Title

Glucagon receptor antagonist volagidemab in type 1 diabetes: a 12-week, randomized, double-blind, phase 2 trial

Journal

Nature Medicine, 28(10)

ISSN

1078-8956

Authors

Pettus, Jeremy
Boeder, Schafer C
Christiansen, Mark P
et al.

Publication Date

2022-10-01

DOI

10.1038/s41591-022-02011-x

Peer reviewed

Published in final edited form as:

Nat Med. 2022 October ; 28(10): 2092–2099. doi:10.1038/s41591-022-02011-x.

Glucagon receptor antagonist volagidemab in type 1 diabetes: a 12-week, randomized, double-blind, phase 2 trial

Jeremy Pettus[1], **Schafer C. Boeder**[1], **Mark P. Christiansen**[2], **Douglas S. Denham**[3], **Timothy S. Bailey**[4], **Halis K. Akturk**[5], **Leslie J. Klaff**[6], **Julio Rosenstock**[7], **Mickie H.M. Cheng**[8], **Bruce W. Bode**[9], **Edgar D. Bautista**[10], **Ren Xu**[10], **Hai Yan**[10], **Dung Thai**[10], **Satish K. Garg**[5], **Samuel Klein**[11]

[1]Division of Endocrinology, University of California San Diego, La Jolla, CA

[2]Diablo Clinical Research, Walnut Creek, CA

[3]Clinical Trials of Texas, San Antonio, TX

[4]AMCR Institute, Escondido, CA

[5]Barbara Davis Center for Diabetes, University of Colorado Anschutz Campus, Aurora, CO

[6]Rainier Clinical Research Center, Renton, WA

Corresponding Author: Jeremy Hodson Pettus MD, Mailing address: Division of Endocrinology, University of California San Diego, 9452 Medical Center Drive, L1W-515, La Jolla CA 92037, Phone: (858) 246-2160, Fax: (858) 246-2141, jpettus@health.ucsd.edu.

Author Contributions

All authors contributed to study concept and study supervision. E.D.B, R.X., H.Y. and D.T. were responsible for study administration. J.P., J.C.B., M.P.C., D.S.D., T.S.B., H.K.A., L.J.K., J.R., M.H.M.C., B.W.B., E.D.B., S.K.G. and S.K. provided patients and conducted the investigation. J.P. and D.T. wrote the original draft of the manuscript. All authors critically reviewed the manuscript.

