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

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OBJECTIVE

Evaluate the safety and efficacy of RVT-1502, a novel oral glucagon receptor antagonist, in subjects with type 2 diabetes inadequately controlled on metformin.

RESEARCH DESIGN AND METHODS

In a phase 2, double-blind, randomized, placebo-controlled study, subjects with type 2 diabetes (n = 166) on a stable dose of metformin were randomized (1:1:1:1) to placebo or RVT-1502 5, 10, or 15 mg once daily for 12 weeks. The primary end point was change from baseline in HbA_{1c} for each dose of RVT-1502 compared with placebo. Secondary end points included change from baseline in fasting plasma glucose (FPG) and safety assessments.

RESULTS

Over 12 weeks, RVT-1502 significantly reduced HbA_{1c} relative to placebo by 0.74%, 0.76%, and 1.05% in the 5-, 10-, and 15-mg groups ($P < 0.001$), respectively, and FPG decreased by 2.1, 2.2, and 2.6 mmol/L ($P < 0.001$). The proportions of subjects achieving an HbA_{1c} <7.0% were 19.5%, 39.5%, 39.5%, and 45.0% with placebo and RVT-1502 5, 10, and 15 mg ($P \leq 0.02$ vs. placebo). The frequency of hypoglycemia was low, and no episodes were severe. Mild increases in mean aminotransferase levels remaining below the upper limit of normal were observed with RVT-1502 but were reversible and did not appear to be dose related, with no other liver parameter changes. Weight and lipid changes were similar between RVT-1502 and placebo. RVT-1502–associated mild increases in blood pressure were not dose related or consistent across time.

CONCLUSIONS

Glucagon receptor antagonism with RVT-1502 significantly lowers HbA_{1c} and FPG, with a safety profile that supports further clinical development with longer-duration studies (NCT02851849).

Glucagon stimulates gluconeogenesis and glycogenolysis through the glucagon receptor, thereby counteracting the role of insulin in the regulation of glucose homeostasis (1). In subjects with diabetes, the normal feedback system becomes imbalanced, and glucagon secretion is dysregulated, remaining elevated in both fasting

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and postprandial states, increasing hepatic glucose production, and exacerbating the existing hyperglycemic state (2,3).

Dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists (GLP1-RAs) reduce glucagon secretion by enhancing the effects of GLP1 (4). However, neither class fully alters glucagon-induced effects on glucose metabolism because they decrease glucagon secretion by only <10% (5–8). Nevertheless, the actions of dipeptidyl peptidase 4 inhibitors and GLP1-RAs on hepatic glucose output suggest that targeting glucagon metabolism can improve glycemic control.

In animal models, glucagon inhibition reduces plasma glucose, increases GLP1 levels, and reduces plasma triglycerides (1,9). Glucagon receptor knockout mice do not develop hyperglycemia or the metabolic disturbances of diabetes, even in the presence of severe insulinopenia (10). Glucagon-inhibiting agents tested in various animal models include antibodies that interfere with glucagon receptor signaling, antisense oligonucleotides that decrease glucagon receptor expression, and peptide and small molecule glucagon receptor antagonists (GRAs). These agents reduced blood glucose and improved glucose tolerance in preclinical studies (11–20). In subjects with type 2 diabetes, small molecule GRAs decrease fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}) (5,6,21–23). However, GRA treatment has been associated with dose-dependent adverse effects, including increases in LDL cholesterol, body weight, blood pressure (BP), hypoglycemia, hepatic fat fraction, and transaminase levels, which have impeded clinical development (24–26).

RVT-1502 (formerly LGD-6972) is a novel, orally bioavailable small molecule GRA being developed to improve glycemic control in adults with diabetes. In vitro, RVT-1502 binds to the glucagon receptor with high affinity and selectivity and suppresses glucagon-stimulated cAMP and glucose production (27). It is structurally distinct from other small molecule GRAs, containing a sulfonic acid tail rather than a carboxylic acid tail (28). Pharmacological activity of RVT-1502 appears to be mediated primarily by glucagon receptor signaling, with minimal evidence of off-target pharmacological effects. Binding and inhibition of the closely related GLP1 receptor and gastric inhibitory polypeptide receptor appear to be minimal, with >3,800-fold selectivity for the glucagon receptor. Similarly, RVT-1502 has >100-fold selectivity for the glucagon receptor versus a broad panel of receptors, ion channels, and transporters (27). In vivo, RVT-1502 reduced acute glucagon-stimulated hyperglycemia as well as chronic hyperglycemia in diabetic mouse models (27), effects that appear to be mediated primarily through inhibition of glucagon receptor signaling. In phase 1 studies, RVT-1502 demonstrated favorable safety, tolerability, and pharmacokinetics in healthy volunteers and subjects with type 2 diabetes in whom dose-dependent FPG reductions of up to 3.2 mmol/L (57 mg/dL) were observed after 14 days without clinically significant changes in liver enzymes or lipids, and no subject experienced a hypoglycemic event (29). Here, we describe the results of a 12-week, phase 2 dose-ranging study of RVT-1502 5, 10, or 15 mg once daily versus placebo in subjects with type 2 diabetes on a stable dose of metformin.

