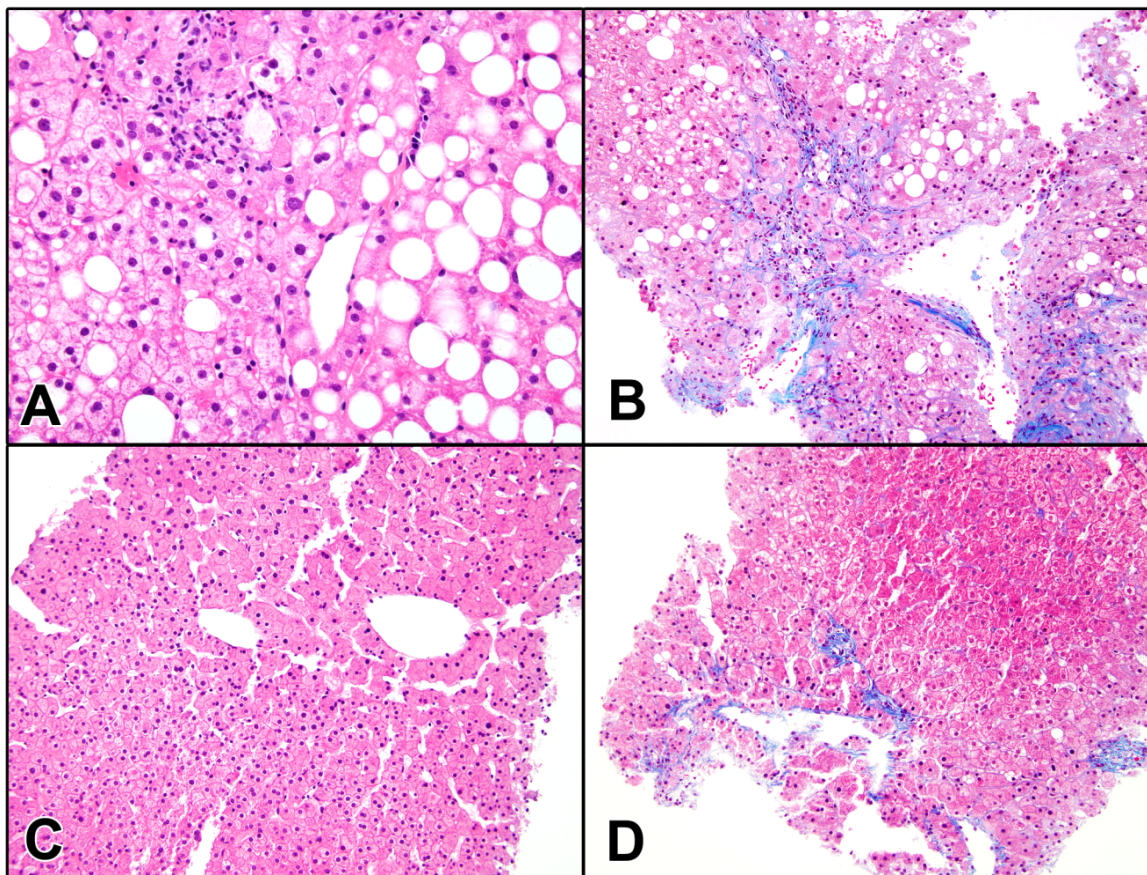


Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675-85. DOI: 10.1056/NEJMoa0907929.

Supplement Figure 1:

Photomicrographs of a patient with marked histological improvement after 96 weeks of treatment. Panels A (H&E, 400x) and B (Masson trichrome, 200x) from the pre-treatment biopsy show the classic features of steatohepatitis: moderate steatosis, prominent ballooning injury, spotty lobular inflammation, and central perisinusoidal fibrosis. Panels C (H&E, 400x) and D (Masson trichrome, 200x) from the post-treatment biopsy show improvement in all features of steatohepatitis: no ballooning injury, minimal steatosis, and rare foci of spotty inflammation with only mild residual perisinusoidal fibrosis remaining.