Competing Interests Statement

J.P. served as an advisor to Novo Nordisk and Sanofi; and served as a consultant to Diasome Pharmaceuticals, Insulet Corporation, Lilly Diabetes, MannKind Corporation, and Tandem Diabetes Care. S.C.B. served as a consultant to Cecelia Health; and received research support from Dexcom. M.P.C. received research support from Abbott Diabetes, Biolinq, Dexcom, Eli Lilly and Company, Medtronic, Merck & Co., Novo Nordisk A/S, Pfizer, and Viacyte. T.S.B. served as a consultant to Abbott, Lifescan, Mannkind, Medtronic, Novo, and Sanofi; received research support from Abbott Diabetes, Abbott Rapid Diagnostics, Biolinq, Capillary Biomedical, Dexcom, Eli Lilly, Kowa, Lexicon, Livongo, Mannkind, Medtronic, Novo Nordisk, REMD, Sanofi, Sanvita, Senseonics, Viacyte, vTv Therapeutics, and Zealand Pharma; and served a speaker for BD, Medtronic, and Sanofi. H.K.A. served as a consultant to the American Diabetes Association; received research support from Dexcom, Eli Lilly and Company, IM Therapeutics, MannKind Corporation, REMD Biotherapeutics, and Senseonics; and served as a speaker for the American Diabetes Association. L.J.K. received research support from Abbott Diabetes, Dong-A ST Co. Ltd., Gan & Lee Pharmaceuticals, Lexicon Pharmaceuticals, Lilly Diabetes, Medtronic, Novo Nordisk, Oramed Pharmaceuticals, Pfizer, and REMD Biotherapeutics. J.R. served as a board member for Applied Therapeutics, Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company, Intarcia Therapeutics, Novo Nordisk, Oramed Pharmaceuticals, and Sanofi; and served as a consultant to Applied Therapeutics, Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company, Intarcia Therapeutics, and Novo Nordisk. B.W.B. served as an advisor to Eli Lilly and Company; served as a consultant to Bigfoot Biomedical, Companion Medical, Lexicon Pharmaceuticals, Medtronic, Novo Nordisk, and Zealand Pharma A/S; received research support from Abvance Therapeutics, Dexcom, Diasome Pharmaceuticals, Dompe, Eli Lilly and Company, Eyenuk, Insulet Corporation, Jaeb Center for Health Research, Medtronic, Nova Biomedical, Novo Nordisk, Provention Bio, REMD Biotherapeutics, Sanofi, Senseonics, Viacyte, vTv Therapeutics, and Xeris Pharmaceuticals; served as a speaker for AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Eli Lilly and Company, MannKind Corporation, Medtronic, Novo Nordisk, and Sanofi; and is a stock/shareholder in AgaMatrix, Aseko, and Glytec, LLC. E.D.B. served as a consultant to REMD Biotherapeutics. R.X. and H.Y. served as board members for REMD Biotherapeutics. D.T. is an employee for REMD Biotherapeutics. S.K.G. served as an advisor to Eli Lilly and Company, Medtronic, Novo Nordisk, and Zealand Pharma A/S; and received research support from Dexcom, Eli Lilly and Company, and Medtronic. S.K. served as an advisor to Altimmune, Janssen, and ProSciento; and received research support from Janssen Research & Development, LLC. D.S.D. and M.G.M.C have no competing interests to disclose.

Peer review information:

Primary Handling editor: Jennifer Sargent, in collaboration with the Nature Medicine team.

Peer review information:

Nature Medicine thanks the anonymous reviewers for their contribution to the peer review of this work.

[7]Dallas Diabetes Research Center, Dallas TX

[8]Marin Endocrine Care and Research, Greenbrae CA

[9]Atlanta Diabetes Associates, Atlanta, GA

[10]REMD Biotherapeutics, Camarillo, CA

[11]Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO and Sansum Diabetes Research Institute, Santa Barbara, CA.

Abstract

Hyperglucagonemia contributes to hyperglycemia in patients with type 1 diabetes (T1D); however, novel therapeutics that block glucagon action could improve glycemic control. This phase 2 study evaluated the safety and efficacy of volagidemab, an antagonistic monoclonal glucagon receptor antibody, as an adjunct to insulin therapy in adults with T1D. The primary endpoint was change in daily insulin use at week 12. Secondary endpoints included change in hemoglobin A1c (HbA1c) at week 13, change in average daily blood glucose concentration and time within target range as assessed by CGM and seven-point glucose profile at week 12, , incidence of hypoglycemic events, proportion of subjects who achieve HbA1c reduction of ≥ 0.4%, volagidemab drug concentrations, and incidence of anti-drug antibodies. . Eligible participants (n=79) were randomized to receive weekly subcutaneous injections of placebo, 35 mg volagidemab, or 70 mg volagidemab. Volagidemab produced a reduction in total daily insulin use at week 12 (35 mg volagidemab: −7.59 U (95% CI: −11.79, −3.39; p=0.040 vs placebo; 70 mg volagidemab: −6.64 U (95% CI: −10.99, −2.29; p=0.084 vs placebo; placebo: −1.27 U (95% CI: −5.4, 2.9)) without meeting the prespecified significance level (p<0.025). At week 13, the placebo-corrected reduction in HbA1c percentage was −0.53 (95% CI = −0.89 to −0.17, nominal p=0.004) in the 35 mg volagidemab group and −0.49 (95% CI = −0.85 to −0.12, nominal p=0.010) in the 70 mg volagidemab group. No increase in hypoglycemia was observed with volagidemab therapy; however, increases in serum transaminases, LDL-cholesterol, and blood pressure were observed. Although the primary end point did not meet the prespecified significance level, we believe that the observed reduction in HbA1c and tolerable safety profile provide a rationale for further randomized studies to define the long-term efficacy and safety of volagidemab in patients with T1D. NCT03117998

Editor summary:

A phase 2 study testing glucagon receptor antagonist volagidemab as an adjunct to insulin therapy in patients was found to be safe and tolerable. Although the primary endpoint of reduction in daily insulin usage was not met, volagidemab therapy was associated with improved glycaemic control compared to placebo.

