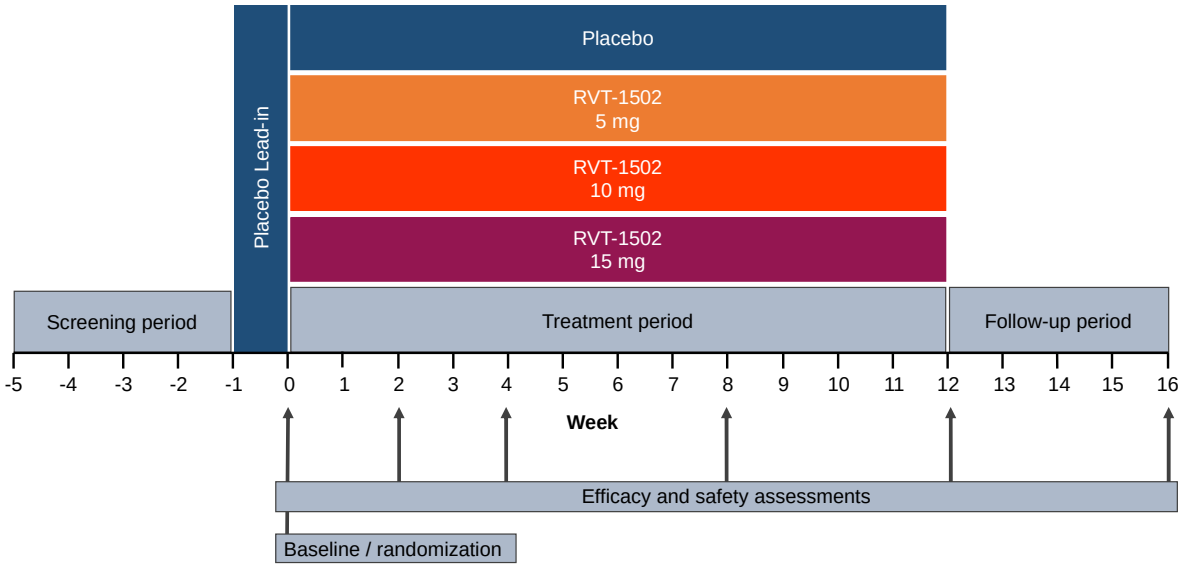
SUPPLEMENTARY DATA

Efficacy and Safety of the Glucagon Receptor Antagonist RVT-1502 in Type 2 Diabetes Uncontrolled on Metformin Monotherapy: A 12-Week Dose-Ranging Study

Jeremy H. Pettus, David D'Alessio, Juan P. Frias, Eric G. Vajda, James D. Pipkin, Julio Rosenstock, Gretchen Williamson, MD, Miriam A. Zangmeister, Lin Zhi, and Keith B. Marschke

SUPPLEMENTARY DATA

Supplementary Figure 1. Study design. Qualified subjects who required adjustment or stabilization of their metformin dose, or washout of antidiabetic medication, participated in a run-in period of up to 12 additional weeks prior to randomization. At baseline and Weeks 2, 4, 8, and 12 during the treatment period, and at Week 16 during the follow-up period, laboratory safety and efficacy evaluations were conducted, along with a concomitant medication review, 12-lead electrocardiogram, and vital signs.



SUPPLEMENTARY DATA

Inclusion and Exclusion Criteria

Inclusion Criteria

To be enrolled in the study, subjects must have met all of the following inclusion criteria:

1. An adult male or female, 21 to 70 years of age
2. If the subject was a woman, she must have been surgically sterile (hysterectomy or bilateral oophorectomy or bilateral tubal ligation), or naturally post-menopausal for at least 12 months and with a follicle-stimulating hormone (FSH) level in the post-menopausal range (if not taking hormone replacement therapy).
3. Willing and able to provide written informed consent
4. Diagnosis of type 2 diabetes according to American Diabetes Association (ADA) criteria
5. Currently on stable metformin or metformin extended-release therapy (unchanged dose [minimum daily dose of 1000 mg] for ≥12 weeks prior to screening) and had an HbA_{1c} value of ≥7.0% to ≤10.5% at the screening visit (or qualifying visit, if applicable) (1 retest was permitted if timing allowed)
    a. At the discretion of the Investigator, subjects who otherwise met eligibility criteria and whose metformin dose had not been stable for at least 12 weeks may have had their metformin dose stabilized if their HbA_{1c} was ≥7.5% to ≤10.5%, inclusive, at the screening visit. Once the metformin dose had been stable for at least 12 weeks, a qualifying visit was performed, at which time the subject's HbA_{1c} value must have been ≥7.0% to ≤10.5% (1 retest was permitted if timing allowed).
    b. Also at the discretion of the Investigator, subjects prescribed metformin and 1 additional oral hypoglycemic agent from the list that follows may have been eligible to enter the study following a washout period of these medications of at least 12 weeks. Subjects prescribed an additional oral hypoglycemic agent that was to be washed off must have had an HbA_{1c} of ≥7.0% and ≤8.5% at screening prior to entering the washout period. Once at least 12 weeks of washout had been completed, a qualifying visit was performed at which time the subject's HbA_{1c} value must have been ≥7.0% to ≤10.5% (1 retest was permitted if timing allowed). Eligibile medications included:
        i. Sulfonylurea
        ii. DPP-IV inhibitor
        iii. Alpha-glucosidase inhibitor
        iv. Sodium-glucose linked transporter-2 (SGLT2) inhibitor
6. Fasting plasma glucose was ≤14.4 mmol/L (260 mg/dL) at the screening or qualification (if applicable) visit. One retest per visit was permitted.
7. BMI between 25 kg/m^2 and 40 kg/m^2, inclusive, with a weight of >45 kg
8. Male subjects must either have had a vasectomy or agreed that they and any female partners would use 2 acceptable forms of contraception, one of which must have been a condom, until 30 days after the last dose of study drug. Other acceptable forms of contraception included hormonal contraceptives that had been at a stable dose for 12 weeks prior to randomization, intrauterine device, Depo Provera®, Norplant® System Implants, bilateral tubal ligation, bilateral oophorectomy, hysterectomy, and contraceptive sponge, foam, or jelly. Also, male subjects must not have donated sperm during the study and for 30 days after the last dose of study drug.

