SUPPLEMENTARY DATA

Inclusion criteria:

Patients must have met all of the following criteria to be considered eligible to participate in the study:
1. Adult patients between the ages of 18 to 75 years, inclusive
2. Male patients and female patients of childbearing potential must agree to use an adequate method of contraception during the study and for 30 days after the follow-up visit.
3. Confirmed diagnosis of type 2 diabetes
4. Screening with the following laboratory values:
    a. Fasting plasma glucose (FPG) $\leq$270 mg/dL
    b. Body mass index $\leq$45 kg/m^2
    c. A1C value of 7% to 10.5% (53.0 mmol/mol to 91.3 mmol/mol)
    d. C-peptide $\geq$1.0 ng/mL
5. Stable dose of metformin monotherapy $\geq$1500 mg/day for at least 8 weeks; lower doses ($\geq$1000 mg/day) are permitted with documentation of GI intolerance
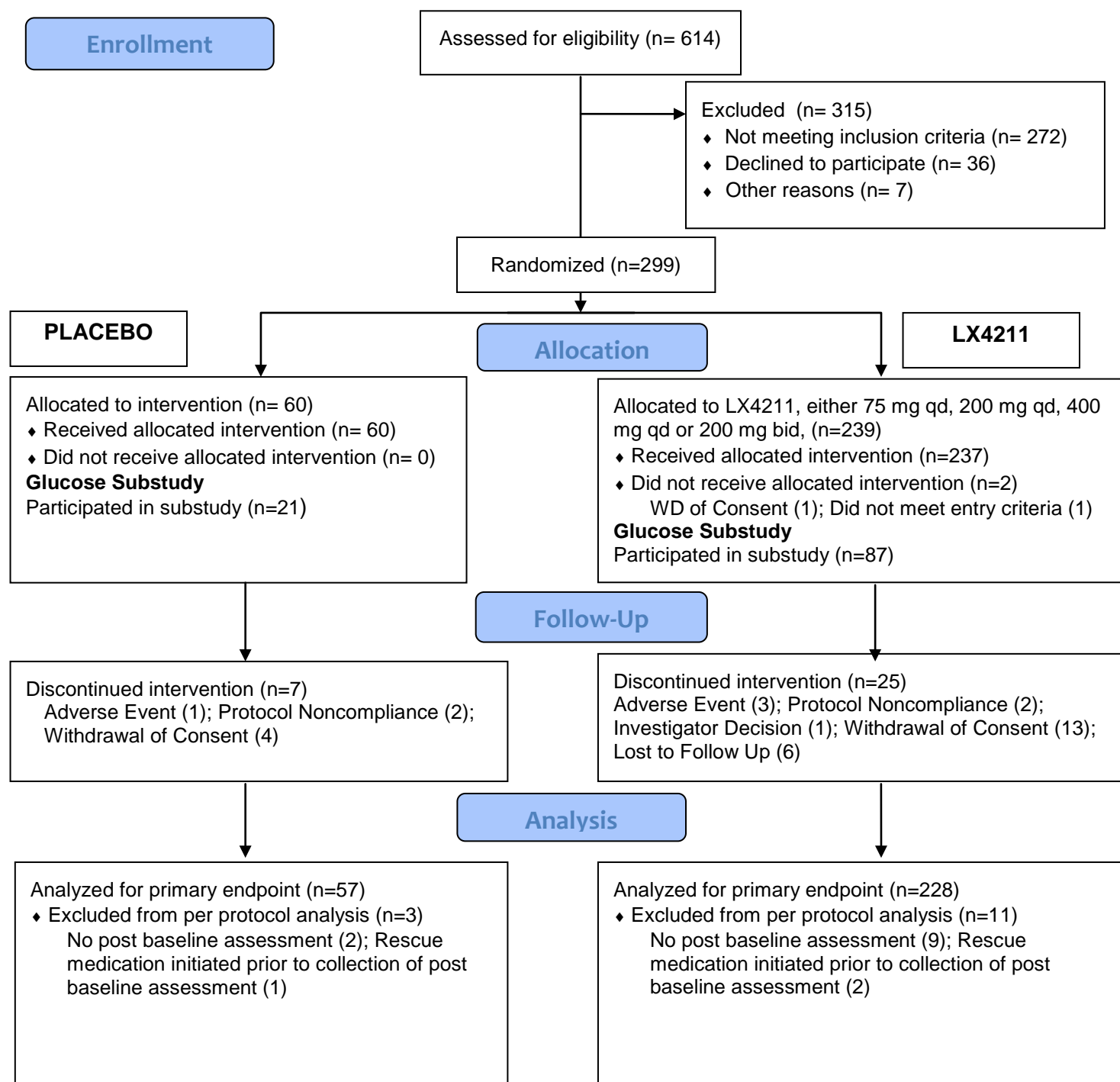
Exclusion criteria:

Patients who met any of the following criteria were excluded from participating in the study:
1. History of any of the following: type 1 diabetes mellitus, diabetic ketoacidosis, hyperosmolar nonketotic syndrome, or diabetes resulting from pancreatic disorder or secondary diabetes History of renal disease or clinically significant abnormal kidney function tests:
    a. Serum creatinine >1.4 mg/dL for females, >1.5 mg/dL for males
    b. Glomerular filtration rate (GFR) <60 mL/min as calculated using the Cockcroft-Gault equation at Screening
    c. Microalbumin:creatinine ratio >300
2. Presence of active hepatic disease or clinically significant abnormal liver function tests: (AST or ALT >2.0 times the upper limit of normal).
3. Patients with a history of myocardial infarction, severe/unstable angina, or coronary revascularization procedure within 6 months History of clinically significant cardiac arrhythmias (within 1 year)
4. Congestive heart failure with ejection fraction <40% and/or New York Heart Association [NYHA] class III or IV symptoms of heart failure
5. Patients with uncontrolled Stage III hypertension
6. The presence of a clinically significant physical, laboratory, or ECG finding at Screening that, in the opinion of the Investigator and/or Sponsor may interfere with any aspect of study conduct or interpretation of results
7. Triglycerides >1000 mg/dL at Screening
8. Patients with significant microscopic hematuria as defined as 4 or more RBCs per HPF for males; and 8 or more RBCs per HPF for females with no identifiable benign causes
9. Known history of human immunodeficiency virus (HIV) or hepatitis C (HCV Ab)
10. Known history of illicit drug or alcohol abuse within 12 months
11. Has had 2 or more emergency room visits, doctors' visits, or hospitalizations due to hypoglycemia within the 6 months
12. Use of any other investigational drug within 30 days prior
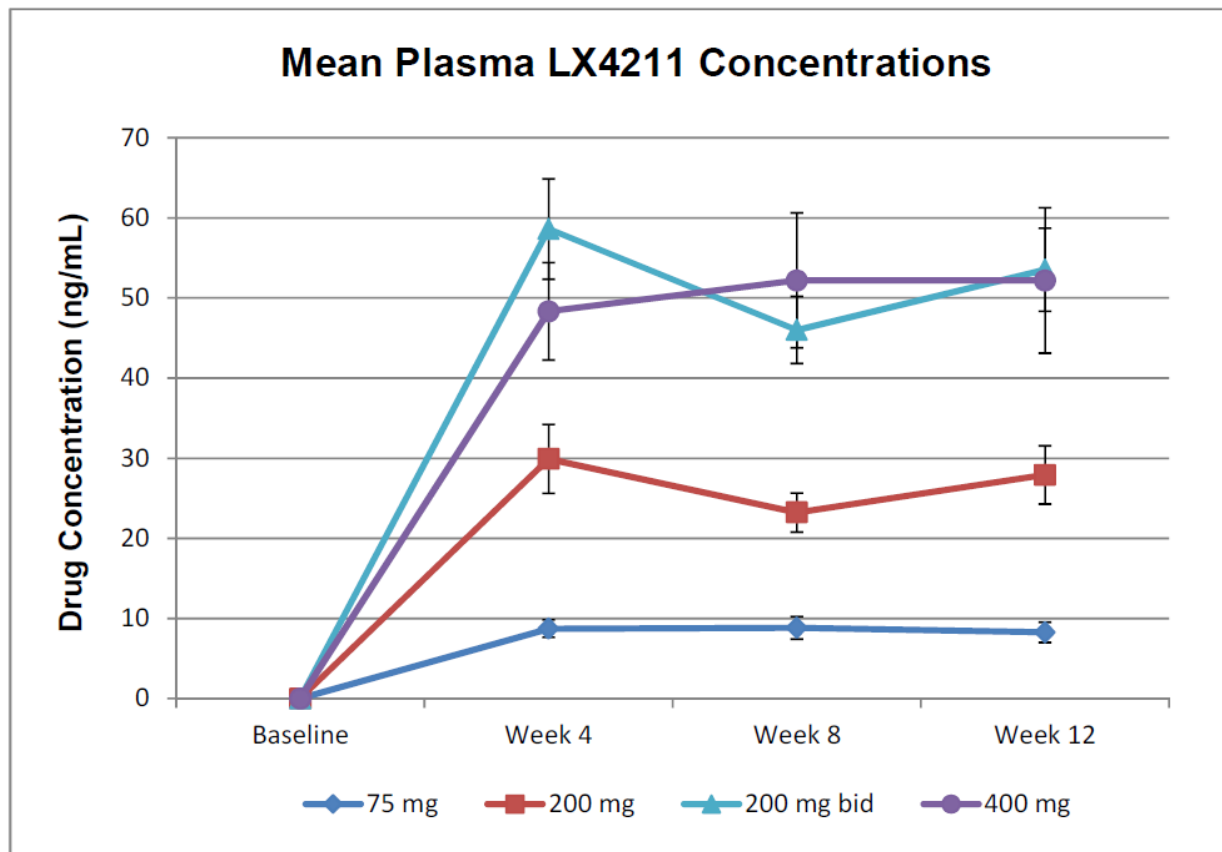
13. Prior exposure to LX4211
14. Use of any medication (prescription or over the counter) or herbal supplements taken for the purpose of weight loss
15. Chronic use of any other antidiabetic therapy besides metformin in the past 3 months Use of corticosteroids (eg, prednisone) within 2 weeks Has undergone major surgery within 6 months prior Patients with >20 cm of bowel resection, any malabsorptive disorder, severe gastroparesis, any GI procedure for the purpose of weight loss), which would slow gastric emptying
16. Any concurrent condition, in the judgment of investigator and/or sponsor, that could interfere with the safety and study conduct or interpretation of study results
17. Women who are pregnant or breast feeding