Introduction

Type 1 diabetes (T1D) is caused by autoimmune destruction of pancreatic β-cells that results in insulinopenia. However, the pathophysiology of T1D involves both an absence of insulin and an increase in post-prandial glucagon concentrations[1]. Increases in glucagon concentrations have been linked to deterioration of glucose control[2]. Excess glucagon

increases endogenous glucose production, raises plasma glucose concentrations, and contributes to the hyperglycemic burden. Correcting hyperglucagonemia represents an approach for the development of novel therapeutics to improve glycemic control in patients with T1D.

The physiological importance of glucagon in T1D has been demonstrated in animal models. In the setting of complete insulin deficiency, glucagon receptor (GCGR) knock-out mice maintain normal blood glucose concentrations and glucose tolerance[3,4]. These mice also have normal body weight, food intake, and energy expenditure. In addition, administration of a glucagon receptor antagonist in mice with absolute insulin deficiency restores euglycemia[4]. Accordingly, blocking glucagon action could have considerable therapeutic effects on glycemic control in patients with T1D.

Volagidemab is a human IgG2 monoclonal antibody that binds to the human GCGR and competitively blocks GCGR interaction with glucagon, inhibiting downstream receptor functions[5,6]. In a phase 1 study, a single dose of volagidemab given to participants with T1D decreased average glucose concentrations by ~27 mg/dl and reduced exogenous insulin requirements by 26%[7]. The present study was a randomized, blinded, placebo-controlled trial conducted to evaluate the efficacy, safety, and pharmacodynamics of chronic dosing with volagidemab (35 mg or 70 mg given subcutaneously once weekly for 12 weeks) in patients with T1D who are unable to achieve adequate glycemic control with insulin treatment alone.

Results

Study participants

Men and women between 18 and 65 years of age with T1D who had a fasting C-peptide <0.7 ng/mL and hemoglobin A1c (HbA1c) >7% and <10% were eligible to participate in this trial. Participants were required to be on a stable insulin treatment regimen, with either multiple daily insulin injections or continuous subcutaneous insulin infusion, for at least 8 weeks before screening. Other inclusion and exclusion criteria are provided in Methods.

A total of 79 participants were enrolled between 23 January 2019 and 14 July 2020. Participants were randomized 1:1:1 to one of three treatment groups: placebo, 35 mg volagidemab, or 70 mg volagidemab, administered by subcutaneous injection once weekly (Figure 1). All study treatment doses were administered in the research clinic. All participants (n=79) were included in the safety analysis; clinical efficacy was evaluated in 78 participants because one participant in the placebo group discontinued the study early due to non-compliance. Baseline characteristics of participants are provided in Table 1. Overall, in all participants, median age was 42 years (interquartile range [IQR]: 28–52 years) and 55.7% of participants were female. Median time since diagnosis of T1D was 19.5 years (IQR: 11.4–33.5 years). Mean average daily total insulin dose at baseline was 42.6 units (SD=15.4), 47.1 units (SD=17.1), and 50.0 units (SD=17.9) in the 35 mg volagidemab, 70 mg volagidemab, and placebo arms, respectively, and mean HbA1c at baseline was 8.1% (SD=0.92), 7.9% (SD=0.80), and 7.8% (SD=0.60), respectively.