SUPPLEMENTARY DATA

Exclusion Criteria

If subjects met any of the following exclusion criteria, they were not to be enrolled in the study:

1. History of type 1 diabetes mellitus or history of diabetic ketoacidosis or persistent hypoglycemia or hypoglycemia unawareness
2. Was a woman of childbearing potential, lactating, or had a positive pregnancy test
3. History or presence of alcoholism or drug abuse within 2 years prior to screening or typical consumption of ≥10 drinks of alcohol weekly or unable to comply with alcohol restrictions
4. Unwilling to comply with study restrictions, including restrictions on strenuous exercise
5. Presence of any of the following conditions:
    a. Renal impairment (defined as history or estimated glomerular filtration rate at screening of <45 mL/min using the Modification of Diet in Renal Disease equation)
    b. Diabetic proliferative retinopathy
    c. Severely symptomatic diabetic neuropathy requiring treatment (based on Investigator's discretion)
    d. Diabetic gastroparesis
    e. Active liver disease (other than asymptomatic nonalcoholic fatty liver disease), cirrhosis, symptomatic gallbladder disease, or pancreatitis
6. Serum triglyceride level >400 mg/dL at the screening or qualification (if applicable) visit. If the triglyceride level was between 400 mg/dL and 500 mg/dL, 1 retest was permitted.
7. Liver transaminase levels (AST or ALT) >150% ULN, total bilirubin >2 × ULN, or creatine kinase (CK) levels >3 × ULN at screening or qualification. Abnormal values at screening or qualification may have been retested
8. History or evidence of clinically significant cardiovascular, pulmonary, renal, endocrine (other than type 2 diabetes), hepatic, neurologic, psychiatric, immunologic, hematologic, gastrointestinal, or metabolic disease or surgical interventions (eg, bariatric surgery) or allergic conditions (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at time of dosing) that posed an increased risk during the study or that may have compromised the integrity of the study data, based on the Investigator's opinion
9. Myocardial infarction, unstable angina, arterial revascularization, stroke, symptomatic peripheral artery disease, deep vein thrombosis, New York Heart Association Functional Class III or IV heart failure, or transient ischemic attack within 6 months prior to screening
10. History of malignant hypertension or a recent history of uncontrolled high blood pressure, or at screening had a seated systolic blood pressure (SBP) >160 mmHg and/or diastolic blood pressure (DBP) >100 mmHg after at least a 5-minute rest. Blood pressure was determined as the mean of triplicate measurements collected at 2-minute intervals after the subject had been sitting quietly for at least 5 minutes according to standardized procedures. Therapy for hypertension (beta blockers excluded) that had been stable for at least 8 weeks prior to screening was permitted.
11. Arm size in excess of the maximum limit of the largest cuff provided with the study blood pressure monitor
12. History of malignancy (except adequately treated basal or squamous cell skin cancer or cervical carcinoma in situ) within 5 years prior to screening
13. History or evidence of QT prolongation or clinically significant QT prolongation (QTcF >450 msec) at the screening or qualification (if applicable) visit, or other significant electrocardiogram (ECG) findings at screening that may have placed the subject at increased risk by participating in the study
14. Treatment with any type of insulin (injected or inhaled) for >6 consecutive days within 6 months prior to screening or any insulin therapy within 12 weeks prior to screening
15. Treated with peroxisome proliferator-activated receptor-gamma agonists (thiazolidinediones [TZDs]), incretin therapy (GLP1 agonists), or amylin mimetics within 12 weeks prior to

screening

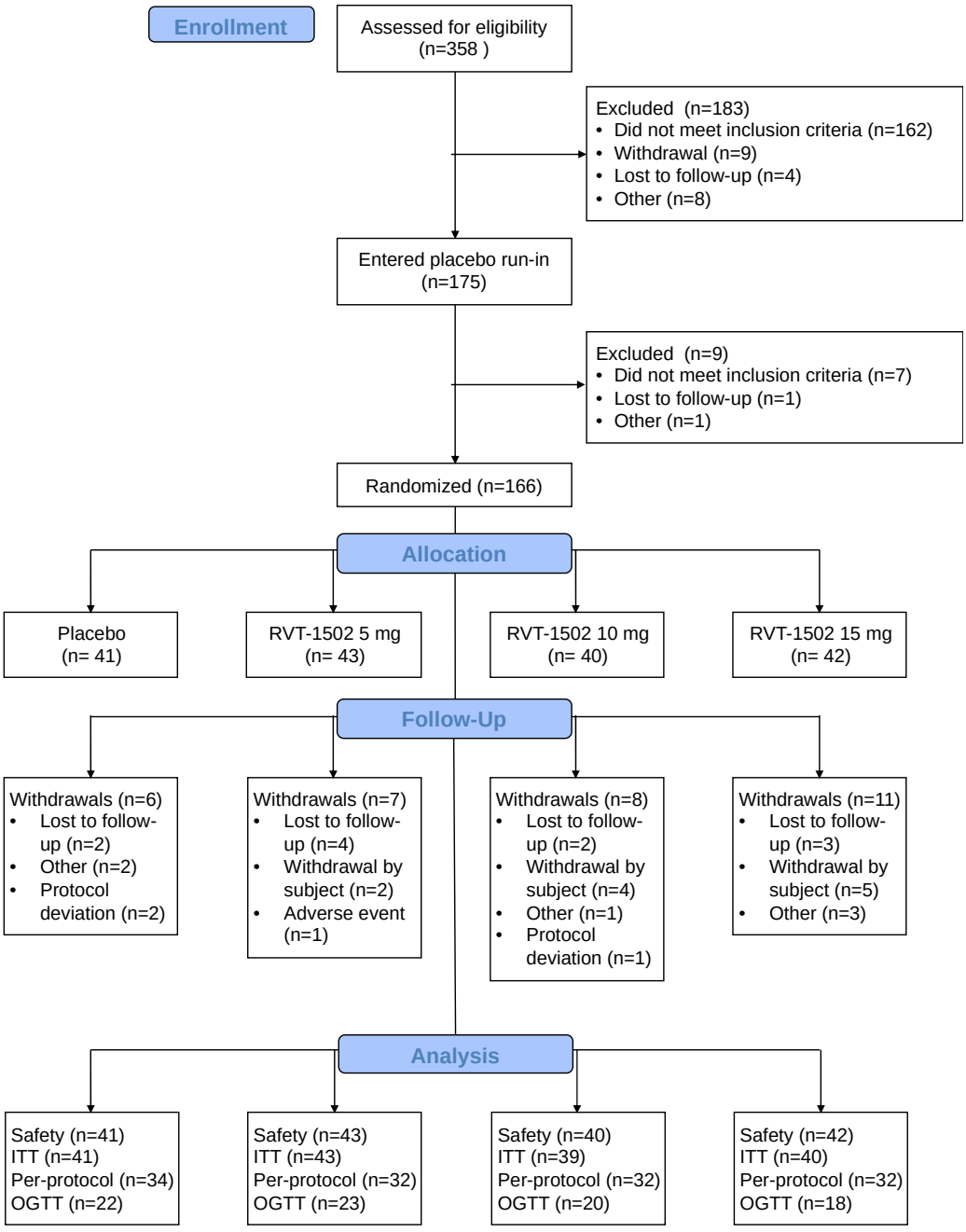
16. Taking one of the following medications:
    a. Antidepressants, antipsychotics, anti-epileptics, hormone replacement therapies (estrogen, progestin), testosterone therapies, and thyroid replacement medications that were not at a stable dose for at least 12 weeks prior to the screening visit
    b. Lipid-modifying medications and anti-hypertensive medications that had not been at a stable dose for at least 8 weeks prior to the screening visit (excluding bile acid sequestrants, ezetimibe, and beta blockers, which were prohibited)
    c. Over-the-counter herbal medications and supplements (aside from QD multivitamins)
17. Treatment with systemic corticosteroids, which must have been discontinued at least 4 weeks prior to the screening visit. Note: Inhaled, intraarticular, intranasal, and topical corticosteroids were permitted
18. Currently treated with weight-loss medications. These must have been discontinued ≥12 weeks prior to screening
19. History or evidence of intravenous illicit drug use, active hepatitis B virus (HBV), hepatitis C virus (HCV), and/or human immunodeficiency virus (HIV) infection
20. Known hypersensitivity or idiosyncratic reaction to GRAs or RVT-1502
21. Participation in another interventional clinical trial within 30 days prior to dosing or treatment with an investigational product within 14 days or 5 half-lives of the screening visit (whichever was longer)
22. The subject had donated ≥450 mL of blood within 56 days of screening or had donated blood products within 30 days of screening
23. Inability to comply with study procedures or to adhere to study-required restrictions as per Investigator discretion as assessed during the stabilization and placebo run-in periods, including poor compliance with self-monitoring of blood glucose (SMBG) assessments.