RESEARCH DESIGN AND METHODS

Design Overview

This phase 2, randomized, double-blind, placebo-controlled, four-arm, parallel-group study evaluated the efficacy and safety of RVT-1502 5, 10, and 15 mg compared with placebo over 12 weeks at 30 sites in the U.S. between September 2016 and June 2017. The study consisted of a 1-week, single-blind placebo lead-in period, active treatment for 12 weeks, and a 4-week posttreatment follow-up period (Supplementary Fig. 1). Randomization was stratified on the basis of HbA_{1c} at the placebo lead-in visit (≤8.5% or >8.5%). The study was conducted in accordance with Good Clinical Practice guidelines, and the institutional review board at each study center reviewed and approved the protocols before initiating the study. All study subjects provided written informed consent.

Study Population

Eligible subjects included males and females 21–70 years of age with type 2 diabetes taking metformin monotherapy at a stable dose (≥1,000 mg daily) for at least 12 weeks before placebo lead-in. Inclusion criteria were an HbA_{1c} of ≥7.0% (53 mmol/mol) to ≤10.5% (91 mmol/mol), FPG ≤14.4 mmol/L (≤260 mg/dL), BMI 25–40 kg/m^2, and weight >45 kg. Female subjects were required to be either surgically sterile or naturally postmenopausal. Male subjects were required to have had a vasectomy or to agree that they and any female partners would use two acceptable forms of contraception, including a condom and another medical or surgical form of contraception (see Supplementary Data). Qualified subjects who required adjustment or stabilization of their metformin dose or washout of other specified oral antidiabetic medications participated in a run-in period of up to 12 additional weeks before randomization (see Supplementary Data).

Key exclusion criteria were a history of diabetic ketoacidosis or hypoglycemia unawareness, renal impairment (glomerular filtration rate <45 mL/min/1.73 m^2), cardiovascular event within the past 6 months, history of uncontrolled BP or a screening systolic BP (SBP) >160 mmHg and/or diastolic BP (DBP) >100 mmHg, alanine transaminase (ALT) or aspartate aminotransferase (AST) levels >150% the upper limit of normal (ULN), or serum triglyceride level >4.52 mmol/L (>400 mg/dL). The full list of inclusion and exclusion criteria appears in the Supplementary Data.

Interventions

Subjects were randomly assigned in a 1:1:1:1 ratio to treatment with placebo or the 5-, 10-, or 15-mg doses of RVT-1502 given as three blinded capsules once daily.

Assessments

The primary efficacy end point was the change from baseline in HbA_{1c} during 12 weeks of treatment. Secondary efficacy end points were changes from baseline to weeks 2, 4, 8, and 12 for HbA_{1c}; FPG; fasting glucagon; total and active GLP1; insulin; insulin resistance by HOMA (HOMA-IR); and β-cell function by HOMA (HOMA-β). The number and percentage of subjects achieving HbA_{1c} <7% at each postbaseline visit was also determined.

As exploratory end points, assessments of least squares mean (LSM) changes in glucose, glucagon, insulin, total GLP1, active GLP1, C-peptide area under the curve between 0 and 4 h (LSM $\Delta AUC_{0-4\,h}$), and percent changes in oral glucose tolerance test (OGTT)

were performed in a subset of randomized subjects. The analytic methods used are described in the Supplementary Data.

Safety end points included changes in lipids, BP, body weight, and BMI from baseline to weeks 2, 4, 8, and 12. The frequency of treatment-emergent adverse events (AEs) and hypoglycemic events was also evaluated at each visit and after the 4-week follow-up period. Hypoglycemic events included symptomatic and asymptomatic events documented by BP values ≤70 mg/dL; probable symptomatic events in which typical hypoglycemia symptoms were not accompanied by a plasma glucose determination but which were presumed to be caused by a plasma glucose concentration ≤70 mg/dL; and severe hypoglycemia, which was defined as hypoglycemia with symptoms requiring assistance from another person. Additional safety assessments included clinical laboratory tests (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), physical examinations, and other vital signs (temperature and pulse rate) at each visit. Trough plasma concentrations of RVT-1502 were assessed in samples collected from subjects in the RVT-1502 dose groups during weeks 2, 4, 8, and 12.