Supplement Table 1. Baseline characteristics by treatment group

	Placebo (n=83)	Vitamin		Total (n=247)	P*		
		E (n=84)	Pioglitazone (n=80)		Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Demographics							
Age (yrs) - mean±SD	45.4	46.6	47.0	46.3±11.9	0.59	0.43	0.83
Female (%)	57.8	61.9	58.8	59.5	0.59	0.91	0.68
Hispanic (%)	7.2	19.0	18.8	15.0	0.02	0.03	0.96
Non-white (%)	11.0	15.2	8.1	11.5	0.43	0.54	0.17
Quality of life† - mean±SD							
SF-36 Physical component							
Physical function	46	47	49	47±10	0.51	0.15	0.42
Role physical	46	48	49	48±11	0.26	0.08	0.49
Bodily pain	48	50	50	50±10	0.25	0.39	0.74
General health	42	44	43	43±10	0.26	0.32	0.90
Physical component summary	47	49	49	48±10	0.35	0.41	0.89
SF-36 Mental component							
Vitality	42	45	45	44±11	0.13	0.16	0.93
Social function	47	50	49	49±10	0.24	0.41	0.73
Role emotional	47	49	51	49±11	0.34	0.02	0.20
Mental health	48	50	50	49±10	0.20	0.16	0.92
Mental component summary	47	49	49	48±10	0.10	0.10	0.96
Serum biochemistry tests - mean±SD							
AST (U/L)	55	59	54	56±30	0.47	0.83	0.33
ALT (U/L)	81	86	82	83±49	0.51	0.90	0.58
GGT (U/L)	69	56	60	61±63	0.60	0.78	0.79
Alkaline phosphatase (U/L)	82	77	86	81±30	0.20	0.43	0.08
Bilirubin - direct (mg/dL)	0.14	0.13	0.16	0.15±0.12	0.99	0.57	0.59
Bilirubin - total (mg/dL)	0.76	0.75	0.77	0.76±0.35	0.48	0.86	0.61
Lipids - mean±SD							
Triglycerides (mg/dL)	165	166	162	165±93	0.94	0.94	0.88
Total cholesterol (mg/dL)	199	195	195	196±39	0.62	0.49	0.84
High density lipoprotein (mg/dL)	43	44	45	44±12	0.98	0.73	0.75
Low density lipoprotein (mg/dL)	125	119	120	122±34	0.27	0.25	0.99
Metabolic characteristics - mean±SD							
HOMA-IR (mg/dL x μU/mL/405)	5.5	5.2	5.0	5.2±4.3	0.78	0.47	0.68
Fasting serum glucose (mg/dL)	95	95	92	94±13	0.79	0.16	0.10
Fasting serum insulin (μU/mL)	23	22	21	22±18	0.68	0.76	0.91
Weight (kg)	99	94	97	97±23	0.13	0.49	0.42
Body mass index (kg/m ²)	35	34	34	34±7	0.28	0.65	0.51
Waist circumference (cm)	109	107	108	108±14	0.35	0.60	0.69
Waist to hip ratio	0.93	0.93	0.94	0.93±0.08	0.81	0.65	0.82
Triceps skinfold (mm)	34	32	34	33±13	0.09	0.95	0.10
Mid-upper arm circumference (cm)	36	35	36	36±5	0.29	0.72	0.45
Trunk (% fat)‡	42	42	43	42±8	0.57	0.95	0.52
Total (% fat)‡	40	39	40	39±9	0.69	0.90	0.58

Supplement Table 1. Baseline characteristics by treatment group

	Placebo (n=83)	Vitamin		Total (n=247)	P*		
		E (n=84)	Pioglitazone (n=80)		Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Liver Histology							
Fibrosis (%)							
None	19.3	16.9	13.8	16.7	0.67	0.40	0.63
Mild, zone 3 perisinusoidal	16.9	27.4	25.0	23.1			
Moderate, zone 3 perisinusoidal	12.0	10.7	18.8	13.8			
Portal/periportal only	1.2	1.2	3.8	2.0			
Zone 3 and periportal	27.7	21.7	23.8	24.4			
Bridging	19.3	20.5	13.8	17.9			
Cirrhosis	3.6	1.2	1.2	2.0			
Grade - mean±SD	1.6	1.5	1.4	1.5±1.0			
Diagnosis of steatohepatitis (%)							
No	10.8	8.4	12.5	10.5	0.49	0.59	0.07
Borderline, zone 3 pattern	16.9	9.6	22.5	16.2			
Borderline, zone 1 pattern	1.2	1.2	0.0	0.8			
Definite	71.1	80.7	65.0	72.5			
Steatosis (%)							
< 5%	2.4	2.4	1.2	2.0	0.65	0.65	0.85
5 - 33%	31.3	33.3	28.8	31.2			
34 - 66%	42.2	33.3	37.5	37.6			
> 66%	24.1	31.0	32.5	29.2			
Grade - mean±SD	1.9	1.9	2.0	1.9±0.8			
Amount (foci) of lobular inflammation (%)							
0	0.0	0.0	0.0	0.0	0.24	0.12	0.36
> 0 and < 2	48.2	38.1	32.5	39.7			
2-4	41.0	42.9	53.8	45.8			
> 4	10.8	19.0	13.8	14.6			
Grade - mean±SD	1.6	1.8	1.8	1.7±0.7			
Portal, chronic inflammation (%)							
None	20.5	15.7	17.5	17.8	0.71	0.89	0.93
Mild	61.4	63.9	63.8	63.2			
More than mild	18.1	20.5	18.8	19.0			
Ballooning degeneration (%)							
None	16.9	17.9	27.5	20.6	0.78	0.26	0.24
Few	36.1	31.0	32.5	33.2			
Many	47.0	51.2	40.0	46.2			
Grade - mean±SD	1.3	1.3	1.1	1.2±0.8			