Analytical Methods

HbA1c was measured using the Tosoh G7/G8/G11 automated HPLC analyzer (Toshoh Bioscience Inc., King of Prussia, PA, USA). Plasma glucose was analyzed by hexokinase enzymatic method using a Beckman Coulter AU5800 chemistry analyzer (Beckman Coulter, Brea, CA, USA), and plasma insulin was measured by electrochemiluminescence immunoassay using the Roche Elecsys E170 (Roche Diagnostics, Indianapolis, IN, USA). Glucagon measurements were performed by sandwich enzyme-linked immunosorbent assay (ELISA) from R&D Systems (Minneapolis, MN, USA). Active plasma GLP1 (7-36) and total plasma GLP1 (7-36 and 9-36) determinations were performed by sandwich ELISA (ALPCO, Salem, NH, USA). Samples were analyzed for glucagon and GLP1 in duplicate, and testing was performed in completed subject sets to eliminate the effects of plate to plate variability in the results from individual subjects. Plasma concentrations of RVT-1502 were measured by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method.

SUPPLEMENTARY DATA

Supplementary Figure 2. Subject disposition (CONSORT diagram). "Withdrawals by subject" were not safety related (e.g., subject moved, transportation issues, conflict with new job, etc).



SUPPLEMENTARY DATA

Supplementary Table 1. Summary of efficacy endpoints in intent-to-treat population.

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
HbA_{1c}, %				
Baseline, mean ± SD	8.2 ± 1.0	8.2 ± 1.1	8.3 ± 0.9	8.2 ± 0.9
Week 12, mean ± SD	8.0 ± 1.3	7.3 ± 0.9	7.4 ± 1.0	7.0 ± 0.6
Week 12, no. subjects (ITT LOCF)	41	43	38	40
Week 12, LSM change from baseline ± SE (*P* value)	-0.2 ± 0.1 (0.1843)	-0.9 ± 0.1 (<0.0001)	-0.9 ± 0.1 (<0.0001)	-1.2 ± 0.1 (<0.0001)
Week 12, LSM change from placebo ± SE		-0.7 ± 0.2	-0.8 ± 0.2	-1.1 ± 0.2
95% CI (*P* value)		-1.1 to -0.4 (<0.0001)	-1.1 to -0.4 (<0.0001)	-1.4 to -0.7 (<0.0001)
FPG, mmol/L (mg/dL)				
Baseline ± SD	9.0 ± 2.5 (161.6 ± 45.5)	9.7 ± 2.6 (175.0 ± 46.5)	9.9 ± 2.6 (178.4 ± 46.9)	9.7 ± 2.0 (175.2 ± 36.3)

SUPPLEMENTARY DATA

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
Week 12, mean ± SD	9.6 ± 3.2 (173.6 ± 57.6)	7.9 ± 2.0 (142.2 ± 36.7)	7.9 ± 2.1 (142.1 ± 37.2)	7.4 ± 1.6 (133.3 ± 29.5)
Week 12, no. subjects (ITT LOCF)	41	43	38	40
Week 12, LSM change from baseline ± SE (*P* value)	0.4 ± 0.3 (7.9 ± 5.5) (0.1579)	-1.7 ± 0.3 (-30.1 ± 5.4) (<0.0001)	-1.8 ± 0.3 (-32.0 ± 5.7) (<0.0001)	-2.2 ± 0.3 (-39.3 ± 5.5) (<0.0001)
Week 12, LSM change from placebo ± SE		-2.1 ± 0.4 (-38.0 ± 7.6)	-2.2 ± 0.4 (-39.9 ± 7.9)	-2.6 ± 0.4 (-47.2 ± 7.7)
95% CI (*P* value)		-2.9 to -1.3 (-53.0 to -23.0) (<0.0001)	-3.1 to -1.3 (-55.4 to -24.3) (<0.0001)	-3.5 to -1.8 (-62.5 to -32.0) (<0.0001)
Glucagon, ng/L				
Baseline ± SD	140.9 ± 77.0	160.7 ± 94.5	130.1 ± 58.8	156.9 ± 104.3