Statistical Methods

Subject information, such as disposition and demographic information, was summarized descriptively. Primary and secondary efficacy analyses were conducted on the intention-to-treat population, which was defined as all randomized subjects who received at least one dose of study drug and had a baseline and at least one postbaseline HbA_{1c} measurement. The safety population included all subjects who received at least one dose of study drug. The OGTT population included all subjects in the safety population who had a baseline OGTT assessment and at least one postrandomization OGTT assessment. The primary end point of change in HbA_{1c} from baseline to week 12 was analyzed by ANCOVA, with treatment group as a factor and baseline HbA_{1c} as a covariate. If the week 12 measurement was missing, the last observation carried forward (LOCF) algorithm was applied to impute the missing week 12 value. A sample size of 33 subjects who completed the study per treatment group was determined to be sufficient to provide >90% power to detect between-group differences in mean HbA_{1c} changes from a baseline of 0.5%, assuming an SD of 0.6% using a two-sided significance level of 0.05. To accommodate a dropout rate of 10% from randomization to study completion, a sample size of 37 randomized subjects per treatment group (148 subjects in total) was planned.

The LSMs, SEs, and two-tailed 95% CI for each treatment group and for each comparison were calculated. Two-sided *P* values were used to test for significance of within–treatment group changes from baseline and to make comparisons between treatment groups. Before this analysis was performed, the data were inspected for normality and homogeneity of variance, and a nonparametric method was applied. The same ANCOVA model and descriptive statistics used for the primary efficacy end point were applied to HbA_{1c}, FPG, GLP1 (total and active), insulin, HOMA-IR, and HOMA-β at each scheduled visit without LOCF and at week 12 with LOCF.

The change in fasting lipids, SBP, DBP, body weight, and BMI from baseline to weeks 2, 4, 8, and 12 without LOCF was analyzed in the safety population (defined as all randomized subjects who received at least one dose of study drug) using a mixed-model repeated-measures procedure implemented with SAS PROC MIXED. The factors in the model were stratification group, treatment group, baseline value, visit, and the treatment group-by-visit interactions. An unstructured covariance matrix was used (TYPE = UN). No imputation was performed. The LSMs for change from baseline at each visit were estimated and compared between treatment groups.

RESULTS

Subject Disposition and Baseline Characteristics

A total of 166 subjects were randomized; 134 (80.7%) completed the study, and 32 (19.3%) withdrew early (Supplementary Fig. 2). Overall, the most common reason for withdrawal was loss to follow-up (6.6%) or withdrawal by subject for personal reasons (6.6%). Only one subject was withdrawn from the study because of an AE, which was assessed by the investigator as not related to study drug.

Table 1 shows baseline characteristics of the study population. Overall, most subjects were white and male, and 65% were Hispanic. A large majority (91.6%) of subjects did not require metformin stabilization or a washout period. At baseline, mean HbA_{1c} was 8.2–8.3% (66–67 mmol/mol), and mean FPG ranged from 9.0 mmol/L (162 mg/dL) to 9.9 mmol/L (178 mg/dL). A total of 108 (65.1%) subjects were stratified to the HbA_{1c} ≤8.5% group, and 58 (34.9%) were stratified to the HbA_{1c} >8.5% group. No meaningful differences in other demographic or baseline characteristics were noted across treatment groups.

Glycemic Efficacy

After 12 weeks of treatment, mean HbA_{1c} changes relative to placebo were −0.7% (95% CI −1.1 to −0.4%; $P < 0.001$), −0.8% (−1.1 to −0.4%; $P < 0.001$), and −1.1% (−1.4 to −0.7%; $P < 0.001$) in the RVT-1502 5-, 10-, and 15-mg groups, respectively (Fig. 1*A* and Supplementary Table 1). The change from baseline was significantly different from placebo ($P \leq 0.0003$) at weeks 2, 4, 8, and 12 for all RVT-1502 dose groups. As shown in Fig. 2, 8 of 41 (19.5%) subjects receiving placebo and 17 of 43 (39.5%), 15 of 38 (39.5%), and 18 of 40 (45.0%) of those receiving RVT-1502 5, 10, and 15 mg, respectively, achieved an HbA_{1c} <7% (odds ratio [OR] vs. placebo 3.7–4.4; $P \leq 0.022$). An HbA_{1c} <6.5% was achieved by 7 of 43 (16.3%), 7 of 38 (18.4%), and 10 of 40 (25.0%) of subjects in the RVT-1502 5-, 10-, and 15-mg groups, respectively, compared with 2 of 41 (4.9%) of the placebo group (OR vs. placebo 4.4–7.9; $P < 0.05$ with RVT-1502 10 and 15 mg) (Fig. 2). FPG changes relative to placebo were −2.1 mmol/L (−38 mg/dL) (95% CI −2.9 to −1.3 mmol/L [−53 to −23 mg/dL]; $P < 0.001$), −2.2 mmol/L (−40 mg/dL) (−3.1 to −1.3 mmol/L [−55 to −24 mg/dL]; $P < 0.001$), and −2.6 mmol/L (−47 mg/dL) (−3.5 to −1.8 mmol/L [−63 to −32 mg/dL]; $P < 0.001$) after 12 weeks (Fig. 1*B*).

