Supplementary Appendix

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

Supplement to: Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. DOI: 10.1056/NEJMoa1506930

PIOGLITAZONE AFTER ISCHEMIC STROKE OR TRANSIENT ISCHEMIC ATTACK

SUPPLEMENTARY APPENDIX

TABLE OF CONTENTS

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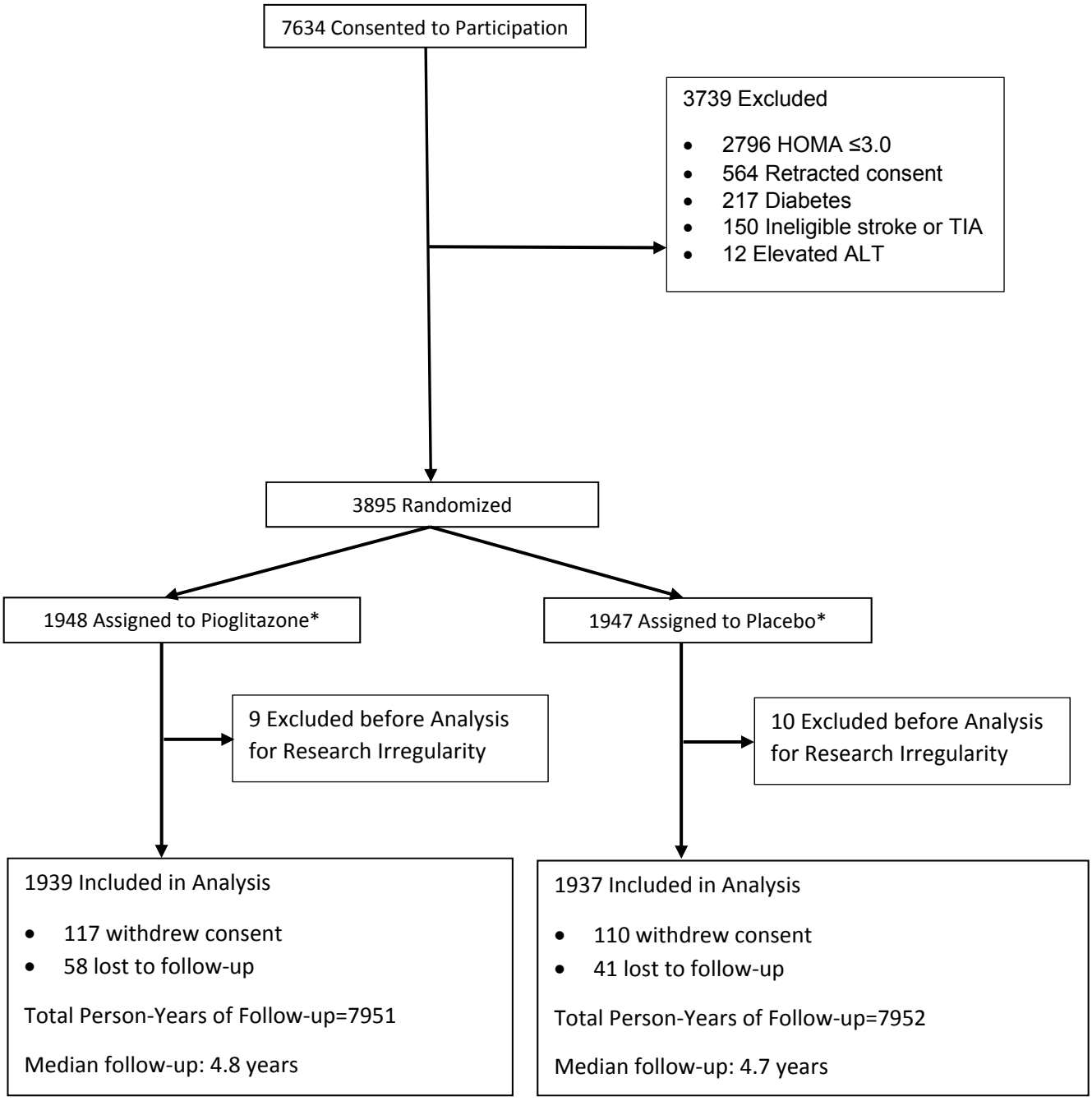
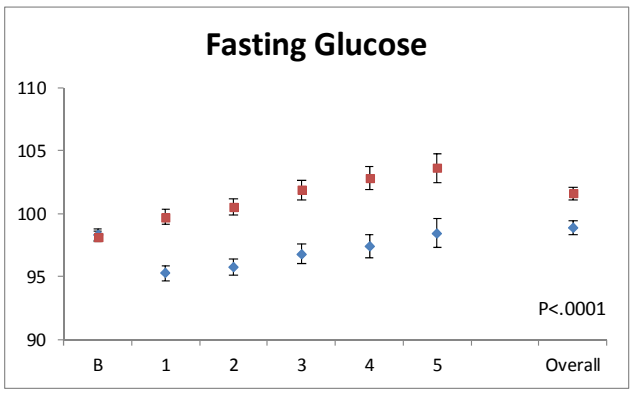
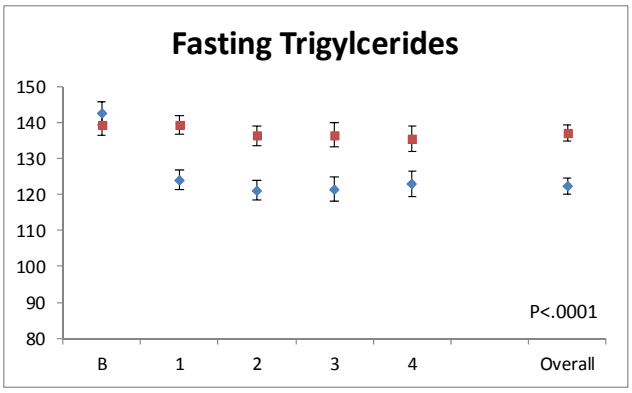