Supplement Table 1. Baseline characteristics by treatment group

	Placebo (n=83)	Vitamin		Total (n=247)	P*		
		E (n=84)	Pioglitazone (n=80)		Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Total NAFLD Activity Score (%)							
2	1.2	6.0	3.8	3.6	0.17	0.32	0.45
3	18.1	6.0	13.8	12.6			
4	27.7	23.8	17.5	23.1			
5	19.3	23.8	32.5	25.1			
6	20.5	22.6	16.2	19.8			
7	12.0	15.5	13.8	13.8			
8	1.2	2.4	2.5	2.0			
Grade - mean±SD	4.8	5.1	5.0	4.9±1.4	0.17	0.46	0.55
Biopsy length							
(mm) - mean±SD	18.6	21.4	19.6	19.8±9.3	0.05	0.45	0.25
% < 10 mm	6.0	12.0	12.7	10.2	0.18	0.15	0.91
Iron status - mean±SD							
Serum iron (µg/dL)	89	90	103	94±36	0.87	0.03	0.03
Serum total iron binding capacity (µg/dL)	359	360	356	358±70	0.94	0.83	0.78
Serum ferritin (ng/mL)	304	223	280	269±313	0.10	0.66	0.17
Dietary supplements (%)							
Milk thistle	4.8	6.0	1.2	4.0	0.75	0.19	0.11
Green tea or green tea extract	1.2	0.0	0.0	0.4	0.31	0.32	--
Selenium	1.2	0.0	0.0	0.4	0.31	0.32	--
Vitamin A	2.4	1.2	0.0	1.2	0.55	0.16	0.33
Vitamin C	12.0	13.1	10.0	11.7	0.84	0.68	0.54
Vitamin D	3.6	7.1	10.0	6.9	0.31	0.10	0.51

*Based on chi-square test for categorical variables or t-test on rank of outcome for continuous variables

†SF-36 standardized to 1998 U.S. general population with mean=50 and SD =10

‡Missing values (4 Placebo, 5 Vitamin E, 6 Pioglitazone) due to patient being heavier than allowed weight were imputed with the 95th percentile

Supplement Table 2. Selected characteristics at week 96 by treatment group

	Placebo	Vitamin E		Total	P*		
		Placebo	Pioglitazone		Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Dietary supplements (%)							
n	74	79	70	223			
Milk thistle	0.0	0.0	0.0	0.0	--	--	--
Green tea or green tea extract	2.7	0.0	0.0	0.9	0.14	0.17	--
Selenium	0.0	0.0	1.4	0.4	--	0.30	0.29
Vitamin A	1.4	0.0	0.0	0.4	0.30	0.33	--
Vitamin C	4.0	10.1	5.7	6.7	0.15	0.64	0.32
Vitamin D	8.1	10.1	8.6	9.0	0.67	0.92	0.75
Liver histology							
Biopsy length							
n	72	80	70	222			
(mm) - mean±SD	18.6	17.1	18.6	18.1±9.4	0.24	0.99	0.32
% < 10 mm	9.7	8.8	12.9	10.4	0.84	0.55	0.42

*Based on chi-square test for categorical variables or t-test on for continuous variables

Supplement Table 3. Clinic events, outcomes and adverse events by treatment group