Efficacy Analyses

Daily Insulin Use—The primary endpoint was change from baseline at week 12 in daily insulin use. At week 12, the least-squares (LS) mean change in total daily insulin dose was 7.59 U (95% CI: −11.79, −3.39; p=0.040 vs placebo) in the 35 mg volagidemab group and 6.64 U (95% CI: −10.99, −2.29; p=0.084 vs placebo) in the 70 mg volagidemab group compared with −1.27 U (95% CI: −5.4, 2.9) in the placebo group (Figure 2A). However, the observed reductions did not meet the prespecified significance level (i.e., both p-values must be <0.05 or the smaller p-value must be <0.025, Methods), precluding further formal statistical comparisons. Percentage change in total, basal, and bolus insulin dosing are shown in Figure 2B–D.

Hemoglobin A1c (HbA1c)—The results for the prespecified secondary endpoint of change in HbA1c at week 13 are shown in Figure 3. The LS mean change in HbA1c at week 13 was −0.64% (95% CI: −0.89, −0.39; p=0.004 vs placebo) in the 35 mg volagidemab group and −0.60% (95% CI: −0.86, −0.34; p=0.010 vs placebo) in the 70 mg volagidemab group compared with −0.11% (95% CI: −0.35, 0.13) in the placebo group.

The proportion of participants who achieved a 0.4% or greater reduction in HbA1c (a noninferiority margin accepted by the FDA[8]) from baseline to week 13 was 54.2% (95% CI: 34.2, 74.2) for 35 mg volagidemab (13 of 24 participants; p=0.15 vs placebo), 54.5% (95% CI: 33.5, 75.5) for 70 mg volagidemab (12 of 22 participants; p=0.14 vs placebo), and 30.8% (95% CI: 12.8, 48.8) for placebo (8 of 26 participants).

Blood Glucose—Seven-point blood glucose profiles were used to assess the effect of volagidemab on glycemic control, with change from baseline at week 12 in average daily glucose concentration and time within target range analyzed as a prespecified secondary endpoint. Seven-point profiles were obtained for 3 consecutive days before Day 1 of study treatment and for 3 consecutive days after study drug dosing during weeks 4, 8 and 12; all timepoints within each of the time periods were combined to determine the average percent of blood glucose readings that were within the target range (70–180 mg/dl), below the target range (<70 or <55 mg/dl) and above the target range (>180mg/dl). Changes from baseline in these variables are shown in Figure 4. At week 12, there was a reduction in average daily glucose concentration, an increase in the percent of blood glucose readings within the target range, and a decrease in the percent above the target range in the volagidemab groups compared with the placebo group, though the p-values were <0.05 and the differences observed at 12 weeks were not as great as at weeks 4 and 8. The percent of blood glucose readings that were below the target range was similar between the volagidemab groups and the placebo group across all timepoints.

Continuous blood glucose monitoring (CGM) was also used to assess the effect of volagidemab on glycemic control. Participants wore a blinded Dexcom G6 for a minimum of 1 week at baseline (before the Day 1 study visit) and for 1 week after the week 4, 8, and 12 study visits. However, a large amount of CGM data was lost due to device and sensor malfunction resulting in a small number of complete datasets that included baseline and week 4, 8, and 12 results (n=12–16 in each group). The data for this limited evaluation are

generally consistent with the findings from the 7-point profile and are provided in Extended Data Figure 1. As the product of the ratio of average glucose (week 12/baseline) and ratio of average insulin use (week 12/baseline) is derived from the CGM data, the results of the product of the ratios could not be reported.

Body Weight—Change in weight from baseline was evaluated as a pre-specified exploratory outcome. Mean (±SD) change from baseline in body weight at week 12 was 1.0 kg (±1.23), 0.8 kg (±2.31), and 0.4 kg (±2.57), in the 35 mg volagidemab, 70 mg volagidemab, and placebo groups, respectively. P-values for the differences in weight change among the three groups were >0.05.

Post-hoc Analyses—A post-hoc analysis of the proportion of participants who achieved a HbA1c level of 7.0% or less at week 13 was performed. The proportion of participants who achieved an HbA1c level of 7.0% or less at week 13 was 50.0% (95% CI: 30.0, 70.0) in the 35 mg volagidemab group (12 of 24 participants; p=0.11 vs placebo), 36.4% (95% CI: 16.4, 56.4) in the 70 mg volagidemab group (8 of 22 participants; p=0.11 vs placebo) and 15.4% (95% CI: 1.4, 29.4) in the placebo group (4 of 26 participants) (Extended Data Figure 2).