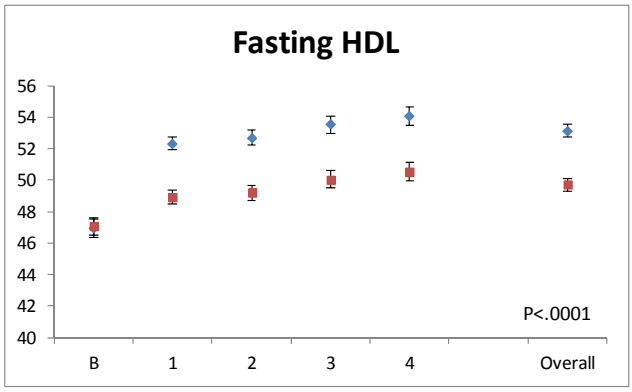
Figure S1. Randomization and Follow-up of Study Participants. Participants were assessed for eligibility before consenting to be tested for insulin resistance, but the number of patients assessed is unknown because screening logs were not maintained. *Includes 30 participants (19 in pioglitazone group and 11 in placebo group) who were randomized in error (i.e., did not meet entry criteria); these participants were retained in follow-up and are included in analysis.

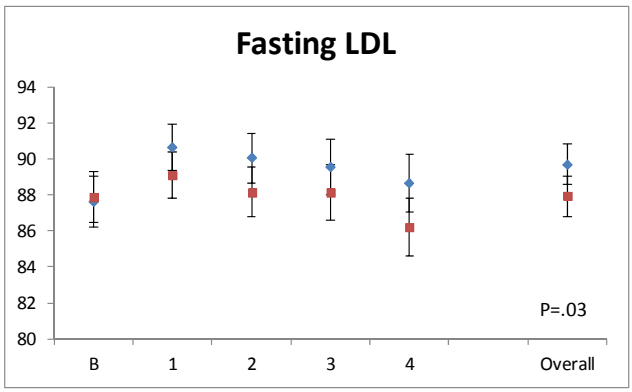




Pioglitazone (N)=	1939	1659	1484	1290	1029	723
Placebo (N)=	1937	1709	1519	1314	1027	719