	Placebo (n=83)	Vitamin E (n=84)	Pioglitazone (n=80)	P	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Clinical events / outcomes					
Hypoglycemia	8	8	15	1.00	0.11
New-onset diabetes	0	4	0	0.12	.-
Cardiovascular event	12	12	10	1.00	0.82
Bone fracture	5	3	3	0.50	0.50
Weight gain > 20% from baseline	0	0	3	.-	0.12
Bone mineral density loss ≥ 1 t-score from baseline*	0	0	1	.-	0.47
Hepatotoxicity					
ALT > 250 U/L	1	4	0	0.37	1.00
ALT > 500 U/L	0	0	0	.-	.-
AST > 250 U/L	3	1	1	0.37	0.62
GGT > 250 U/L	2	1	1	0.62	1.00
Bilirubin > 3 mg/dL	0	1	2	1.00	0.24
Adverse events by severity†				0.77	0.51
Mild	20	24	25		
Moderate	20	19	16		
Severe					
Arthritis	0	0	1		
Hepatotoxicity	3	0	0		
Cataract	1	0	0		
Fracture	2	0	0		
Gastroenteritis	0	1	0		
Gout	1	0	0		
Hyperglycemia	0	1	0		
Infection	2	0	0		
Pain	1	3	0		
Syncope	0	1	0		
Transient ischemic attack	0	0	1		
Urticaria	0	1	0		
Life-threatening or disabling					
Cardiac ischemia/infarction	0	1	0		
Liver dysfunction	0	1	0		
Death‡	0	1	0		
Total	50	53	43		

*Number of patients with DEXA scan at both week 96 and baseline are 50, 51, and 49 for placebo, vitamin E and pioglitazone groups respectively

†As reported by study physician at time of event

‡Cause of death was pneumonia and liver failure secondary to sepsis from gram-negative bacteremia

Supplement Table 4. Changes from baseline to 96 weeks in symptoms of liver disease*

Symptom of liver disease	Change in degree of bother†			P‡		
	Placebo (n=74)	Vitamin E (n=77)	Pioglitazone (n=70)	Vitamin E vs Placebo	Pioglitazone vs Placebo	Vitamin E vs Pioglitazone
Pain over liver (right upper quadrant)	-0.07	-0.08	-0.09	0.55	0.53	0.97
Nausea	-0.12	-0.10	0.03	0.17	0.79	0.29
Poor appetite	-0.01	-0.05	0.24	0.35	0.51	0.05
Fatigue	-0.03	-0.14	-0.03	0.37	0.66	0.70
Weight loss	0.03	0.04	-0.11	0.68	0.62	0.33
Diarrhea	-0.16	0.04	-0.03	0.70	0.77	0.57
Muscle aches or cramps	0.03	0.12	0.27	0.95	0.29	0.44
Muscle weakness	0.00	0.23	0.09	0.56	0.77	0.36
Headaches	0.11	0.18	0.29	0.92	0.65	0.78
Easy bruising	-0.03	-0.12	0.14	0.46	0.57	0.24
Itching	-0.01	0.08	0.21	0.73	0.28	0.42
Irritability	0.15	0.08	0.27	0.18	0.42	0.04
Depression / sadness	0.20	-0.06	0.28	0.05	0.61	0.02
Trouble sleeping	0.24	0.09	0.27	0.17	0.64	0.46
Trouble concentrating	0.15	0.05	0.28	0.46	0.73	0.27
Jaundice	0.08	0.01	0.09	0.22	0.95	0.36
Dark urine	0.05	-0.09	0.00	0.19	0.46	0.57
Swelling of ankles	0.14	-0.01	0.29	0.26	0.22	0.01
Swelling of abdomen	-0.08	0.01	-0.01	0.62	0.74	0.87

*Question on Symptoms of Liver Disease form: "During the last month, how much have you been bothered by the following"

†Degree of bother coded as 1=none at all, 2=a little bit, 3=moderately, 4=quite a bit, 5=extremely

‡Based on ANCOVA model regressing change from baseline at 96 weeks on treatment group and baseline value of the outcome

Supplement Table 5. Improvement in NASH and changes in other histologic features by treatment group