Supplementary Figure 1. Patient disposition (CONSORT flow diagram)

Enrollment

Assessed for eligibility (n= 614)

Excluded (n= 315)
- Not meeting inclusion criteria (n= 272)
- Declined to participate (n= 36)
- Other reasons (n= 7)

Randomized (n=299)

PLACEBO

Allocation

LX4211

Allocated to intervention (n= 60)
- Received allocated intervention (n= 60)
- Did not receive allocated intervention (n= 0)

Glucose Substudy
Participated in substudy (n=21)

Allocated to LX4211, either 75 mg qd, 200 mg qd, 400 mg qd or 200 mg bid, (n=239)
- Received allocated intervention (n=237)
- Did not receive allocated intervention (n=2)
  WD of Consent (1); Did not meet entry criteria (1)

Glucose Substudy
Participated in substudy (n=87)

Follow-Up

Discontinued intervention (n=7)
Adverse Event (1); Protocol Noncompliance (2); Withdrawal of Consent (4)

Discontinued intervention (n=25)
Adverse Event (3); Protocol Noncompliance (2); Investigator Decision (1); Withdrawal of Consent (13); Lost to Follow Up (6)

Analysis

Analyzed for primary endpoint (n=57)
- Excluded from per protocol analysis (n=3)
  No post baseline assessment (2); Rescue medication initiated prior to collection of post baseline assessment (1)

Analyzed for primary endpoint (n=228)
- Excluded from per protocol analysis (n=11)
  No post baseline assessment (9); Rescue medication initiated prior to collection of post baseline assessment (2)

Supplementary Figure 2. Pharmacokinetics

Mean ± SE

SUPPLEMENTARY DATA

Supplementary Table 1. Systolic and diastolic sitting blood pressure, change from baseline by week