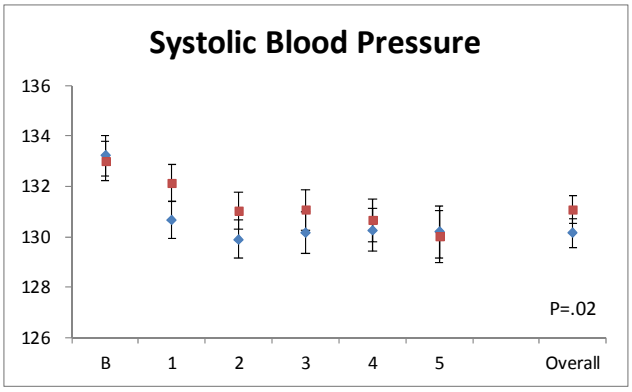
1935	1683	1553	1370	1099
1934	1723	1588	1384	1102

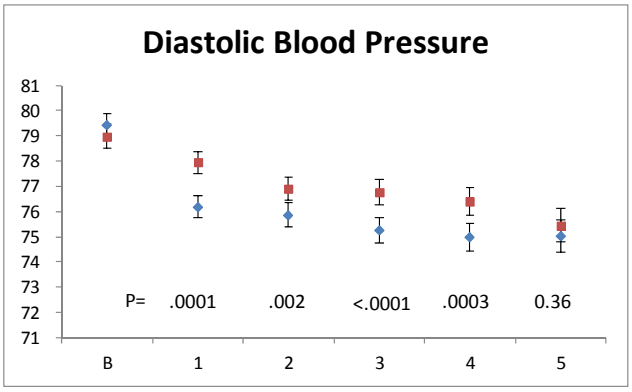




Pioglitazone (N)=	1934	1682	1552	1370	1098
Placebo (N)=	1934	1723	1586	1384	1102

1918	1675	1541	1363	1092
1920	1705	1576	1373	1087





Pioglitazone (N)=	1993	1711	1570	1378	1111	803
Placebo (N)=	1931	1741	1595	1403	1126	791

1933	1711	1570	1378	1111	803
1931	1741	1595	1403	1126	790

Figure S2. Selected Measures over time by Treatment Group (Pioglitazone ◆; Placebo ■).

Least square means with 95% confidence intervals are from a repeated measures covariance pattern model assuming missing at random at follow-up time points and for overall estimate. Overall p values are for the treatment effect for years 1 to 4 adjusted for baseline (for lipids) and for years 1 to 5 adjusted for baseline (for glucose and systolic blood pressure). For diastolic blood pressure, p-values are shown separately for each follow-up year because of a significant treatment by year effect.

Table S1. Features of Baseline Stroke and TIA Events by Treatment Group

	Pioglitazone		Placebo	
Subtype	N	%	N	%
Lacunar	584	30%	559	29%
Embolic	147	8%	137	7%
Large vessel	500	26%	504	26%
Uncertain	697	36%	730	38%
NA (not eligible stroke/TIA)	11	1%	7	0%
Distribution				
Left Anterior/Carotid	665	34%	659	34%
Right Anterior/Carotid	601	31%	604	31%
Vertebral/Basilar	470	24%	469	24%
Multiple	55	3%	45	2%
Uncertain	137	7%	153	8%
NA (not eligible stroke/TIA)	11	1%	7	0%
Modified Rankin Scale				
0	761	39%	774	40%
1	653	34%	679	35%
2	345	18%	322	17%
3	125	6%	118	6%
4	44	2%	36	2%
Unknown	0	0%	1	0%
NA (not eligible stroke/TIA)	11	1%	7	0%
Stroke Severity (NIH Stroke Scale)				
Mild impairment (<5)	1835	95%	1843	95%
Moderately severe impairment (5-14)	92	5%	84	4%
Severe impairment (15-24)	0	0%	2	0%
Very severe impairment (>25)	0	0%	0	0%
Unknown	1	0%	1	0%
NA (not eligible stroke/TIA)	11	1%	7	0%

