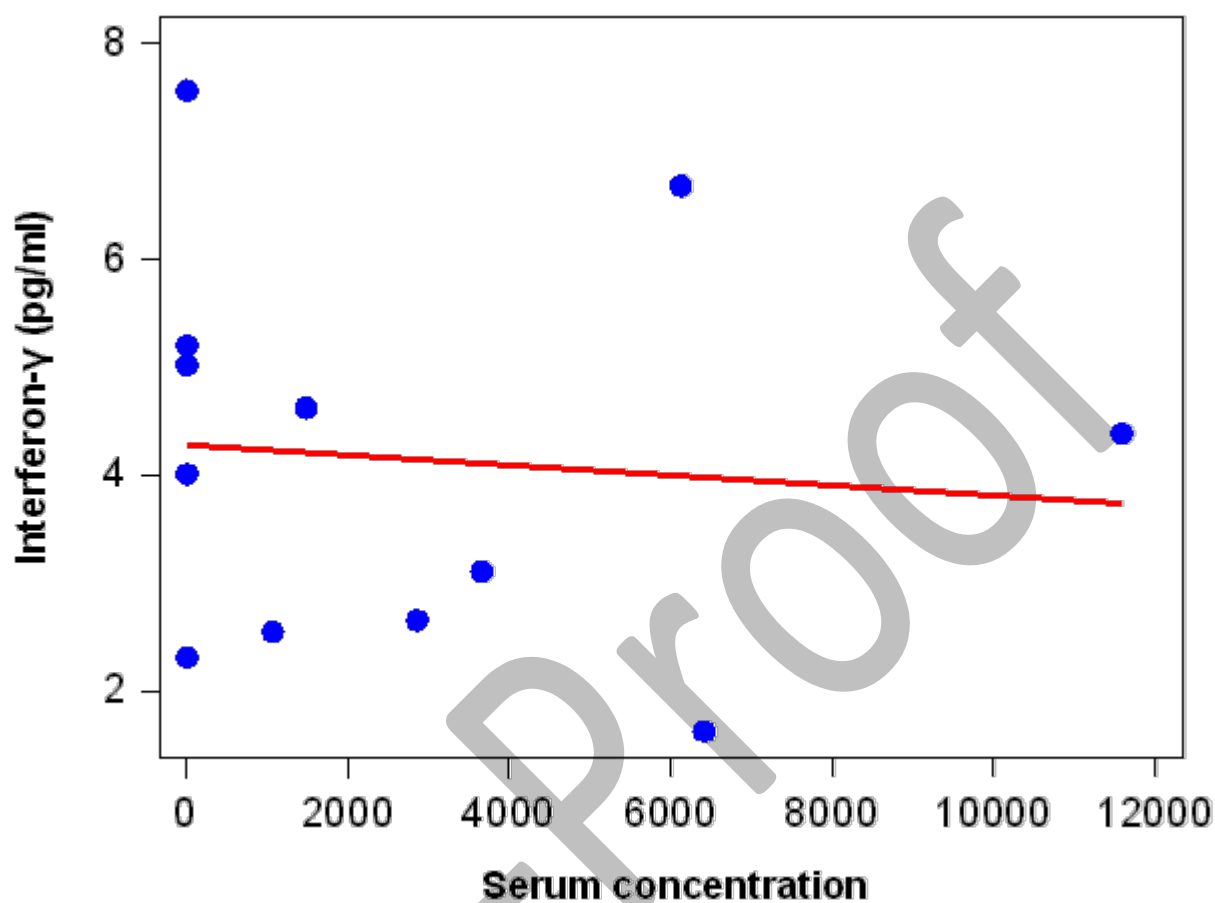
Change in Eosinophils (absolute eosinophil count at week 12 minus absolute eosinophil count at week 0) vs Week 12 BAL doxycycline concentration. A regression line showing the linear relationship between the change in eosinophil count and week 12 BAL doxycycline level is shown in red.

Supplemental Figure 9.