	Week 96 - Baseline			Total	P*		
	Placebo	Vitamin E	Pioglitazone		Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Primary outcome: Histologic improvement in NASH†							
Number randomized	83	84	80	247			
Percent improved	19	43	34	32	0.001	0.04	0.20
Changes in liver histology, baseline to 96 weeks							
Number with two biopsies	72	80	70	222			
Fibrosis							
% worse	22	19	17	19	0.27	0.13	0.64
% same	47	41	39	42			
% better	31	41	44	38			
Mean change	-0.1	-0.3	-0.4	-0.3	0.19	0.10	0.78
Steatosis							
% worse	21	8	4	11	0.001	<0.0001	0.07
% same	49	39	27	38			
% better	31	54	69	51			
Mean change	-0.1	-0.7	-0.8	-0.6	<0.0001	<0.0001	0.41
Lobular inflammation							
% worse	17	8	6	10	0.01	0.001	0.43
% same	49	39	34	41			
% better	35	54	60	50			
Mean change	-0.2	-0.6	-0.7	-0.5	0.008	0.0009	0.59
Portal inflammation							
% worse	22	19	13	18	0.30	0.13	0.66
% same	67	64	71	67			
% better	11	18	16	15			
Ballooning degeneration							
% worse	21	14	9	14	0.02	0.02	0.96
% same	50	36	47	44			
% better	29	50	44	41			
Mean change	-0.2	-0.5	-0.4	-0.4	0.03	0.01	0.59
Total NAFLD Activity Score							
% worse	31	11	9	17	0.0007	<0.0001	0.39
% same	19	14	10	14			
% better	50	75	81	69			
Mean change	-0.5	-1.9	-1.9	-1.5	<0.0001	<0.0001	0.27
Diagnosis of NASH							
% worse	12	4	7	8	0.0008	0.01	0.55
% same	60	44	43	49			
% better	28	52	50	44			
% resolved‡	21	36	47	35	0.05	0.001	0.19

*P-values derived from Mantel-Haenszel chi-square test stratified by clinic for primary outcome, Cochran's chi-square test for trend for ordered outcomes, chi-square test for binary outcomes, or ANCOVA model regressing change from baseline at 96 weeks on treatment group and baseline value of the outcome for continuous outcomes

†Primary outcome is defined as 1) no worsening in fibrosis; and 2) improvement in ballooning; and either 3a) NAFLD Activity Score \leq 3; or 3b) decrease in NAFLD Activity Score of at least 2 and improvement in lobular inflammation or steatosis; 11 Placebo, 4 Vitamin E, and 10 Pioglitazone assigned patients with missing histology at week 96 were imputed with no improvement.

Supplement Table 5. Improvement in NASH and changes in other histologic features by treatment group

				P*		
Week 96 - Baseline				Vitamin E	Pioglitazone	Vitamin E
Placebo	Vitamin E	Pioglitazone	Total	vs. Placebo	vs. Placebo	vs. Pioglitazone

‡ Defined as no NASH at week 96

Supplement Table 6. Change from baseline at week 96 in serum biochemical tests, quality of life and metabolic factors by treatment group