SUPPLEMENTARY DATA

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
Week 12, mean ± SD	135.5 ± 64.3	296.2 ± 178.6	386.8 ± 202.9	497.4 ± 290.2
Week 12, no. subjects (ITT LOCF)	39	40	35	38
Week 12, LSM change from baseline ± SE (*P* value)	1.4 ± 27.2 (0.9594)	119.2 ± 26.6 (<0.0001)	269.0 ± 28.4 (<0.0001)	336.2 ± 27.3 (<0.0001)
Week 12, LSM change from placebo ± SE		117.8 ± 37.7	267.6 ± 38.9	334.8 ± 38.1
95% CI (*P* value)		43.4 to 192.3 (0.0021)	190.8 to 344.5 (<0.0001)	259.5 to 410.0 (<0.0001)
Active GLP1, pmol/L				
Baseline ± SD	1.69 ± 1.11	3.78 ± 6.97	4.49 ± 8.77	2.62 ± 5.03
Week 12, mean ± SD	1.78 ± 1.27	4.69 ± 8.85	5.63 ± 9.93	2.79 ± 4.44
Week 12, no. subjects (ITT LOCF)	39	39	35	37
Week 12, LSM change from baseline ± SE	0.18 ± 0.37	0.93 ± 0.36	0.89 ± 0.38	0.31 ± 0.37

SUPPLEMENTARY DATA

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
(*P* value)	(0.6250)	(0.0111)	(0.0217)	(0.4029)
Week 12, LSM change from placebo ± SE		0.75 ± 0.51	0.71 ± 0.53	0.13 ± 0.51
95% CI (*P* value)		-0.26 to 1.76 (0.1452)	-0.34 to 1.75 (0.1836)	-0.88 to 1.15 (0.7997)
Total GLP1, pmol/L				
Baseline ± SD	4.82 ± 9.06	8.09 ± 14.74	6.15 ± 11.67	5.52 ± 10.47
Week 12, mean ± SD	4.78 ± 8.78	11.04 ± 17.79	8.08 ± 12.06	6.61 ± 11.10
Week 12, no. subjects (ITT LOCF)	38	40	36	38
Week 12, LSM change from baseline ± SE (*P* value)	0.11 ± 0.54 (0.8447)	1.25 ± 0.52 (0.0178)	1.99 ± 0.55 (0.0004)	1.26 ± 0.53 (0.0192)
Week 12, LSM change from placebo ± SE		1.15 ± 0.74	1.88 ± 0.76	1.15 ± 0.75
95% CI (*P* value)		-0.32 to 2.61	0.38 to 3.38	-0.33 to 2.63

SUPPLEMENTARY DATA

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
		(0.1253)	(0.0145)	(0.1256)
Insulin, mIU/L				
Baseline ± SD	13.84 ± 8.04	17.14 ± 15.01	14.19 ± 10.49	13.87 ± 8.80
Week 12, mean ± SD	15.51 ± 11.78	15.79 ± 9.87	16.31 ± 14.83	15.46 ± 10.99
Week 12, no. subjects (ITT LOCF)	41	41	37	40
Week 12, LSM change from baseline ± SE	1.59 ± 1.49	-0.52 ± 1.49	2.22 ± 1.56	1.47 ± 1.50
(*P* value)	(0.2873)	(0.7250)	(0.1554)	(0.3285)
Week 12, LSM change from placebo ± SE		-2.12 ± 2.09	0.63 ± 2.13	-0.12 ± 2.09
95% CI (*P* value)		-6.24 to 2.01	-3.58 to 4.84	-4.25 to 4.01
		(0.3124)	(0.7677)	(0.9539)
HOMA-IR				
Baseline ± SD	5.52 ± 3.74	7.73 ± 7.84	6.66 ± 6.35	5.88 ± 3.52

SUPPLEMENTARY DATA

	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
Week 12, mean ± SD	6.89 ± 7.79	5.57 ± 3.76	6.35 ± 8.29	5.14 ± 4.22
Week 12, no. subjects (ITT LOCF)	41	41	37	40
Week 12, LSM change from baseline ± SE (*P* value)	1.10 ± 0.90 (0.2202)	-1.46 ± 0.89 (0.1055)	-0.03 ± 0.93 (0.9710)	-0.88 ± 0.90 (0.3319)
Week 12, LSM change from placebo ± SE		-2.56 ± 1.26	-1.14 ± 1.28	-1.98 ± 1.25
95% CI (*P* value)		-5.04 to -0.07 (0.0436)	-3.67 to 1.40 (0.3765)	-4.46 to 0.50 (0.1163)
HOMA-β				
Baseline ± SD	61.56 ± 46.30	60.67 ± 48.43	47.48 ± 29.93	50.91 ± 43.46
Week 12, mean ± SD	62.11 ± 48.69	75.65 ± 87.27	55.12 ± 146.38	145.91 ± 407.88
Week 12, no. subjects (ITT LOCF)	41	41	37	40
Week 12, LSM change from baseline ± SE	-6.40 ± 34.58	9.61 ± 34.44	1.75 ± 36.42	88.88 ± 34.95