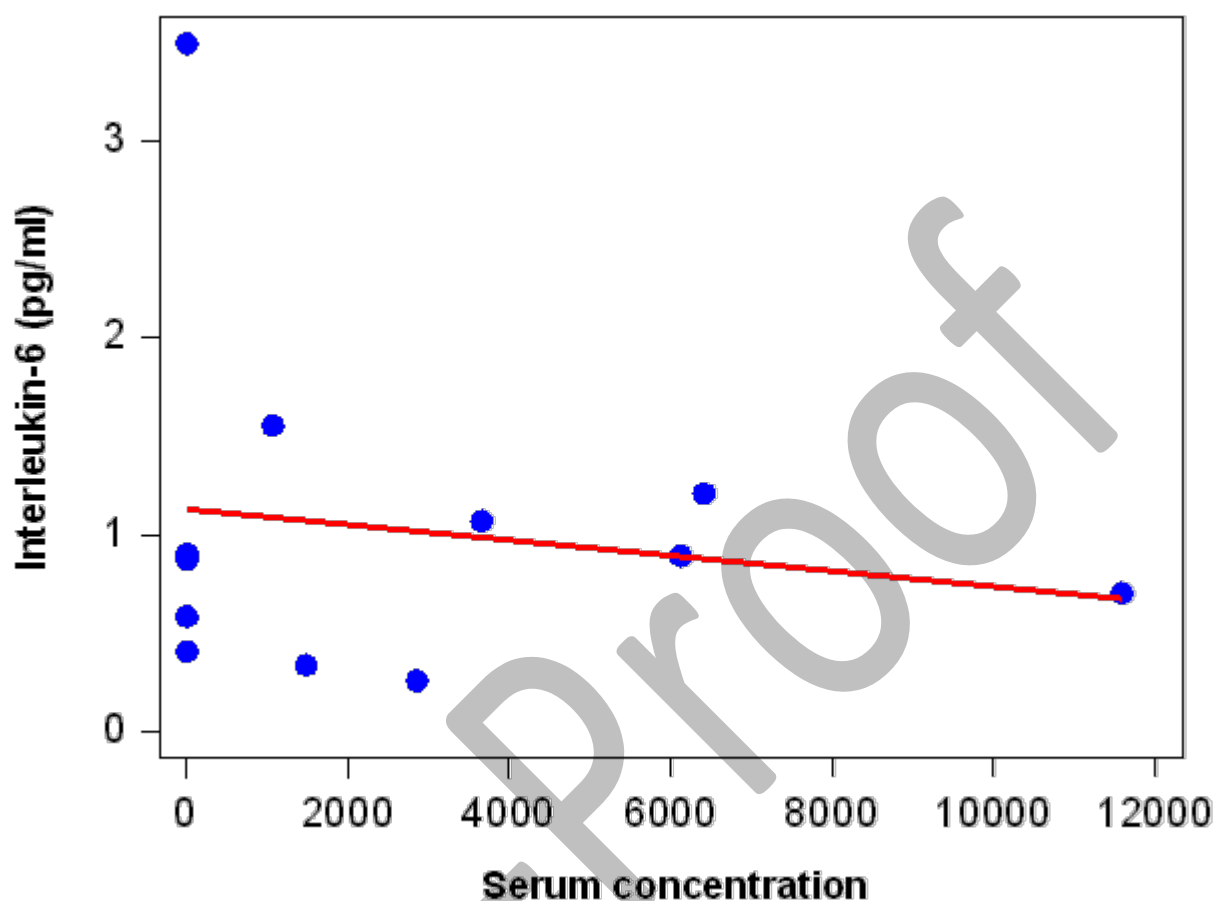
Serum C-Reactive Protein (CRP) vs Serum Doxycycline Concentration at Week 24. A regression line showing the linear relationship between CRP and doxycycline concentration is shown in red.

Supplemental Figure 10.