	Week 96 - Baseline				P*		
	Placebo (n=74)	Vitamin E (n=78)	Pioglitazone (n=70)	Total (n=222)	Vitamin E vs. Placebo	Pioglitazone vs. Placebo	Vitamin E vs. Pioglitazone
Change in serum enzymes and bilirubin, baseline to 96 weeks							
AST (U/L)	-3.8	-21.3	-20.4	-15.2	0.0001	<0.0001	0.30
ALT (U/L)	-20.1	-37.0	-40.8	-32.6	0.001	<0.0001	0.19
GGT (U/L)	-4.0	-14.0	-21.1	-12.9	0.003	0.0002	0.25
Alkaline phosphatase (U/L)	-3.8	-9.3	-12.0	-8.3	0.008	0.004	0.87
Bilirubin - direct (mg/dL)	0.022	0.043	-0.003	0.022	0.43	0.90	0.38
Bilirubin - total (mg/dL)	0.064	0.037	-0.040	0.022	0.56	0.07	0.23
Change in lipids, baseline to 96 weeks							
Triglycerides (mg/dL)	-6.7	-0.6	-19.8	-8.6	0.45	0.16	0.07
Total cholesterol (mg/dL)	-9.6	-13.6	-11.4	-11.6	0.25	0.50	0.51
High density lipoprotein (mg/dL)	-1.9	-0.9	1.1	-0.6	0.51	0.008	0.17
Low density lipoprotein (mg/dL)	-5.8	-12.0	-8.1	-8.7	0.07	0.26	0.33
Change in metabolic characteristics, baseline to 96 weeks							
HOMA-IR [†] (mg/dL × μU/mL/405)	0.4	0.4	-0.7	-0.2	0.80	0.03	0.02
Fasting serum glucose (mg/dL)	1.8	1.8	-3.1	0.2	0.81	0.006	0.008
Fasting serum insulin (μU/mL)	1.8	0.6	-2.0	-1.0	0.76	0.06	0.04
Weight (kg)	0.7	0.4	4.7	1.8	0.65	0.0001	<0.0001
Body mass index (kg/m ²)	0.4	0.1	1.8	0.7	0.50	0.0002	<0.0001
Waist circumference (cm)	0.2	-0.4	3.3	1.0	0.53	0.06	0.03
Waist to hip ratio	-0.0086	-0.0086	-0.0094	-0.0089	0.76	0.92	1.00
Triceps skinfold (mm)	0.6	-0.6	2.2	0.7	0.21	0.33	0.01
Mid-upper arm circumference (cm)	0.3	-0.2	1.3	0.4	0.27	0.02	0.01
Trunk (% fat)	0.5	0.6	1.6	0.9	0.89	0.12	0.12
Total (% fat)	0.0	0.4	2.7	1.0	0.50	<0.0001	0.0005
Change in quality of life measures, baseline to 96 weeks							
Physical component [¶]							
Physical function	-0.6	-0.6	-2.3	-1.1	0.95	0.45	0.49
Role physical	-0.5	-0.3	-1.6	-0.8	0.58	0.85	0.83
Bodily pain	-0.7	0.3	-1.4	-0.5	0.31	0.98	0.38
General health	1.7	1.6	0.8	1.3	0.78	0.59	0.43
Physical component summary	-0.3	0.4	-0.9	-0.3	0.45	0.93	0.54
Mental component [¶]							
Vitality	0.7	1.2	-0.3	0.6	0.33	0.84	0.32
Social function	-0.7	-2.0	-3.0	-1.9	0.62	0.22	0.50
Role emotional	0.4	-0.4	-2.2	-0.7	0.66	0.48	0.81
Mental health	0.1	-0.5	-1.6	-0.7	0.90	0.24	0.38
Mental component summary	0.4	-0.5	-1.9	-0.6	0.76	0.23	0.47

*P-values derived from ANCOVA model regressing change from baseline at 96 weeks on treatment group and baseline value of the outcome

[†]Four patients assigned to Vitamin E developed new onset diabetes; Their HOMA-IR values at 96 weeks were imputed with the 95th percentile value at baseline. Analyses using ranks were used due to asymmetry in the distribution of change in HOMA-IR and fasting serum insulin.

[¶]SF-36 standardized to 1998 US general population with mean=50 and SD=10

Supplement Table 7. Changes in serum biochemical tests, metabolic factors, and quality of life after 96 weeks of treatment and after 120 weeks (96 weeks of treatment followed by 24 weeks off-treatment)