Study Week Statistics	LX4211				Placebo (N=60)
	75 mg qd (N=59)	200 mg qd (N=60)	200 mg bid (N=60)	400 mg qd (N=60)	
Sitting Systolic Blood Pressure mm Hg Change from Baseline to Week 1					
N	54	59	58	56	59
Mean (SD)	-1.5 (11.4)	-2.4 (9.0)	-3.8 (11.6)	-3.4 (12.0)	1.0 (10.7)
P-value [1]	0.322	0.045	0.015	0.038	0.497
LS Mean (SE)	-0.7 (1.4)	-1.9 (1.3)	-4.7 (1.3)	-3.7 (1.3)	0.8 (1.3)
LS Mean Difference from Placebo (SE)	-1.5 (1.9)	-2.6 (1.8)	-5.5 (1.8)	-4.4 (1.9)	---
95% CI for Mean Difference from Placebo	(-5.2,2.2)	(-6.2,1.0)	(-9.1,-1.8)	(-8.1,-0.8)	---
P-value vs. Placebo	0.418	0.153	0.003	0.018	---
Change from Baseline to Week 2					
N	55	59	58	59	59
Mean (SD)	-2.8 (11.3)	-4.0 (10.5)	-5.3 (11.1)	-5.5 (9.6)	-0.7 (10.9)
P-value [1]	0.066	0.005	<.001	<.001	0.640
LS Mean (SE)	-2.2 (1.3)	-3.5 (1.3)	-6.1 (1.3)	-5.7 (1.3)	-0.8 (1.3)
LS Mean Difference from Placebo (SE)	-1.4 (1.8)	-2.7 (1.8)	-5.3 (1.8)	-4.8 (1.8)	---
95% CI for Mean Difference from Placebo	(-5.0,2.2)	(-6.2,0.9)	(-8.8,-1.7)	(-8.4,-1.3)	---
P-value vs. Placebo	0.450	0.137	0.004	0.008	---
Change from Baseline to Week 4					
N	55	59	58	59	59
Mean (SD)	-2.2 (12.5)	-2.6 (12.0)	-4.4 (10.0)	-3.5 (14.1)	0.7 (13.2)
P-value [1]	0.194	0.102	0.002	0.065	0.704
LS Mean (SE)	-1.4 (1.5)	-1.9 (1.4)	-5.4 (1.5)	-3.7 (1.4)	0.5 (1.4)
LS Mean Difference from Placebo (SE)	-1.8 (2.1)	-2.4 (2.0)	-5.9 (2.1)	-4.1 (2.0)	---
95% CI for Mean Difference from Placebo	(-5.9,2.3)	(-6.4,1.7)	(-9.9,-1.9)	(-8.1,-0.1)	---
P-value vs. Placebo	0.377	0.247	0.004	0.045	---

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SUPPLEMENTARY DATA

| Study Week | LX4211 | | | | Placebo |
| | 75 mg qd (N=59) | 200 mg qd (N=60) | 200 mg bid (N=60) | 400 mg qd (N=60) | |
Statistics					(N=60)
Change from Baseline to Week 8					
N	55	59	58	59	59
Mean (SD)	-3.1 (12.8)	-3.0 (13.6)	-3.0 (11.7)	-3.4 (14.8)	-0.9 (13.9)
P-value [1]	0.083	0.096	0.055	0.079	0.632
LS Mean (SE)	-2.3 (1.7)	-2.4 (1.6)	-4.0 (1.6)	-3.6 (1.6)	-1.1 (1.6)
LS Mean Difference from Placebo (SE)	-1.3 (2.3)	-1.3 (2.3)	-2.9 (2.3)	-2.6 (2.3)	---
95% CI for Mean Difference from Placebo	(-5.9,3.3)	(-5.8,3.2)	(-7.5,1.6)	(-7.1,1.9)	---
P-value vs. Placebo	0.590	0.561	0.204	0.262	---
Change from Baseline to Week 12					
N	57	60	59	59	60
Mean (SD)	-0.1 (12.7)	-3.9 (12.2)	-4.5 (12.1)	-5.7 (12.4)	-0.3 (13.6)
P-value [1]	0.942	0.017	0.007	<.001	0.872
LS Mean (SE)	0.5 (1.5)	-3.2 (1.5)	-5.4 (1.5)	-5.9 (1.5)	-0.5 (1.5)
LS Mean Difference from Placebo (SE)	1.1 (2.2)	-2.7 (2.1)	-4.8 (2.1)	-5.4 (2.1)	---
95% CI for Mean Difference from Placebo	(-3.2,5.3)	(-6.9,1.5)	(-9.0,-0.6)	(-9.6,-1.2)	---
P-value vs. Placebo	0.624	0.202	0.024	0.012	---
Continued on next page					
Sitting Diastolic Blood Pressure mm Hg Change from Baseline to Week 1					
N	54	59	58	56	59
Mean (SD)	-1.3 (8.2)	-2.0 (6.2)	-0.5 (8.1)	-2.0 (7.2)	0.3 (7.1)
P-value [1]	0.249	0.016	0.642	0.044	0.762
LS Mean (SE)	-0.9 (0.9)	-1.4 (0.9)	-1.0 (0.9)	-2.3 (0.9)	0.1 (0.9)
LS Mean Difference from Placebo (SE)	-0.9 (1.2)	-1.4 (1.2)	-1.1 (1.2)	-2.3 (1.2)	---
95% CI for Mean Difference from Placebo	(-3.4,1.5)	(-3.8,1.0)	(-3.5,1.3)	(-4.7,0.1)	---
P-value vs. Placebo	0.447	0.243	0.363	0.060	---