An additional post-hoc analysis was performed to examine HbA1c reduction in the subset of participants with baseline HbA1c ≥7.5%. In these participants, the LS mean reduction in HbA1c was −0.93% (95% CI: −1.27, −0.59) in those treated with 35 mg volagidemab (n=16; p=0.003 vs placebo), −0.54% (95% CI: −0.87, −0.21) in those treated with 70 mg volagidemab (n=17; p=0.094 vs placebo), and −0.12% (95% CI: −0.48, 0.24) in those treated with placebo (n=15).

Pharmacokinetic Assessment

Plasma concentrations of volagidemab at week 13, after administration of multiple doses by SC injection, were approximately dose-proportional, with a mean plasma concentration of 7,040 ng/mL (coefficient of variance [CV] = 40.6%) in the 35 mg volagidemab group and 15,700 ng/mL (CV = 27.8%) in the 70 mg volagidemab group (Supplementary Table 1).

Anti-Drug Antibodies

A small proportion of participants (2 participants in each treatment group) had low levels of pre-existing (pre dosing) anti-volagidemab antibodies. No increase in the proportion of participants with anti-volagidemab antibodies was observed with volagidemab dosing through the end of the study (Day 162) (Supplementary Table 2).

Safety and Tolerability

Overall, volagidemab was well-tolerated. Adverse events of any grade occurred with similar frequencies in the volagidemab and placebo treatment groups (69.2% in both 35 mg and 70 mg volagidemab and 74.1% in placebo). Upper respiratory tract infection was reported at a higher incidence in the volagidemab treatment groups compared with the placebo group (Table 2). Most adverse events were grade 1 or 2 as reported by the Investigator based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. CTCAE grade 3

or higher adverse events were reported in 3.8%, 11.5%, and 11.1% of participants treated with 35 mg volagidemab, 70 mg volagidemab, and placebo, respectively. The only Grade ≥3 event reported in more than 1 participant was hypoglycemia.

Hypoglycemia of any grade was reported as an adverse event by the Investigator with similar frequency in volagidemab and placebo treatment arms, occurring in two participants treated with 35 mg volagidemab (7.7%), one treated with 70 mg volagidemab (3.8%), and two treated with placebo (7.4%) (Table 2). Two of these events were CTCAE grade 3 (defined as <40 mg/dL): in one participant treated with 70 mg volagidemab (3.8%) and one participant (3.7%) treated with placebo. One of these grade 3 events required a visit to the emergency room and was considered a serious adverse event possibly related to study treatment. Hypoglycemia levels defined by the American Diabetes Association (ADA; i.e., levels 1–3) were not reported because the current study was designed before the development of the ADA classification.

Abnormal laboratory values and vital signs observed previously with other GCGR inhibitors were analyzed as AEs of special interest, and included increases in serum ALT and AST activity, low-density lipoprotein (LDL) cholesterol, and blood pressure (Extended Data Figure 3). Increases in serum ALT and AST activity were greater in participants treated with volagidemab compared with placebo-treated participants (Extended Data Figure 3A –B). Mean increases in ALT and AST activity tended to peak between week 5 and week 7 at approximately 2-fold above baseline values and then trend toward the normal range with continued volagidemab dosing. Peak mean ALT activity was 40U/L (95% CI: 28.0, 52.0) at week 7 in the 35 mg volagidemab group and 46 U/L (95% CI: 31.7, 60.3) at week 5 in the 70 mg volagidemab group; peak mean AST activity was 39 U/L (95% CI: 29.5, 48.5) at week 13 in the 35 mg vola group and 38 U/L (95% CI: 31.9, 44.1) at week 5 in the 70 mg volagidemab group). Volagidemab treatment was rarely associated with transaminase increases that were more than 3 × upper limit of normal (ULN) and transaminase increases did not result in any participant discontinuing therapy. An ALT value that was ≥3 × ULN was observed in one participant at weeks 2 and 3 in the 35 mg volagidemab group and in one participant at weeks 3–9 in the 70 mg volagidemab group. An AST value ≥3 × ULN was observed in one participant at weeks 7 and 13 in the 35 mg volagidemab group and in one participant at week 13 in the 70 mg volagidemab group. No participant met criteria for Hy's Law of drug induced liver injury, which is defined as ALT and/or AST >3 × ULN and concomitant bilirubin ≥2 × ULN[9]. All abnormal transaminase activity returned to normal at the follow-up visit conducted at 12 weeks after discontinuation of therapy (Extended Data Figure 3A–B).