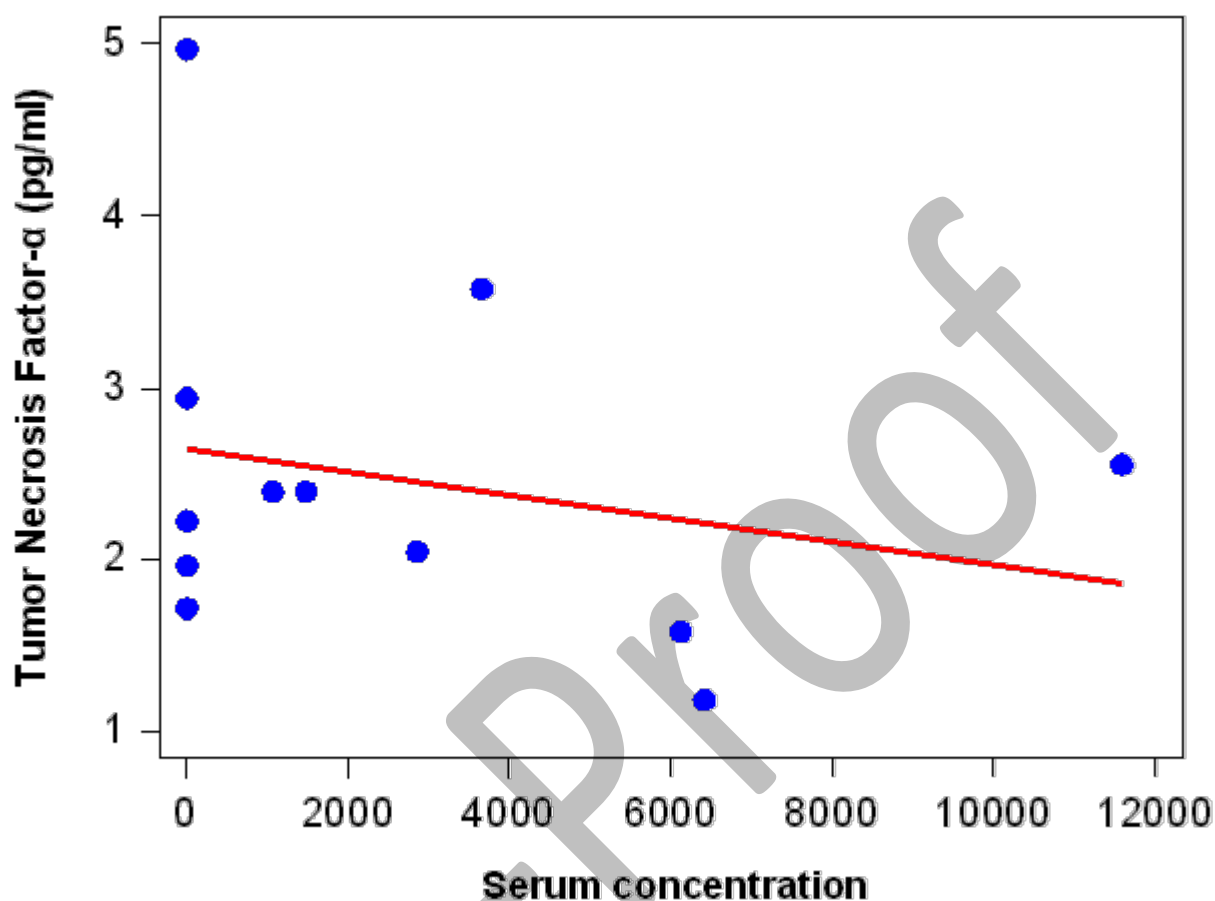
Serum Interferon- γ (IFN- γ) vs Serum Doxycycline Concentration at Week 24. A regression line showing the linear relationship between IFN- γ and doxycycline concentration is shown in red.

Supplemental Figure 11.