	Placebo	Vitamin E	Pioglitazone	P*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Number of paired observations					
Baseline to 96 weeks	74	78	70		
Baseline to 120 weeks	68	71	63		
Change in serum enzymes and bilirubin					
ALT (U/L)					
Baseline to 96 weeks	-20.1	-37.0	-40.8	0.001	<0.0001
Baseline to 120 weeks	-26.0	-19.7	-24.8	0.41	0.58
AST (U/L)					
Baseline to 96 weeks	-3.8	-21.3	-20.4	0.0001	<0.0001
Baseline to 120 weeks	-10.5	-12.5	-12.2	0.85	0.25
GGT (U/L)					
Baseline to 96 weeks	-4.0	-14.0	-21.1	0.003	0.0002
Baseline to 120 weeks	NA	NA	NA		
Alkaline phosphatase (U/L)					
Baseline to 96 weeks	-3.8	-9.3	-12.0	0.008	0.004
Baseline to 120 weeks	-4.8	-8.3	-4.2	0.05	0.59
Bilirubin - total (mg/dL)					
Baseline to 96 weeks	0.06	0.04	-0.04	0.56	0.07
Baseline to 120 weeks	0.04	0.09	0.01	0.53	0.41
Change in lipids					
Triglycerides (mg/dL)					
Baseline to 96 weeks	-6.7	-0.6	-19.8	0.45	0.16
Baseline to 120 weeks	-8.6	0.4	-4.1	0.42	0.77
Cholesterol (mg/dL)					
Baseline to 96 weeks	-9.6	-13.6	-11.4	0.25	0.50
Baseline to 120 weeks	-13.4	-16.5	-15.4	0.28	0.42
High density lipoprotein (mg/dL)					
Baseline to 96 weeks	-1.9	-0.9	1.1	0.51	0.008
Baseline to 120 weeks	-1.7	-0.9	-2.0	0.61	0.92
Low density lipoprotein (mg/dL)					
Baseline to 96 weeks	-5.8	-12.0	-8.1	0.07	0.26
Baseline to 120 weeks	-10.0	-13.3	-11.9	0.16	0.26
Change in metabolic characteristics					
Fasting serum glucose (mg/dL)					
Baseline to 96 weeks	1.8	1.8	-3.1	0.81	0.006
Baseline to 120 weeks	2.0	2.7	1.9	0.45	0.66
HOMA-IR† ([mg/dL × μU/mL]/405)					
Baseline to 96 weeks	0.4	0.4	-0.7	0.80	0.03
Baseline to 120 weeks	0.1	0.4	0.2	0.24	0.42
Weight (kg)					
Baseline to 96 weeks	0.7	0.4	4.7	0.65	0.0001
Baseline to 120 weeks	0.9	-0.4	3.7	0.21	0.008
Body mass index (kg/m ²)					
Baseline to 96 weeks	0.4	0.1	1.8	0.50	0.0002

Supplement Table 7. Changes in serum biochemical tests, metabolic factors, and quality of life after 96 weeks of treatment and after 120 weeks (96 weeks of treatment followed by 24 weeks off-treatment)

	Placebo	Vitamin E	Pioglitazone	P*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Baseline to 120 weeks	0.4	-0.2	1.4	0.16	0.006
Waist circumference (cm)					
Baseline to 96 weeks	0.2	-0.4	3.3	0.53	0.06
Baseline to 120 weeks	1.6	-0.6	2.9	0.05	0.19
Body composition (% fat)					
Baseline to 96 weeks	0.0	0.4	2.7	0.50	<0.0001
Baseline to 120 weeks	-0.1	0.1	1.7	0.69	0.002
Change in quality of life measures					
SF-36‡ Physical component summary					
Baseline to 96 weeks	-0.3	0.4	-0.9	0.45	0.93
Baseline to 120 weeks	-1.3	-0.0	-1.0	0.15	0.46
SF-36‡ Mental component summary					
Baseline to 96 weeks	0.4	-0.5	-1.9	0.76	0.23
Baseline to 120 weeks	0.7	1.0	-2.5	0.60	0.11

*P-values derived from ANCOVA models regressing change from baseline to 96 weeks or 120 weeks on treatment group and baseline value of the outcome measure

†Four patients assigned to Vitamin E developed new onset diabetes and were not given an oral glucose tolerance test at 96 weeks or 120 weeks. Their HOMA-IR values at 96 weeks and 120 weeks were imputed with the 95th percentile value at baseline. Analyses using ranks were used due to asymmetry in the distribution of change in HOMA-IR.

‡SF-36 standardized to 1998 US general population with mean=50 and SD=10

Supplement Table 8. Sensitivity analyses

	Histologic improvement						P*		
	Placebo		Vitamin E		Pioglitazone		Vitamin E vs Placebo	Pioglitazone vs Placebo	Vitamin E vs Pioglitazone
	%	N	%	N	%	N			
Primary outcome as stated in protocol									
Missed week 96 biopsies imputed as no improvement	19%	83	43%	84	34%	80	0.001	0.04	0.20
Sensitivity analyses									
Exclude if missed	22%	72	45%	80	39%	70	0.004	0.05	0.38
Exclude if missed or outside time window	21%	70	45%	76	38%	66	0.003	0.04	0.39
Exclude if no ballooning at baseline	23%	69	52%	69	47%	58	0.0004	0.002	0.41
Redefine ballooning component to no worsening for biopsies with no ballooning at baseline	25%	83	51%	84	48%	80	0.0007	0.003	0.59
Redefine ballooning component and exclude if missed	29%	72	54%	80	54%	70	0.003	0.004	0.98
Exclude if biopsy length < 10mm at baseline or week 96	15%	73	39%	69	30%	63	0.001	0.03	0.28
Local reading at baseline, central reading at week 96									
Overall	23%	83	48%	84	52%	80	0.0008	<0.0001	0.57
Exclude if missing	26%	72	50%	80	60%	70	0.004	<0.0001	0.23
Exclude if missing or outside time window	27%	70	49%	76	61%	66	0.008	0.0001	0.13