Increases in mean LDL-cholesterol concentrations were observed in participants treated with volagidemab compared with placebo (Extended Data Figure 3C). Mean LDL-cholesterol concentrations were 111 mg/dL (95% CI: 99.6, 122.4) and 111 mg/dL (95% CI: 103.4, 188.6) at baseline in the 35 mg and 70 mg volagidemab-treated participants, respectively. Peak mean increases of 11 mg/dL (95% CI: 3.6, 18.4) and 17 mg/dL (95% CI: 9.6, 24.4) in participants treated with 35 mg volagidemab and 70 mg volagidemab, respectively, were observed at week 3 and tended to be lower at the next visit at week 5. At week 13, the differences relative to baseline were 2.7 mg/dL (95% CI: −3.9, 9.3) and 8.5 mg/dL

(95% CI: 1.9, 15.1) in participants treated at 35 mg volagidemab and 70 mg volagidemab, respectively.

Systolic and diastolic blood pressure increased from baseline in the volagidemab groups compared with the placebo group, with a maximum mean increase in systolic pressure of 4 mm Hg (95% CI: 0.0, 8.0) at week 2 in participants treated with 35 mg volagidemab and 5 mm Hg (95% CI: 0.8, 9.4) at week 5 in participants treated with 70 mg volagidemab (Extended Data Figure 3D–E).

Circulating amino acid (AA) concentrations were evaluated in a subset of participants. Alanine, arginine, citrulline, glutamate, glutamine, glycine, ornithine, and proline were measured in the fasting state at baseline, end of treatment (week 13), and follow up (week 24). All AAs were elevated with treatment by 1.4–2.3 fold. In general, elevations were numerically higher with the 70 mg dose compared to 35 mg. AA concentrations returned to baseline values after drug discontinuation by week 24 (Supplementary Table 3).

Discussion

Volagidemab is a monoclonal antibody antagonist that competes with glucagon for binding at the active site of the glucagon receptor. This phase 2, randomized controlled trial of volagidemab as an adjunct to insulin dosing in patients with T1D did not meet the primary endpoint of changes in daily insulin dosing at 12 weeks compared with placebo. No increase in hypoglycemia was observed with volagidemab therapy; however, increases in serum transaminases, LDL-cholesterol, and blood pressure were observed.

Reduction of insulin dose was chosen as the primary endpoint as hyperinsulinemia has been associated with increases in insulin resistance, endothelial dysfunction, and obesity in T1D[10–12]. Reducing hyperinsulinemia might ultimately be a novel target in the management of patients with T1D. Although a nominal reduction in daily insulin requirement at 12 weeks was observed in the 35 mg volagidemab group compared to placebo, the p-value was not significant (p=0.040) and the reduction observed may not have varied greatly from the reduction observed in the 70 mg volagidemab group compared with placebo (p=0.084). We believe these dose reductions are clinically significant; however, they are not of the magnitude that would be predicted by the so-called glucagon-centric view of diabetes[13]. Preclinical work has shown that either knocking out the glucagon receptor or treating with a glucagon receptor antagonist in mouse models of T1D can eliminate the need for exogenous insulin to maintain euglycemia[3,4]. By contrast, we report non-significant insulin dose reductions of up to −7.59U in patients with T1D. Several potential reasons could explain the lack of larger insulin dose reductions observed in our study. First, glucagon blockade has been shown to increase functional beta cell mass in mouse models of T1D[14]. The mechanism for this increased beta cell mass is believed to occur via alpha cell hyperplasia with resulting alpha to beta cell transdifferentiation. In humans, however, there is no evidence that this transdifferentiation occurs. Second, human islets have been shown to have markedly different cell composition, relative alpha cell content, and architecture compared with murine islets[15–17]. These species differences could explain the observed differential effects of glucagon receptor antagonist treatment in this study.