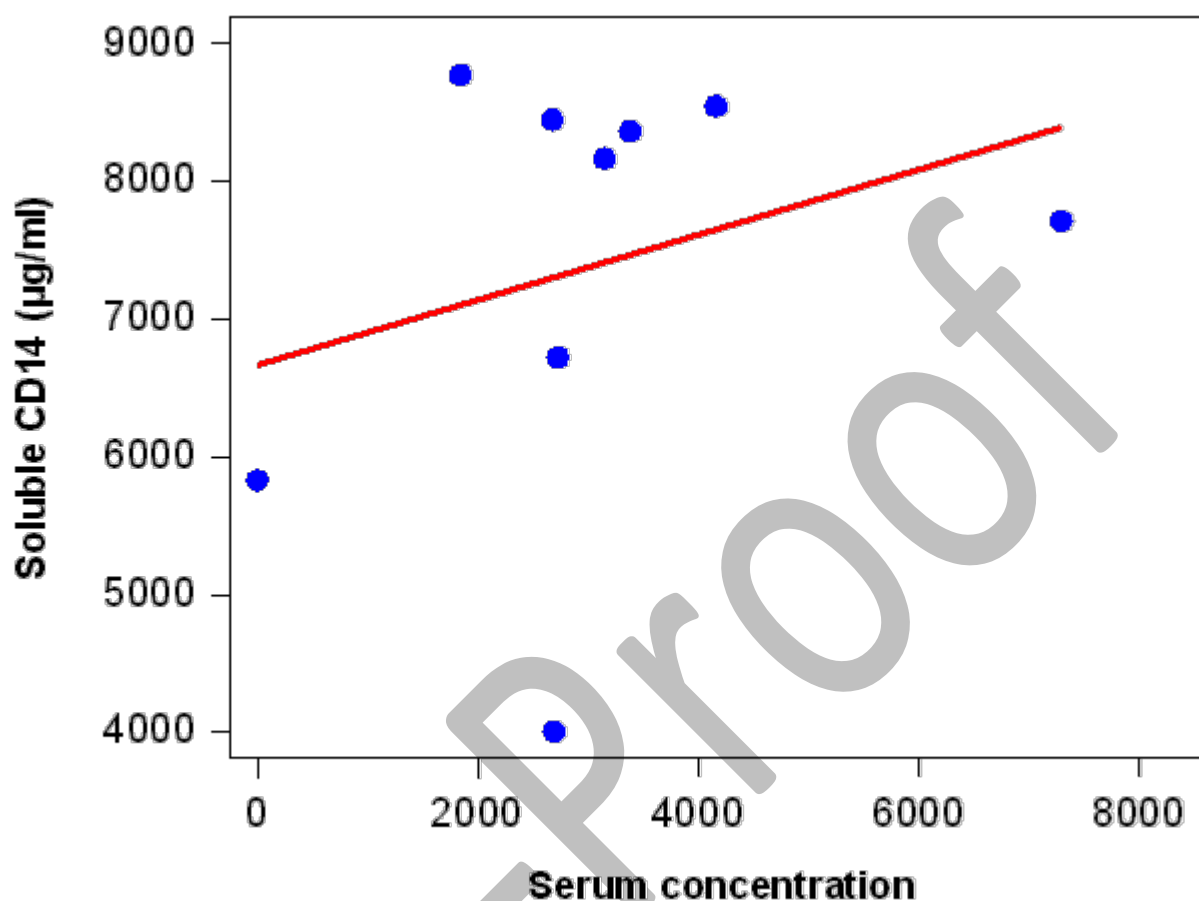
Serum Interleukin-6 (IL-6) vs Serum Doxycycline Concentration at Week 24. A regression line showing the linear relationship between IL-6 and doxycycline concentration is shown in red.

Supplemental Figure 12.



Serum Tumor Necrosis Factor- α (TNF- α) vs Serum Doxycycline Concentration at Week 24. A regression line showing the linear relationship between TNF- α and doxycycline concentration is shown in red.

Supplemental Figure 13.



Serum Soluble CD14 (sCD14) vs Serum Doxycycline Concentration at Week 12. A regression line showing the linear relationship between sCD14 and doxycycline concentration is shown in red.