Nonglycemic End Points

Mean fasting glucagon increased relative to placebo by 118 ng/L (95% CI 43–192 ng/L; $P = 0.0021$), 268 ng/L (191–345 ng/L; $P < 0.0001$), and 335 ng/L (260–410 ng/L; $P < 0.0001$) after 12 weeks with RVT-1502 5, 10, and 15 mg, respectively (Supplementary Table 1). Mean fasting active GLP1 increased significantly from baseline with RVT-1502 5 and 10 mg, although differences from placebo were not statistically significant (Supplementary Table 1). Fasting total GLP1 increased significantly

Table 1—Baseline demographics and characteristics

Characteristic	Placebo (n = 41)	RVT-1502 5 mg (n = 43)	RVT-1502 10 mg (n = 40)	RVT-1502 15 mg (n = 42)	Total (N = 166)
Age (years), mean (SD)	56.0 (8.0)	56.9 (8.5)	54.4 (9.0)	58.1 (8.1)	56.4 (8.4)
Female, *n* (%)	17 (41.5)	25 (58.1)	15 (37.5)	18 (42.9)	75 (45.2)
Race and ethnicity, *n* (%)					
White	35 (85.4)	32 (74.4)	28 (70.0)	36 (85.7)	131 (78.9)
Black	6 (14.6)	10 (23.3)	9 (22.5)	5 (11.9)	30 (18.1)
Asian	0 (0.0)	1 (2.3)	2 (5.0)	1 (2.4)	4 (2.4)
Other	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.6)
Hispanic or Latino	29 (70.7)	28 (65.1)	25 (62.5)	26 (61.9)	108 (65.1)
HbA_{1c}, mean (SD)					
%	8.2 (1.0)	8.2 (1.1)	8.3 (0.9)	8.2 (0.9)	8.2 (1.0)
mmol/mol	66 (11.0)	66 (11.7)	67 (10.2)	66 (9.8)	66 (10.6)
FPG, mean (SD)					
mmol/L	9.0 (2.5)	9.7 (2.6)	9.9 (2.6)	9.5 (2.2)	9.5 (2.5)
mg/dL	161.6 (45.5)	175.0 (46.5)	177.5 (46.7)	171.8 (38.7)	171.5 (44.5)
Weight (kg), mean (SD)	88.4 (18.2)	86.1 (13.8)	84.4 (16.8)	85.4 (16.2)	86.1 (16.2)
BMI (kg/m^2), mean (SD)	31.8 (5.1)	31.9 (4.2)	30.5 (4.3)	31.2 (4.0)	31.4 (4.4)
Stratification group, *n* (%)					
HbA_{1c} ≤8.5%	27 (65.9)	28 (65.1)	26 (65.0)	27 (64.3)	108 (65.1)
HbA_{1c} >8.5%	14 (34.1)	15 (34.9)	14 (35.0)	15 (35.7)	58 (34.9)
Required metformin stabilization or washout period, *n* (%)	1 (2.4)	4 (9.3)	5 (12.5)	4 (9.5)	14 (8.4)

Baseline was defined as the measurement at week 1, day 1. If missing, the last valid measurement on or before the first date administration of study drug was used as baseline.

from baseline with all three RVT-1502 doses, and the difference between the 10-mg dose and placebo was significant (LSM difference from placebo 1.88 pmol/L [95% CI 0.38–3.38]; $P = 0.0145$) (Supplementary Table 1). The LSM difference in HOMA-IR between RVT-1502 5 mg and placebo was −2.56 (−5.04 to −0.07; $P = 0.0436$). No other statistically significant differences from placebo were observed for fasting insulin, HOMA-IR, or HOMA-β. Mean HOMA-β increased from baseline in the 15-mg group ($P = 0.0120$), and there was a trend toward an increase with all RVT-1502 treatment groups and a decrease with placebo (Supplementary Table 1).

Postprandial End Points

During the exploratory OGTT evaluation, the mean fasting glucose before oral glucose administration (preglucose load) was reduced at week 12 compared with week 1 in subjects administered RVT-1502, and the incremental change (LSM $\Delta AUC_{0–4\ h}$) in glucose was decreased (Supplementary Fig. 3*A*). For example, in the 15-mg group, there was a 31.7% decrease in the glucose LSM $\Delta AUC_{0–4\ h}$. Although the mean preglucose load glucagon level was increased with RVT-1502 treatment at week 12 compared with week 1, the incremental change in glucagon generally decreased compared with week 1 (Supplementary Fig. 3*B*). In contrast, while the preglucose load insulin levels were unchanged at week 12, insulin incrementally increased with RVT-1502 treatment compared with week 1 (Supplementary Fig. 3*C*). The incremental change in C-peptide mirrored the increases seen in insulin (data not shown). Subjects receiving placebo exhibited no incremental changes between weeks 1 and 12 for glucose, glucagon, or insulin (Supplementary Fig. 3). The LSM $\Delta AUC_{0–4\ h}$ for total and active GLP1 did not change significantly between weeks 1 and 12 in any treatment group (Supplementary Fig. 3).