P-values determined from three pairwise Mantel-Haenszel chi-square tests stratified by clinic

Supplement Table 9: Multiple Imputation and Best/Worst Case Scenario for missing week 96 biopsy**Number of completed and missing week 96 biopsies**

	Vitamin E (n=84)	Placebo (n=83)	Pioglitazone (n=80)
Completed week 96 biopsy	80	72	70
Missing week 96 biopsy	4	11	10
No ballooning on baseline biopsy*	2	2	2
Some ballooning on baseline biopsy†	2	9	8

*Imputed as no response in multiple imputation and best/worst case scenario imputations

†Available for multiple imputation and best/worst case scenario imputations

Regression analyses

	Vitamin E vs. Placebo			Pioglitazone vs. Placebo		
	OR*	95% CI	P-value	OR*	95% CI	P-value
Per protocol†	3.1	1.6-6.3	0.001	2.1	1.0-4.3	0.04
Multiple imputation‡	2.7	1.2-5.9	0.01	2.1	1.0-4.4	0.04
Worst case scenario¶	1.7	0.9-3.3	0.09	1.2	0.6-2.3	0.62
Best case scenario§	3.5	1.7-6.9	<0.001	3.3	1.6-6.6	0.001

*Odds ratio of histologic improvement estimated from logistic regression

†Observations with missing week 96 biopsy imputed as no improvement

‡Observations with missing week 96 biopsy and some ballooning at baseline were imputed using 50 datasets. Imputation model included the following variables at baseline: treatment group indicator, ballooning, inflammation, steatosis, NAFLD Activity score, and fibrosis.

¶Observations with missing week 96 biopsy and some ballooning at baseline were imputed as improvement for patients assigned to Placebo and no improvement for patients assigned to either Vitamin E or Pioglitazone

§Observations with missing week 96 biopsy and some ballooning at baseline were imputed as no improvement for patients assigned to Placebo and improvement for patients assigned to either Vitamin E or Pioglitazone

Supplement Table 10. Subgroup analyses

	Histologic improvement						Interaction P*		
	Placebo		Vitamin E		Pioglitazone		Vitamin E vs Placebo	Pioglitazone vs Placebo	Vitamin E vs Pioglitazone
	%	N	%	N	%	N			
Race†									
White	14%	73	46%	67	32%	68	0.007	0.74	0.06
Non-white	56%	9	33%	12	67%	6			
Gender									
Female	16%	48	42%	52	36%	47	0.49	0.22	0.64
Male	26%	35	44%	32	30%	33			
Age at baseline - yrs									
< 46	15%	47	43%	46	36%	45	0.41	0.30	0.86
≥ 46	25%	36	42%	38	31%	35			
Ethnicity									
Non-Hispanic	17%	77	43%	68	34%	65	0.15	0.13	0.93
Hispanic	50%	6	44%	16	33%	15			
BMI at baseline - kg/m ²									
< 35	22%	49	50%	50	36%	47	0.56	0.92	0.53
≥ 35	15%	33	34%	32	30%	33			
NAS at baseline									
2-4	18%	39	23%	30	29%	28	0.04	0.70	0.15
5-8	20%	44	54%	54	37%	52			
Ballooning at baseline									
None	0%	14	0%	15	0%	22	NA	NA	NA
Few or many	23%	69	52%	69	47%	58			
Treatment adherence‡									
< 80%	27%	11	44%	9	0%	8	0.77	0.02	0.09
≥ 80%	21%	61	45%	71	44%	62			
Treatment adherence‡									
< 90%	30%	23	52%	21	36%	22	0.90	0.35	0.46
≥ 90%	18%	49	42%	59	40%	48			

*P-value determined from three pairwise logistic regressions of probability of histologic improvement on indicator variables for treatment group, risk factor, and interaction of treatment group and risk factor

†1 Placebo, 5 Vitamin E, and 6 Pioglitazone patients had missing values for race

‡Patients missing a biopsy at 96 weeks were excluded; Defined as the percent of days from randomization to biopsy at 96 weeks taking both drugs based on pill counts