SUPPLEMENTARY DATA

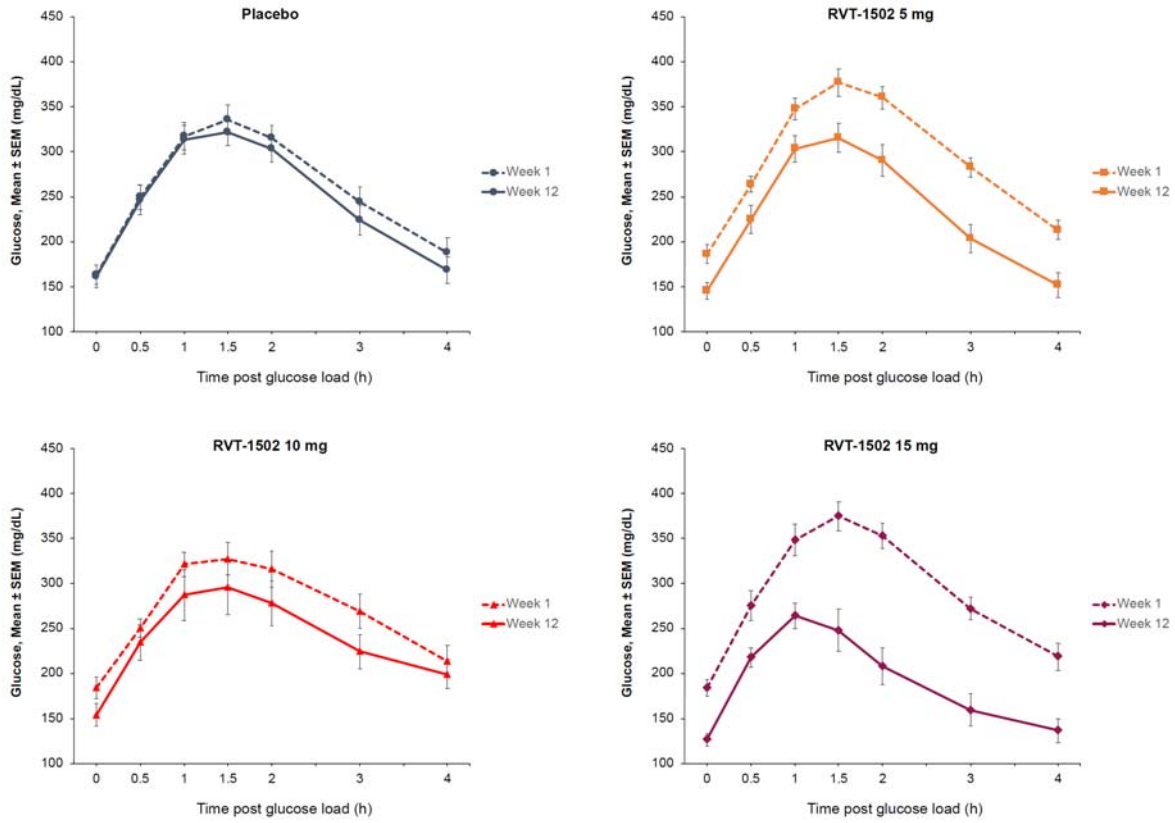
	Placebo (n = 41)	**RVT-1502 5 mg (n = 43)**	**RVT-1502 10 mg (n = 39)**	**RVT-1502 15 mg (n = 40)**
(*P* value)	(0.8535)	(0.7806)	(0.9618)	(0.0120)
Week 12, LSM change from placebo ± SE		16.00 ± 48.22	8.14 ± 49.80	95.28 ± 48.70
95% CI (*P* value)		-79.25 to 111.26 (0.7404)	-90.24 to 106.52 (0.8703)	-0.94 to 191.49 (0.0523)

For data reported as ITT LOCF, data are from only subjects with non-missing baseline and Week 12 with LOCF. Baseline was defined as the measurement at Week 1, Day 1. If missing, the last valid measurement on or prior to the first date administration of study drug was used as baseline. LSMs, SEs, CIs, and *P* values for HbA_{1c} were from an ANCOVA model with treatment group as a factor and baseline HbA_{1c} as a covariate. Other LSMs, SEs, CIs, and P values were from an ANCOVA model with treatment group and stratification group (HbA_{1c} ≤8.5% or >8.5%) as factors and baseline value of the given parameter as a covariate. ANCOVA, analysis of covariance; CI, confidence interval; FPG, fasting plasma glucose; GLP1, glucagon-like peptide 1; HOMA, homeostatic model assessment; IR, insulin resistance; ITT, intent to treat; LOCF, last observation carried forward; LSM, least squares mean; SD, standard deviation; SE, standard error.

SUPPLEMENTARY DATA

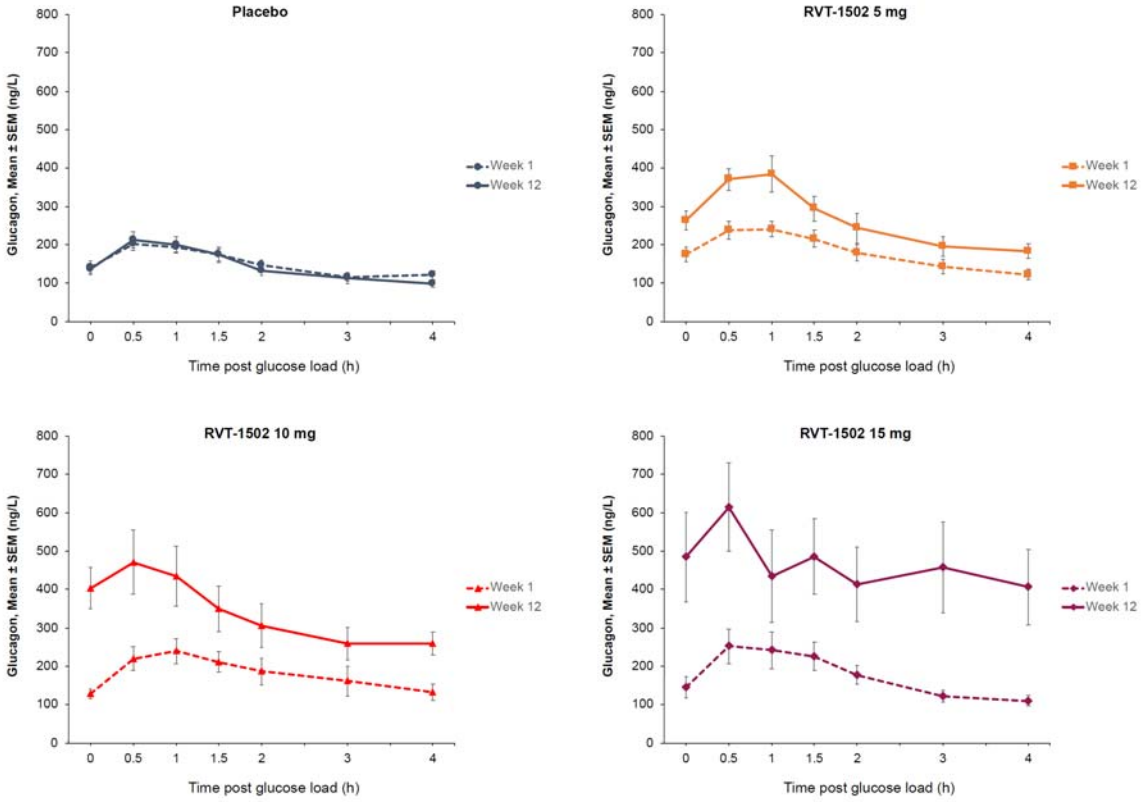
Supplementary Figure 3. Effect of RVT-1502 on mean (± SEM) plasma glucose (*A*), glucagon (*B*), insulin (*C*), total GLP1 (*D*), and active GLP1 (*E*) in response to an oral glucose load during an oral glucose tolerance test (OGTT). Error bars represent standard error of the mean (SEM).