Safety and Tolerability

All three doses of RVT-1502 were safe and well tolerated after 12 weeks on the basis of evaluation of AEs, clinical laboratory variables, ECG observations, and vital signs. Overall, 59 (35.5%) subjects experienced an AE during or after treatment with RVT-1502: 17 (39.5%), 11 (27.5%), and 16 (38.1%) subjects receiving RVT-1502 5, 10, and 15 mg, respectively, and 15 (36.6%) receiving placebo (Supplementary Table 2). The majority of AEs were considered mild or moderate in severity.

No deaths occurred during the study. Three patients experienced serious AEs: one receiving placebo (pyelonephritis, acute kidney injury, leukocytosis, and liver function test elevation), one receiving RVT-1502 10 mg (transient ischemic attack, which occurred 30 days after the last dose), and one receiving RVT-1502 15 mg (angina pectoris). None of these events were considered related to study drug, and no subjects were withdrawn because of these events.

AEs experienced by five (11.6%), three (7.5%), and four (9.5%) subjects receiving RVT-1502 5, 10, and 15 mg, respectively, and one (2.4%) receiving placebo were determined to be treatment related (Supplementary Table 2). No dose-related trends were observed. The most frequently reported study drug–related AEs were diarrhea, increased AST, proteinuria, and urinary tract infection (Supplementary Table 2).

Hypoglycemia

Overall, 10 (8.0%) subjects randomized to RVT-1502 had 19 mild hypoglycemic events during the study as defined by blood glucose ≤70 mg/dL (Supplementary Table 3). Eight subjects had events categorized as asymptomatic (three, one, and four subjects in the RVT-1502 5-, 10-, and 15-mg groups, respectively). One subject (5-mg group) had a documented symptomatic event, and one (5-mg group) had a probable symptomatic event. One subject in the

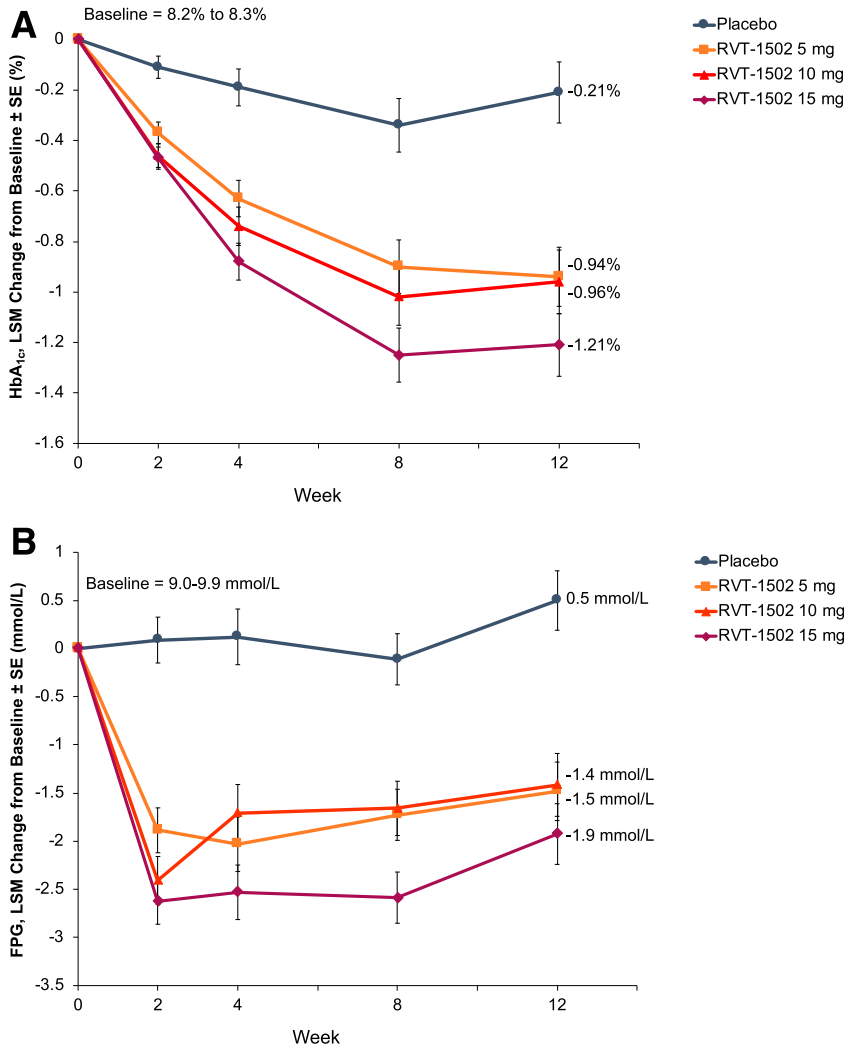

Figure 1—Glycemic control over 12 weeks in the intention-to-treat population (data are from patients with nonmissing values from baseline and the specified visit). *A*: LSM change from baseline in HbA_{1c}. Placebo-adjusted differences at week 12 were −0.7% (95% CI −1.1 to −0.4%), −0.8% (−1.1 to −0.4%), and −1.1% (−1.4 to −0.7%) for RVT-1502 5, 10, and 15 mg, respectively ($P <$ 0.001 vs. placebo for all doses). *B*: LSM change from baseline in FPG. Placebo-adjusted differences at week 12 were −2.1 mmol/L (95% CI −2.9 to −1.3 mmol/L), −2.2 mmol/L (−3.1 to −1.3 mmol/L), and −2.6 mmol/L (−3.5 to −1.8 mmol/L) for RVT-1502 5, 10, and 15 mg, respectively ($P <$ 0.001 vs. placebo for all doses). Error bars represent SE.