Continued on next page

SUPPLEMENTARY DATA

Study Week Statistics	LX4211				Placebo (N=60)
	75 mg qd (N=59)	200 mg qd (N=60)	200 mg bid (N=60)	400 mg qd (N=60)	
Change from Baseline to Week 2					
N	55	59	58	59	59
Mean (SD)	-1.5 (7.1)	-1.8 (7.1)	-1.5 (6.8)	-1.1 (7.2)	-0.6 (6.1)
P-value [1]	0.117	0.059	0.091	0.227	0.426
LS Mean (SE)	-1.2 (0.8)	-1.2 (0.8)	-2.0 (0.8)	-1.4 (0.8)	-0.8 (0.8)
LS Mean Difference from Placebo (SE)	-0.4 (1.2)	-0.4 (1.2)	-1.2 (1.2)	-0.6 (1.2)	---
95% CI for Mean Difference from Placebo	(-2.7,1.9)	(-2.7,1.9)	(-3.5,1.1)	(-2.9,1.7)	---
P-value vs. Placebo	0.726	0.709	0.317	0.618	---
Change from Baseline to Week 4					
N	55	59	58	59	59
Mean (SD)	-1.7 (7.8)	-2.7 (8.0)	-1.0 (7.0)	-1.7 (8.6)	-0.1 (8.0)
P-value [1]	0.120	0.012	0.298	0.124	0.936
LS Mean (SE)	-1.3 (0.9)	-1.9 (0.9)	-1.6 (0.9)	-2.1 (0.9)	-0.3 (0.9)
LS Mean Difference from Placebo (SE)	-0.9 (1.3)	-1.6 (1.3)	-1.3 (1.3)	-1.8 (1.3)	---
95% CI for Mean Difference from Placebo	(-3.5,1.6)	(-4.2,0.9)	(-3.8,1.3)	(-4.3,0.8)	---
P-value vs. Placebo	0.468	0.206	0.332	0.172	---
Change from Baseline to Week 8					
N	55	59	58	59	59
Mean (SD)	-0.7 (8.8)	-1.0 (7.5)	-1.0 (7.7)	-1.0 (9.3)	0.1 (8.2)
P-value [1]	0.554	0.301	0.335	0.416	0.933
LS Mean (SE)	-0.3 (1.0)	-0.2 (1.0)	-1.6 (1.0)	-1.3 (1.0)	-0.1 (1.0)
LS Mean Difference from Placebo (SE)	-0.1 (1.4)	-0.1 (1.4)	-1.5 (1.4)	-1.2 (1.3)	---
95% CI for Mean Difference from Placebo	(-2.8,2.6)	(-2.8,2.6)	(-4.1,1.2)	(-3.8,1.5)	---
P-value vs. Placebo	0.924	0.946	0.281	0.380	---

Continued on next page

SUPPLEMENTARY DATA

Study Week Statistics	LX4211				Placebo (N=60)
	75 mg qd (N=59)	200 mg qd (N=60)	200 mg bid (N=60)	400 mg qd (N=60)	
Change from Baseline to Week 12					
N	57	60	59	59	60
Mean (SD)	-0.6 (8.8)	-2.8 (7.9)	-2.2 (7.9)	-1.6 (8.9)	-0.5 (9.1)
P-value [1]	0.598	0.007	0.035	0.164	0.697
LS Mean (SE)	-0.2 (1.0)	-2.1 (1.0)	-2.8 (1.0)	-2.0 (1.0)	-0.7 (1.0)
LS Mean Difference from Placebo (SE)	0.5 (1.4)	-1.4 (1.4)	-2.2 (1.4)	-1.3 (1.4)	---
95% CI for Mean Difference from Placebo	(-2.4,3.3)	(-4.2,1.4)	(-5.0,0.6)	(-4.1,1.5)	---
P-value vs. Placebo	0.748	0.327	0.130	0.355	---