T**able S2. Baseline Metabolic Characteristics by Treatment Group**		
Characteristic	Pioglitazone (N=1939)	Placebo (N=1937)
Fasting glucose, no (%)		
<100 mg/dL	1126 (58.1)	1137 (58.7)
100-109 mg/dL	546 (28.2)	543 (28.0)
110-125 mg/dL	267 (13.8)	257 (13.3)
Insulin (µU/mL), median (Q25,Q75)	19 (16,26)	19 (16,25)
HOMA-IR, median (Q25,Q75)	4.7 (3.8,6.2)	4.6 (3.7,6.2)
HbA_{1c}, no (%)		
<5.7%	672 (34.7)	690 (35.6)
5.7-6.4%	1150 (59.3)	1118 (57.7)
6.5-6.9%	116 (6.0)	129 (6.7)
Diabetes Status[Ψ], no (%)		
Euglycemia	457 (23.6)	473 (24.4)
Pre-diabetes	1366 (70.4)	1335 (68.9)
Diabetes	116 (6.0)	129 (6.7)

[Ψ]According to ADA 2010 criteria: Euglycemia: Fasting Glucose <100 mg/dL and HbA1c <5.7%; Pre-diabetes: Fasting Glucose 100-125 mg/dL or HbA1c 5.7-6.4%; Diabetes: HbA1c 6.5-6.9%

Table S3. Achievement of Selected Secondary Stroke Prevention Goals by Year of Participation and Treatment Group

Prevention Goal		Pioglitazone			Placebo		
		No. Pts. in Trial [χ]	No. Pts. missing data[γ]	% Pts. Achieving Goal[φ]	No. Pts. in Trial [χ]	No. Pts. missing data[γ]	% Pts. Achieving Goal[φ]
Blood Pressure <140/90	Baseline	1939	6	66	1937	6	67
	Year 1	1894	183	71	1881	140	69
	Year 2	1834	265	73	1838	243	70
	Year 3	1684	307	74	1679	276	71
	Year 4	1422	312	73	1396	270	72
	Year 5	1021	219	75	1008	218	73
On Anti-Thrombotics[†]	Baseline	1939	2	99	1937	1	99
	Year 1	1894	128	97	1881	99	97
	Year 2	1834	159	97	1838	130	97
	Year 3	1684	177	97	1679	154	96
	Year 4	1422	166	95	1396	143	96
	Year 5	1021	106	95	1008	112	95
On Statin	Baseline	1939	7	83	1937	5	82
	Year 1	1894	128	79	1881	103	80
	Year 2	1834	161	80	1838	135	80
	Year 3	1684	176	79	1679	151	78
	Year 4	1422	172	79	1396	144	79
	Year 5	1021	108	77	1008	112	77
Non-Smoker	Baseline	1939	2	83	1937	1	85
	Year 1	1894	120	83	1881	93	84
	Year 2	1834	156	83	1838	130	84
	Year 3	1684	166	84	1679	148	85
	Year 4	1422	161	85	1396	143	85
	Year 5	1021	104	85	1008	108	86

[χ]Number of participants in trial (excludes participants who had died, withdrawn consent or completed the final follow-up interview before beginning of year).

[γ]Number of participants with missing data on prevention goal.

[φ]Percent of participants in trial who met prevention goal (denominator is number of participants in trial minus number participants missing data).

[†]Taking an anti-platelet or anti-coagulant medication.

Table S4. Study Drug Adherence by Year of Participation and at Exit by Treatment Group

		Study Drug Status at End of Year (%)					Adherence by Pill Counts by Year		
	No. Pts.[φ]	Removed by ISC†	Off Drug for Other Reason	15 mgs/day[γ]	30 mgs/day	45 mgs/day	Mgs/day, median	%Maximum Dose[α], mean	%Pts with Good Adherence[‡]
Pioglitazone									
Year 1	1894	2%	22%	5%	4%	67%	37	73	61
Year 2	1834	4%	26%	5%	4%	61%	40	65	55
Year 3	1684	5%	29%	6%	4%	56%	38	61	52
Year 4	1422	7%	32%	6%	3%	51%	35	56	49
Year 5	1021	9%	31%	6%	3%	50%	38	61	52
Exit	1692	8%	32%	7%	3%	49%	29	61	47
Placebo									
Year 1	1881	1%	14%	2%	2%	81%	39	81	75
Year 2	1838	3%	19%	3%	2%	73%	43	75	69
Year 3	1679	4%	24%	3%	1%	68%	42	71	64
Year 4	1396	6%	27%	4%	1%	61%	42	66	61
Year 5	1008	7%	29%	4%	1%	59%	42	68	62
Exit	1689	6%	27%	4%	2%	61%	37	71	60

[φ]Number of participants in trial (excludes participants who had died, withdrawn consent or completed the final follow-up interview before beginning of year). Participants who were unable to be located were classified as off study drug.