RVT1502 5-mg group and one in the 10-mg group had a blood glucose <54 mg/dL, and no subjects had a severe hypoglycemic event.

Liver Function

Mild increases in mean ALT and AST levels were observed with RVT-1502 treatment. Mean values remained within normal limits, were reversible, and did not appear to be dose related (Fig. 3). No concomitant increases were observed in mean γ-glutamyl transferase, alkaline phosphatase, or total bilirubin levels. No occurrences of Hy's Law were observed. One subject in the RVT-1502 10-mg group experienced a single incidence of elevated ALT >3× ULN at week 2, and one subject in the RVT-1502 15-mg group experienced a single incidence of elevated AST >3× ULN at week 4. In both cases, transaminase elevations were not present when measured at subsequent visits. Neither subject had an associated increase in bilirubin. No notable changes from baseline in mean values were observed for any other chemistry laboratory parameters.

Cardiovascular and Other Safety End Points

Transient increases in lipid parameters occurred during the treatment period, but no significant differences between RVT-1502 and placebo were observed at week 12 (Supplementary Fig. 4). From baseline to week 12, SBP increased by 5.0 mmHg (95% CI 1.4–8.7 mmHg), 2.1 mmHg (−1.8 to 6.0), and 1.7 mmHg (−2.1 to 5.5) with RVT-1502 5, 10, and 15 mg, respectively, and decreased by 1.8 mmHg (−5.5 to 2.0) with placebo. LSM changes in DBP from baseline to week 12 were 2.6 mmHg (0.4–4.9), 3.2 mmHg (0.8–5.7), 1.6 mmHg (−0.8 to 4.0), and −1.1 mmHg (−3.4 to 1.3) with RVT-1502 5, 10, and 15 mg and placebo, respectively. The increases in SBP and DBP compared with placebo were neither dose related nor consistent across time (Supplementary Fig. 5). No notable changes from baseline in body weight (Supplementary Fig. 6), BMI, ECGs, heart rate, or other vital signs were observed.

CONCLUSIONS

In this phase 2 study of RVT-1502, a novel GRA, all doses of the drug were well tolerated and significantly reduced HbA_{1c} and FPG over 12 weeks relative to placebo. Placebo-adjusted changes in both HbA_{1c} and FPG were statistically significant at week 2 and remained so throughout the treatment period, with 12-week differences from placebo of 1.1% and 2.6 mmol/L (47 mg/dL), respectively. The incidence of hypoglycemia was low, and no severe events occurred during the study. These results support this GRA as a potential novel treatment for type 2 diabetes.

Glucagon receptor antagonism to treat hyperglycemia in type 2 diabetes by reducing hepatic glucose production (5,6) has been pursued for several decades, but no drugs with this mechanism of action are currently available for clinical use. Despite promising efficacy results with previous compounds, adverse effects on lipids, BP, weight, and liver enzymes (particularly isolated ALT and AST) and increases in hypoglycemia have so far hampered clinical development of GRAs (5,6,24–26,30). RVT-1502 shows similar reductions in HbA_{1c} at lower doses than other GRAs tested to date, which could potentially reduce the risk of off-target adverse effects during chronic therapy. In addition, the distinct chemical structure of RVT-1502 compared with other small molecule GRAs may lead to a unique receptor pharmacology that plays a role

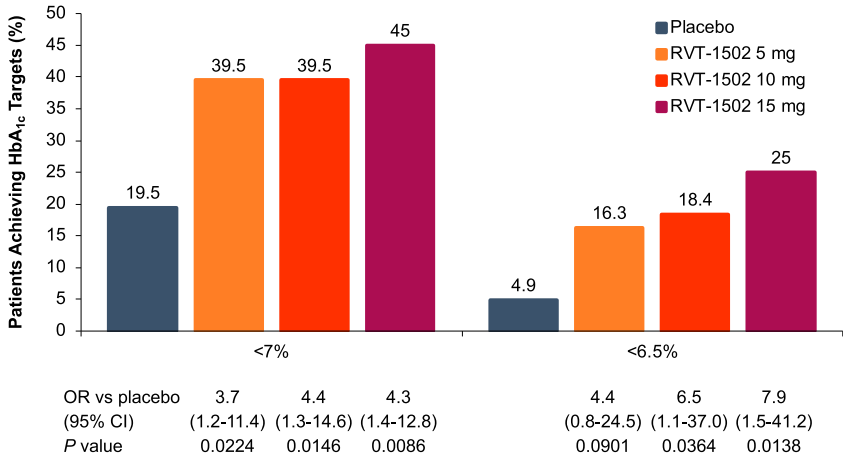

Figure 2—HbA_{1c} target achievement in each group after 12 weeks of therapy. OR, 95% CI, and *P* values are based on a logistic regression model with treatment group as a factor and baseline HbA_{1c} as a covariate. Data are week 12 LOCF.