A. Glucose



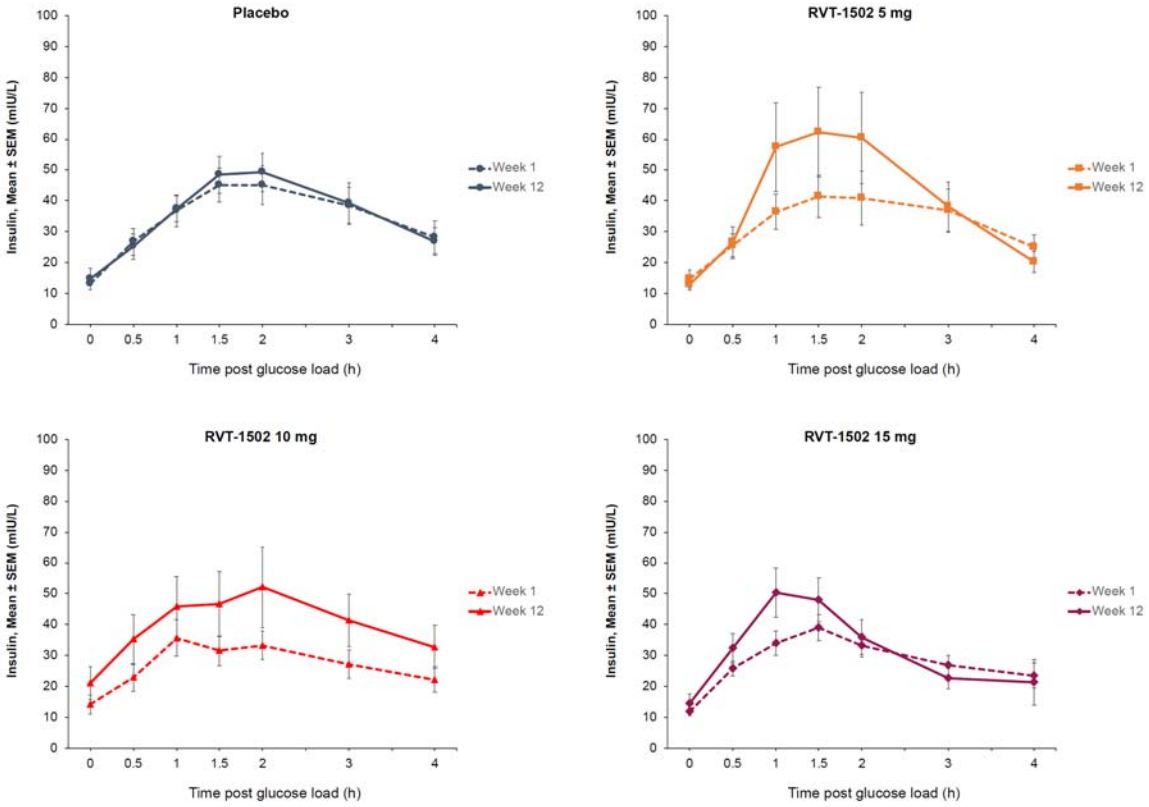
SUPPLEMENTARY DATA

B. Glucagon



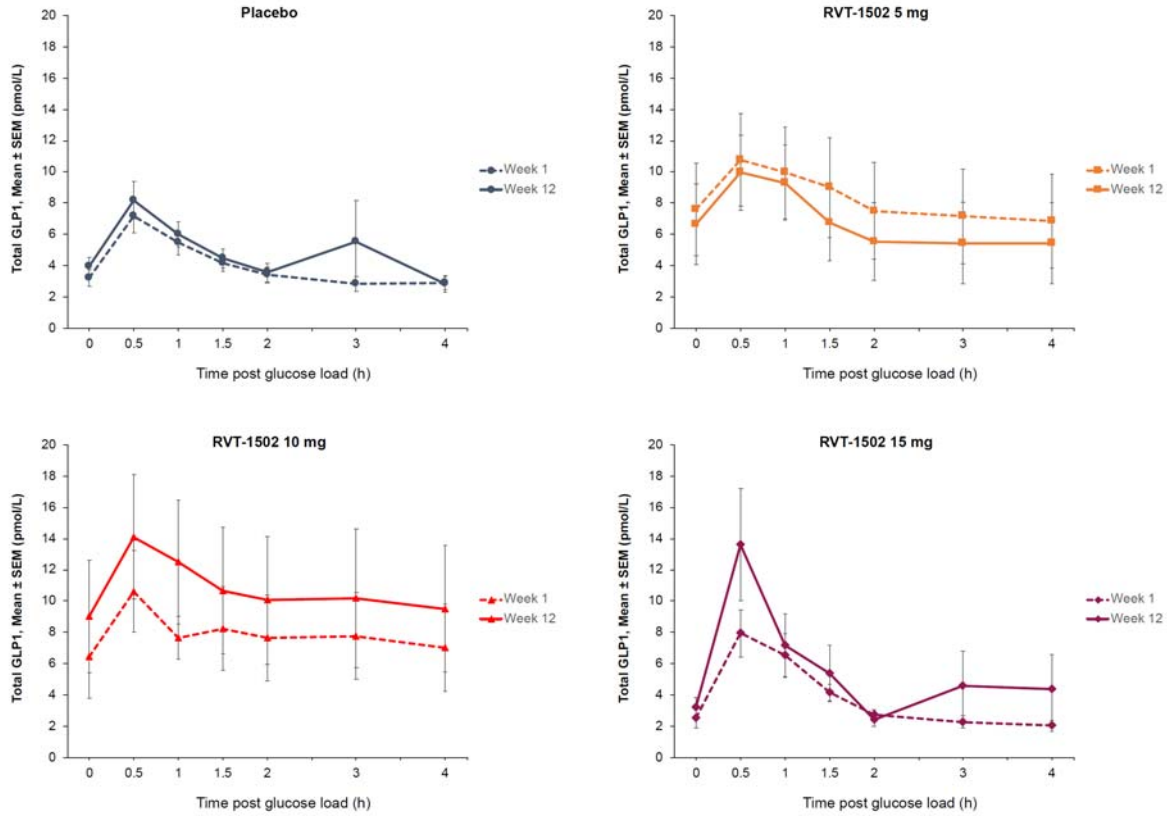
SUPPLEMENTARY DATA

C. Insulin



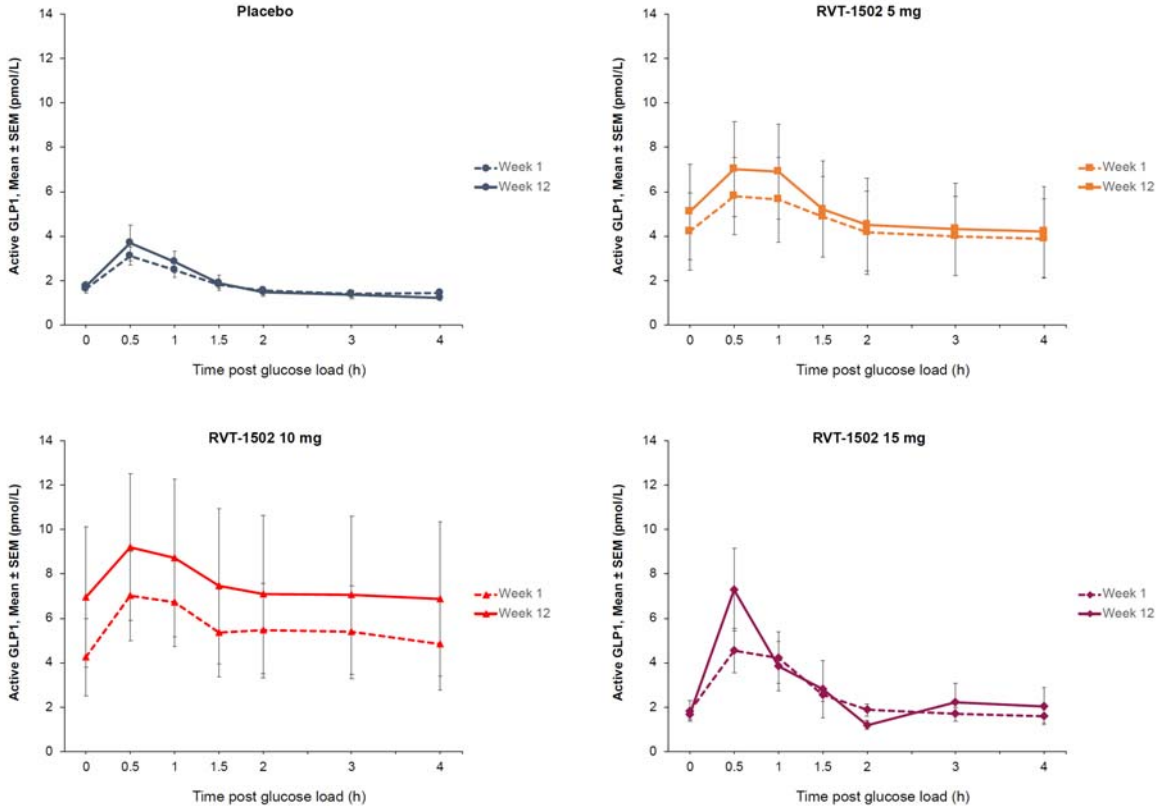
SUPPLEMENTARY DATA

D. Total GLP1



SUPPLEMENTARY DATA

E. Active GLP1



SUPPLEMENTARY DATA

Supplementary Table 2. Overview of adverse events and incidence of study drug–related adverse events by system organ class and preferred term in the safety population

Treatment-emergent adverse events, n (%)	**Placebo (n=41)**	**RVT-1502 5 mg (n=43)**	**RVT-1502 10 mg (n=40)**	**RVT-1502 15 mg (n=42)**
Any AE	15 (36.6)	17 (39.5)	11 (27.5)	16 (38.1)
Any study drug–related AE	1 (2.4)	5 (11.6)	3 (7.5)	4 (9.5)
Any SAE	1 (2.4)	0 (0.0)	1 (2.5)	1 (2.4)
Any study drug related SAE	0	0	0	0
Study drug–related AE leading to withdrawal	0	0	0	0
Study drug–related AEs				
Gastrointestinal disorders	0	1 (2.3)	1 (2.5)	1 (2.4)
Diarrhea	0	1 (2.3)	1 (2.5)	1 (2.4)
Abdominal pain upper	0	0	1 (2.5)	0
Infections and infestations	1 (2.4)	1 (2.3)	0	1 (2.4)