SUPPLEMENTARY DATA

Supplementary Table 2. Week 12 A1C <7% and fasting plasma glucose (change from baseline) and fasting lipid parameters (change from baseline by week)

Study Week Statistics	LX4211				Placebo (N=60)
	75 mg qd (N=59)	200 mg qd (N=60)	200 mg bid (N=60)	400 mg qd (N=60)	
Hemoglobin A1C Week 12					
N	56	58	57	57	57
N with A1C <7% (%)	16 (28.6%)	15 (25.9%)	17 (29.8%)	22 (38.6%)	14 (24.6%)
p-value	0.41	0.22	0.036	0.022	---
FPG Week 12, mean change from baseline					
N	56	60	58	59	60
Mean (SD)	-9.5 (27.4)	-17.4 (40.5)	-26.9 (35.1)	-27.1 (38.5)	2.2 (45.4)
p-value	0.012	0.002	<.001	<.001	0.71
Direct HDL-C (mg/dL) Change from Baseline to Week 4					
N	53	57	57	55	55
Mean (SD)	1.5 (4.6)	-1.1 (6.9)	1.2 (4.3)	1.4 (6.5)	2.1 (6.9)
P-value *	0.019	0.23	0.043	0.11	0.030
Change from Baseline to Week 8					
N	54	57	57	55	55
Mean (SD)	1.8 (4.9)	0.9 (7.0)	1.9 (5.5)	1.6 (6.3)	1.2 (6.4)
P-value *	0.011	0.33	0.011	0.06	0.17
Change from Baseline to Week 12					
N	56	58	57	57	58
Mean (SD)	1.7 (4.1)	0.2 (6.9)	2.4 (6.2)	2.1 (7.4)	1.2 (6.3)
P-value *	0.002	0.81	0.005	0.032	0.17

Continued on next page

Study Week Statistics	LX4211				Placebo (N=60)
	75 mg qd (N=59)	200 mg qd (N=60)	200 mg bid (N=60)	400 mg qd (N=60)	
LDL Chol-Friedwald 3rd (mg/dL) Change from Baseline to Week 4					
N	50	55	56	54	54
Mean (SD)	-0.7 (17.4)	-0.1 (19.1)	1.7 (25.4)	4.1 (24.1)	3.4 (19.9)
P-value *	0.76	0.96	0.61	0.22	0.22
Change from Baseline to Week 8					
N	52	55	56	54	54
Mean (SD)	3.3 (21.0)	4.2 (19.9)	1.2 (25.8)	4.3 (25.2)	4.1 (17.4)
P-value *	0.26	0.12	0.73	0.22	0.09
Change from Baseline to Week 12					
N	55	56	56	56	57
Mean (SD)	3.1 (22.5)	2.8 (18.7)	7.3 (29.5)	4.6 (26.0)	2.5 (19.9)
P-value *	0.32	0.27	0.07	0.19	0.34
Triglycerides (GPO) (mg/dL) Change from Baseline to Week 4					
N	53	57	57	55	55
Mean (SD)	-3.1 (101.9)	5.3 (57.6)	-17.5 (66.4)	-26.7 (139.1)	-23.9 (196.4)
P-value *	0.83	0.49	0.052	0.16	0.37
Change from Baseline to Week 8					
N	54	57	57	55	55
Mean (SD)	0.0 (107.3)	-9.4 (60.7)	-14.0 (81.0)	-22.5 (136.0)	-19.1 (195.9)
P-value *	1.00	0.25	0.20	0.23	0.47
Change from Baseline to Week 12					
N	56	58	57	57	58
Mean (SD)	-16.2 (84.2)	6.6 (77.1)	-16.9 (73.1)	-16.8 (121.9)	-30.5 (201.9)
P-value *	0.16	0.51	0.09	0.30	0.26

* P-value for testing mean change from baseline within each treatment group is zero, based on paired sample t-test.