in the clinical profile observed in phase 2 studies (28). In this study, the glycemic reductions observed with RVT-1502 were not accompanied by clinically significant, dose-related changes in lipids (including total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) and body weight. Although hypoglycemia was observed, the frequency was low relative to the associated glucose reduction. Mild elevations in BP were inconsistent and not dose responsive and will require further evaluation in longer studies with more-precise BP evaluations.

Elevations in ALT, and to a lesser extent AST, have been observed in the clinical trials of other GRAs, including small molecules (21–23,31,32), a monoclonal antibody (33), and an antisense oligonucleotide (34), suggesting that these changes may be a pharmacological effect of interfering with glucagon receptor signaling. Although the mechanism is not known, it is possible that the changes in liver enzymes may be due to increased glycogen content or an alteration in the handling of amino acids that would otherwise be used for gluconeogenesis (35–37). There was an increase in hepatic fat in the study of GRA LY2409021, which suggests other pathophysiologic mechanisms may be at work (24,35). In the current study, mild increases in mean ALT and AST were observed but were not dose related or associated with increases in bilirubin or other symptoms of liver toxicity, and levels returned to baseline during the follow-up period. Two subjects experienced transient transaminase increases $>3\times$ ULN, but these had resolved by subsequent visits with continued dosing. Larger clinical trials of longer duration will be required to fully examine the effects of RVT-1502 on liver metabolism.

In the current study, mean fasting glucagon increased relative to placebo with all three RVT-1502 doses, as has been reported with other GRAs (21,22,30–32). In addition, there were increases in total and active GLP1 relative to baseline with some doses of RVT-1502, and a significant increase in total GLP1 with RVT-1502 10 mg compared with placebo. Preclinical models have demonstrated that GLP1 contributes to the improved glucose tolerance in the setting of reduced glucagon receptor signaling (38,39). Taken together with our results, these findings suggest a mechanism that merits further investigation.

Mean fasting insulin concentrations exhibited no significant change from baseline during 12 weeks of treatment with all dose groups of RVT-1502. Considered in the context of the reduction in HbA_{1c} and FPG, this result may reflect increased hepatic insulin sensitivity in the fasting state. The trends observed in HOMA-IR and HOMA-β tend to support this possibility. Although fasting insulin did not change from baseline in response to RVT-1502, insulin levels increased during the OGTT. As might be expected, the increased insulin levels in subjects who received RVT-1502 during the OGTT were followed by a greater decrement in subsequent glucose levels compared with placebo. This confirms a previous observation made during an OGTT conducted in the phase 1 multiple-ascending dose study (29). Exogenous administration of GLP1-RAs has been shown to increase insulin levels during an OGTT (40,41). Thus, the apparent improvement in insulin sensitivity and insulin secretion in response to glucose load in subjects who received RVT-1502 may be related to the observed increases in fasting total and active GLP1 in this study. The increases in fasting total and active GLP1, as well as the higher postprandial insulin levels, may be responsible for the decrease in glucagon levels after glucose load because glucagon secretion is normally highly sensitive to insulin and GLP1 levels. The clinical significance of these findings suggests that inhibition of the glucagon response by RVT-1502 in the fasted state may abrogate the increased overnight gluconeogenesis found in early type 2 diabetes, as reflected by the decrease in FPG, while the potential concomitant improvements in fasting insulin sensitivity and insulin secretion in response to an oral glucose load may address the impaired insulin action in the fed state in clinically manifest type 2 diabetes.

RVT-1502 was generally well tolerated and demonstrated a low frequency and severity of AEs during the study similar to placebo. There were no drug-related serious AEs, and no subjects were withdrawn from the study because of a drug-related AE. Mild increases in mean transaminase levels were observed, but overall values remained below the ULN. There were no other clinically meaningful or dose-dependent changes in hematology, clinical chemistry, urinalysis, ECG, or vital signs. The overall frequency of study drug–related AEs was higher with RVT-1502 versus placebo, but no AE occurred in more than one subject in any treatment group, and no dose-related trends were observed. The GRA mechanism of action is potentially associated with hypoglycemia. However, in this study, as in the recent phase 2 trials of LY2409021 and PF-06291874 (22,30), improvements in HbA_{1c} were associated with a relatively low incidence of hypoglycemia, with no severe events and very few symptomatic events. Weight increased modestly but significantly in the PF-06291874 study (30). In this trial, weight remained stable in all treatment groups.