Urinary tract infection	0	1 (2.3)	0	1 (2.4)
Asymptomatic bacteriuria	1 (2.4)	0	0	0

SUPPLEMENTARY DATA

Treatment-emergent adverse events, n (%)	**Placebo (n=41)**	**RVT-1502 5 mg (n=43)**	**RVT-1502 10 mg (n=40)**	**RVT-1502 15 mg (n=42)**
Investigations	0	1 (2.3)	1 (2.5)	1 (2.4)
Aspartate aminotransferase increased	0	1 (2.3)	1 (2.5)	1 (2.4)
Alanine aminotransferase increased	0	1 (2.3)	0	0
Blood alkaline phosphatase increased	0	1 (2.3)	0	0
Gamma-glutamyltransferase increased	0	1 (2.3)	0	0
Metabolism and nutrition disorders	0	1 (2.3)	1 (2.5)	0
Decreased appetite	0	0	1 (2.5)	0
Hypertriglyceridaemia	0	1 (2.3)	0	0
Nervous system disorders	0	1 (2.3)	0	0
Headache	0	1 (2.3)	0	0
Renal and urinary disorders	0	0	1 (2.5)	1 (2.4)

SUPPLEMENTARY DATA

Treatment-emergent adverse events, n (%)	**Placebo (n=41)**	**RVT-1502 5 mg (n=43)**	**RVT-1502 10 mg (n=40)**	**RVT-1502 15 mg (n=42)**
Proteinuria	0	0	1 (2.5)	1 (2.4)
Skin and subcutaneous tissue disorders	0	0	0	1 (2.4)
Skin hyperpigmentation	0	0	0	1 (2.4)

AE, adverse event; SAE, serious adverse event.