†Participants were only classified as removed if they had been instructed to stop taking the study drug by the IRIS Internal Safety Committee.

[γ]Includes participants on less than 15mg/day dosing regimen.

[α]%Maximum dose= (mg consumed per day as estimated by pill countbacks)/(maximum mg as stipulated by protocol if dose is never adjusted and treatment is not interrupted for any reason).

[‡]Good Adherence=taking ≥80% of maximum dose as stipulated by protocol.

Table S5. Features of Primary and Secondary Stroke Outcome Events by Treatment Group

Feature	Stroke Events in Primary Outcome (Stroke or MI)				Stroke Events in Secondary Outcome (Stroke alone)			
	Pioglitazone		Placebo		Pioglitazone		Placebo	
	N	%	N	%	N	%	N	%
Number	123		150		127		154	
Stroke Type								
Ischemic	109	89%	136	91%	112	88%	140	91%
Non-fatal	104	85%	129	86%	107	84%	132	86%
Fatal	5	4%	7	5%	5	4%	8	5%
Hemorrhagic	13	11%	14	9%	14	11%	14	9%
Non-fatal	10	8%	8	5%	10	8%	8	5%
Fatal	3	2%	6	4%	4	3%	6	4%
Uncertain (fatal)	1	1%	0	0%	1	1%	0	0%
Ischemic Stroke Subtype								
Lacunar	9	8%	17	13%	9	8%	17	12%
Embolic	15	14%	19	14%	16	14%	20	14%
Large vessel	17	16%	22	16%	17	15%	22	16%
Uncertain	68	62%	78	57%	70	63%	81	58%
Ischemic Stroke Distribution								
Carotid	72	66%	92	68%	74	66%	93	66%
Vertebral/Basilar	17	16%	31	23%	18	16%	32	23%
Multiple	7	6%	2	1%	7	6%	3	2%
Uncertain	13	12%	11	8%	13	12%	12	9%
NIH Stroke Scale								
0-4	82	67%	88	59%	84	66%	89	58%
5-14	26	21%	36	24%	27	21%	37	24%
15-41	3	2%	6	4%	3	2%	7	5%
42 (fatal)	9	7%	13	9%	10	8%	14	9%
Missing	3	2%	7	5%	3	2%	7	5%
Mean (SD)	6.8 (10.9)		7.9 (11.7)		6.9 (11.1)		8.2 (12.0)	
Mean change from Baseline								
All strokes	5.5 (10.8)		6.4 (11.7)		5.7 +11.1		6.8 +12.0	
Non-fatal strokes	2.6 (4.2)		3.0 (4.7)		2.6 +4.1		3.2 +5.1	
Days to NIHSS (median)	15		17		16		17	

Table S6. Changes in Selected Measures from Baseline to Year 1 by Treatment Group

Measure	Pioglitazone Baseline	Pioglitazone Year 1	Pioglitazone Change	Placebo Baseline	Placebo Year 1	Placebo Change	P-value for mean change[Y]
HOMA							
(N)	(1440)			(1458)			
Mean	5.4	4.1	-1.3	5.3	5.7	0.4	<.0001
SD	2.7	2.8	3.1	2.6	6.6	6.5	
Median	4.6	3.4	-1.3	4.5	4.4	-0.3	
IQR	2.4	2.1	2.2	2.5	3.0	2.5	
Insulin, µU/mL							
(N)	(1449)			(1460)			
Mean	22.3	17.2	-5.1	22.0	22.5	0.5	<.0001
SD	10.2	9.9	11.2	9.7	17.8	17.0	
Median	19	15	-5	19	18	-1	
IQR	9	9	8	9	11	10	
Fasting Glucose, mg/dL							
(N)	(1659)			(1709)			
Mean	98.2	95.1	-3.0	98.3	99.7	1.4	<.0001
SD	10.0	11.0	10.5	9.9	16.6	15.0	
Median	97	94	-3	98	97	0	
IQR	14	13	12	14	14	12	
C-Reactive Protein, mg/L							
(N)	(1628)			(1665)			
Mean	4.5	3.3	-1.2	4.7	4.4	-0.3	0.02
SD	8.9	7.5	10.5	8.8	9.8	11.8	
Median	2.1	1.3	-0.4	2.3	2.0	-0.2	
IQR	3.7	2.6	2.1	3.7	3.4	2.0	

[Y]P-value from T-test for comparison of mean change from baseline to year 1 between treatment groups.