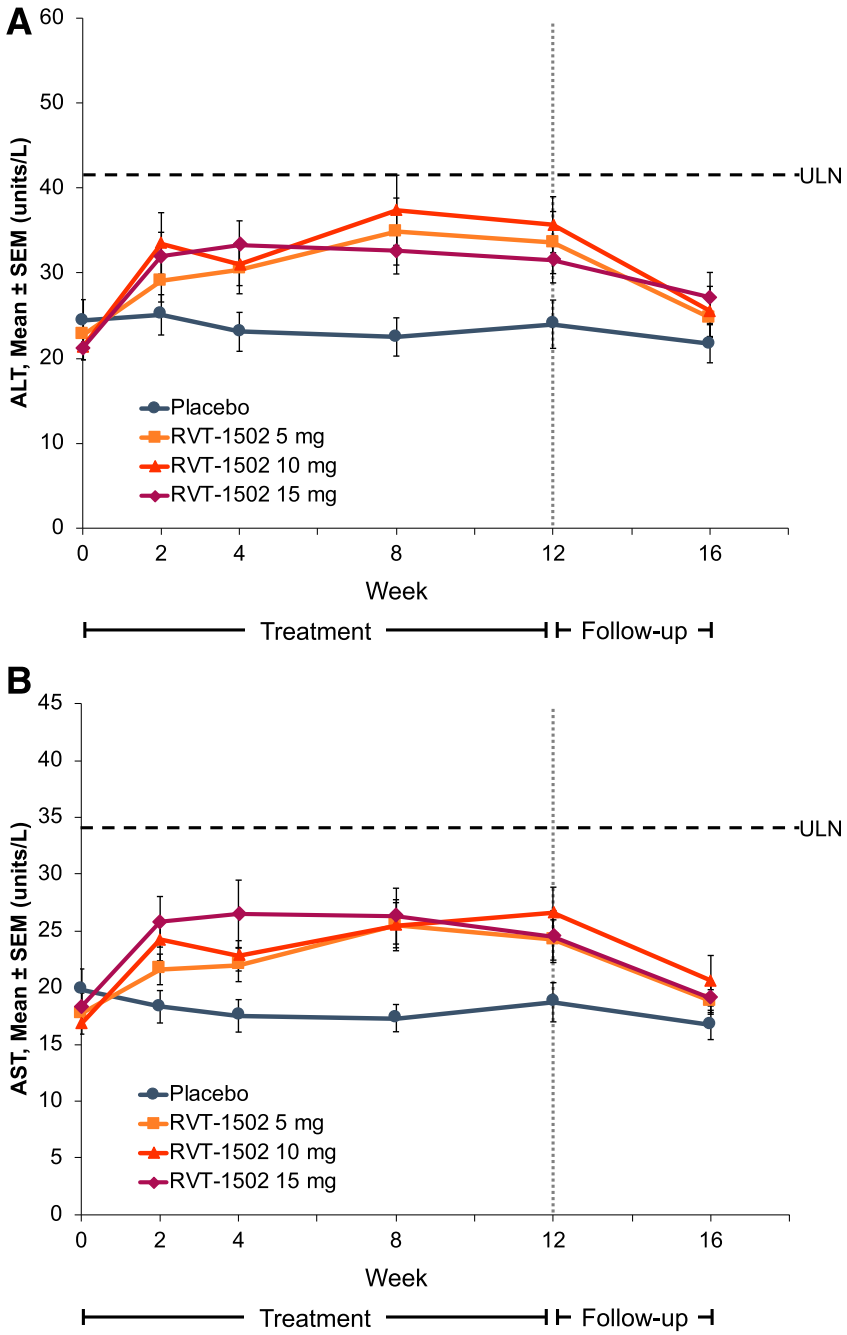

Figure 3—Mean ALT (*A*) and AST (*B*) levels over the 12-week treatment and 4-week follow-up periods. Error bars represent SEM.

Mild increases in average SBP and DBP were observed at week 12 in the RVT-1502 dose groups, but no consistent time- or dose-related increases in SBP and DBP compared with placebo were observed during 12 weeks of treatment. Elevations in BP have been observed in clinical trials with other GRAs, including in a 6-week study of LY2409021 using 24-h ambulatory BP monitoring in subjects with type 2 diabetes (23,30, 33,34). The mechanism by which GRAs could increase BP remains unexplained.

In conclusion, glucagon receptor antagonism with RVT-1502 significantly lowers HbA_{1c} and FPG levels, with a low incidence of hypoglycemia. Transient changes in liver enzymes, mild increases in BP, and the incidence of hypoglycemia observed in this study warrant further investigation. Possible end points to be considered for future clinical trials would include measurement of liver fat, 24-h BP monitoring, and continuous glucose monitoring. The results of the current study support continued clinical development of RVT-1502 in subjects with type 2 diabetes.

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As of March 2018, Metavant Sciences GmbH holds certain rights to develop and commercialize RVT-1502.

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