SUPPLEMENTARY DATA

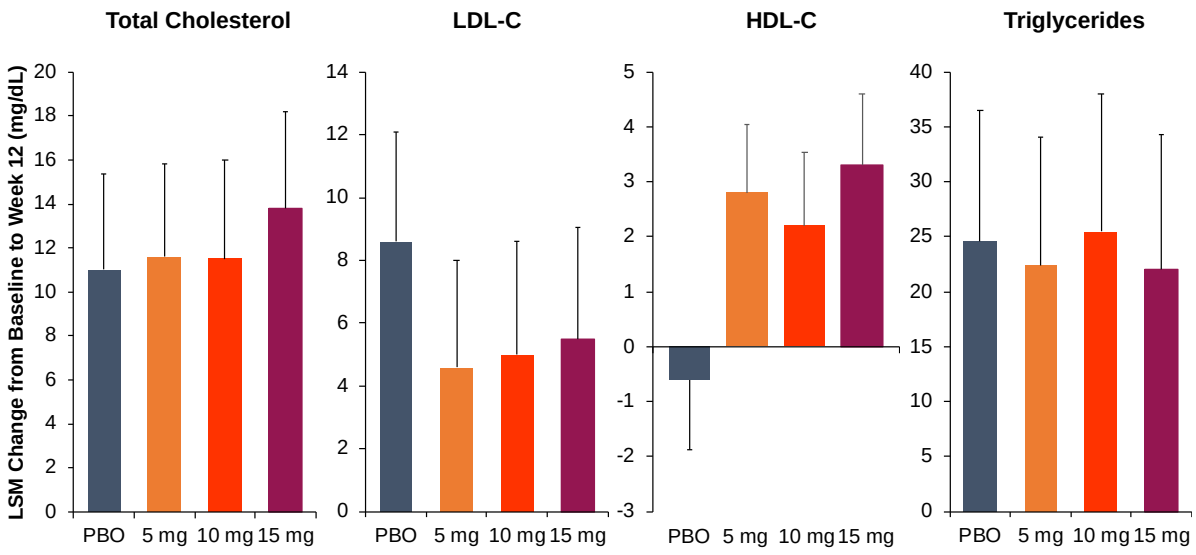
Supplementary Table 3. Incidence of hypoglycemic events in the safety population.

Subjects with hypoglycemic events, n (%)	**Placebo (n=41)**	**RVT-1502 5 mg (n=43)**	**RVT-1502 10 mg (n=40)**	**RVT-1502 15 mg (n=42)**
Any hypoglycemic event	0 (0.0)	5 (11.6)	1 (2.5)	4 (9.5)
Documented asymptomatic	0 (0.0)	3 (7.0)	1 (2.5)	4 (9.5)
Documented symptomatic	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Probable symptomatic	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Documented asymptomatic hypoglycemia: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).
Documented symptomatic hypoglycemia: An event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).
Probable symptomatic hypoglycemia: An event during which symptoms typical of hypoglycemia were not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).
Severe hypoglycemia: An event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

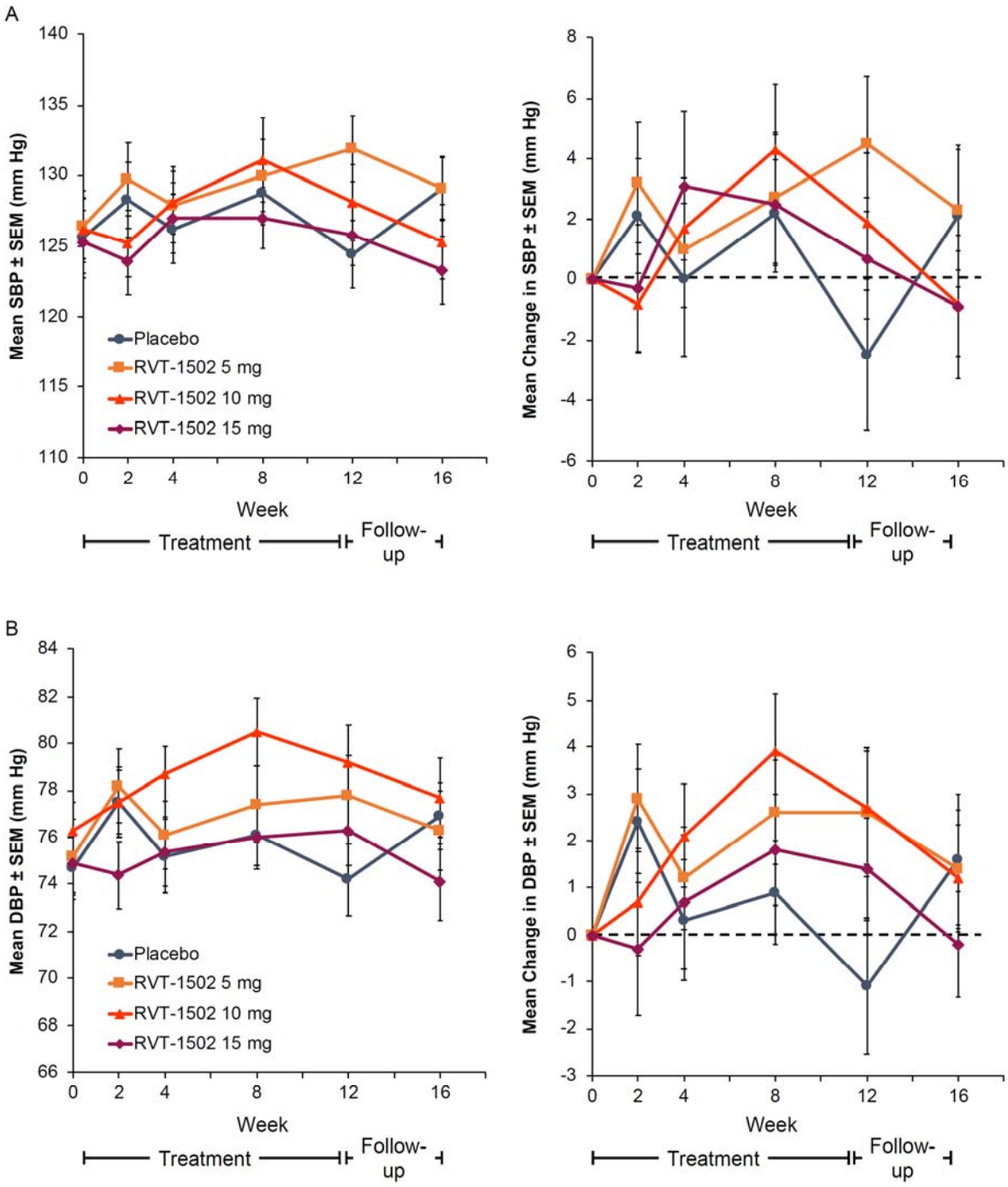
SUPPLEMENTARY DATA

Supplementary Figure 4. Least squares mean (LSM) change from baseline in lipids in the safety population. Error bars represent standard error.



SUPPLEMENTARY DATA

Supplementary Figure 5. Mean and change from baseline in (*A*) systolic blood pressure (SBP) and (*B*) diastolic blood pressure (DBP). Error bars represent standard error of the mean (SEM).



SUPPLEMENTARY DATA

Supplementary Figure 6. Mean and change from baseline in body weight. Error bars represent standard error of the mean (SEM).