Table S7. All Adverse Events Potentially Related to Pioglitazone by Treatment Group			
Event	**Pioglitazone (N=1939)**	**Placebo (N=1937)**	**P-value**
Weight Gain			
> 10 lbs (4.5 kgs)[ψ]	1013 (52.2)	653 (33.7)	<.001
> 30 lbs (13.5 kgs) [ψ]	221 (11.4)	88 (4.5)	<.001
At Year 1, mean	3.9 lbs (1.8 kgs)	-0.7 lbs (-0.3 kgs)	<.001
At Year 4, mean	5.8 lbs (2.6 kgs)	-1.2 lbs (-0.5 kgs)	<.001
Edema[α]			
Any	691 (35.6)	483 (24.9)	<.001
Severe	348 (17.9)	235 (12.1)	<.001
Myalgia[λ]			
Any	676 (34.9)	650 (33.6)	0.39
Severe	76 (3.9)	74 (3.8)	0.87
Shortness of Breath[δ]	342 (17.6)	292 (15.1)	0.03
Bone Fracture[μ]			
Any	218 (11.2)	145 (7.5)	<.0001
Serious	99 (5.1)	62 (3.2)	0.003
Incident Cancer			
Any	133 (6.9)	150 (7.7)	0.29
Non-melanoma skin	21 (1.1)	32 (1.6)	0.13
Prostate	28 (1.4)	25 (1.3)	0.68
Breast	10 (0.5)	16 (0.8)	0.24
Lung	13 (0.7)	11 (0.6)	0.68
Bladder	12 (0.6)	8 (0.4)	0.37
Colon and Rectum	7 (0.4)	8 (0.4)	0.79
Melanoma	8 (0.4)	5 (0.3)	0.41
Kidney	3 (0.2)	8 (0.4)	0.13
Lymphoma	5 (0.3)	4 (0.2)	0.74
Uncertain	3 (0.2)	4 (0.2)	0.70
Other *(types with n<6)*	29 (1.5)	33 (1.7)	0.61
Heart Failure[χ]			
Any	74 (3.8)	71 (3.7)	0.80
Serious	51 (2.6)	42 (2.2)	0.35
Alanine aminotransferase			
>upper limit of normal	26 (1.3)	59 (3.0)	<.001
>2.5 upper limit of normal	7 (0.4)	14 (0.7)	0.13
Macular Edema[β]	3 (0.2)	2 (0.1)	0.66
Other Symptoms and Complaints[γ]			
Tooth problems	555 (28.6)	601 (31.0)	0.10
Frequent headaches	395 (20.4)	410 (21.2)	0.54
Sinus infection	229 (11.8)	241 (12.4)	0.55
Throat infection	120 (6.2)	133 (6.9)	0.39

[ψ]Weight change from baseline at any time in trial.
[α]Self-report at quarterly interview of new or worse swelling of feet or lower legs; severe=persisting after leg elevation or associated with discomfort, redness, skin breakdown or difficulty getting shoes on feet.
[λ]Self-report at quarterly interview of new or worse muscle aches; severe=diffuse muscle aches associated with limitation in mobility or substantial discomfort.
[δ]Self-report at quarterly interview of new or worse shortness of breath or difficulty breathing.
[ρ]Other types of cancer with frequency < 6.
[μ]Adjudicated bone fracture; serious=fracture resulting in hospitalization, surgery or procedure.
[χ]Adjudicated heart failure; serious=heart failure causing or prolonging hospitalization or causing death.
[β]Adjudicated episode of macular edema.
[γ]Symptoms/complaints by self-report at annual interview: Tooth problems, infections requiring a visit to a dentist/doctor.