Although the observed reductions in insulin dosing for either dose of vola were not statistically significant, we observed improvements in glycemic control (HbA1c) in patients treated with volagidemab. The mean decrease in HbA1c from baseline was ~0.5% greater in the volagidemab groups than in the placebo group. HbA1c reductions were larger in participants with higher baseline HbA1c values. Specifically, in participants with baseline HbA1c >7.5%, 35 mg volagidemab reduced HbA1c by 0.93%. The available results of the seven-point profile provide additional evidence for an improvement in glycemic control with volagidemab therapy and demonstrated an increase in the percent of blood glucose readings within the target range at selected timepoints in participants treated with volagidemab versus placebo. No differences in the percent of blood glucose readings below the target range (<55 or <70 mg/dL) were observed with either dose of volagidemab compared with placebo. We plan to confirm the effects of volagidemab treatment on HbA1c in larger, phase 3 studies.

Considering the current treatment landscape, we consider the reductions in HbA1c observed in this study to be clinically meaningful. Other tested adjunctive therapies in T1D include sodium glucose cotransporter-2 inhibitors (SGLT-2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs). While these compounds achieve very robust HbA1c reductions in patients with T2D, their results in T1D are much more modest. Large trials in patients with T1D have demonstrated HbA1c reductions of 0.2–0.4% for both SGLT-2i and GLP-1 RAs[18]. Furthermore, GLP-1 RA therapy was associated with higher rates of hypoglycemia and hyperglycemia with ketosis; similarly, SGLTi therapy increased rates of diabetic ketoacidosis[19–21]. Thus, neither therapy is actively being pursued in patients with T1D, and a large unmet need to help patients achieve glycemic targets still exists.

The safety profile of volagidemab was consistent with other GCGR antagonists[22,23]. There was no change in weight or increase in hypoglycemia. However, treatment did increase liver transaminase levels, blood pressure, and LDL cholesterol. We observed an increase in serum ALT and AST concentrations with volagidemab treatment which subsided over time. These increases were usually transient and were not associated with an increase in serum bilirubin concentration, which is a sign of severe drug-induced liver injury. Indeed, we are not aware of any reports that have found drugs that block glucagon signaling cause changes in liver biochemistries meeting the criteria for Hy’s law, which is an index of severe drug-induced liver injury. Treatment with a small molecule GCGR antagonist, LY2409021, has been associated with increases in serum transaminase and intrahepatic triglyceride in patients with type 2 diabetes[9]. It is possible that the increase in serum transaminase activity that was observed with volagidemab therapy in our participants was also due to changes in amino acid metabolism and represent a physiologic adaptation, rather than a pathologic effect, of GCGR blockade[1]. Future, phase 3 studies will utilize MRI-PDFF examinations to determine if elevations in AST/ALT are associated with increases in hepatic fat.

Volagidemab therapy was also associated with increases in serum LDL-cholesterol concentration and blood pressure. A similar effect on serum LDL-cholesterol has been observed previously with other GCGR antagonists[24,25]. The increase in serum LDL-cholesterol concentrations declined after reaching a peak value despite continued volagidemab therapy, suggesting a transient effect. An increase in systolic and diastolic blood pressure was also observed previously with other GCGR antagonists[26]. One potential

explanation for this effect is that the excess glucagon from secondary hyperglucagonemia may increase cardiac ionotrophy[27]. The variance of blood pressure data collected in our participants was high. A larger data set with ambulatory blood pressure monitoring is necessary to fully define the effect of GCGR blockade on blood pressure.

This study also has several limitations. Device malfunction resulted in a substantial loss of CGM data, which makes it difficult to make meaningful assessment of those data. The study was only 12 weeks in duration, so we are unable to determine the effect of longer-term therapy. We excluded patients with T1D who had a history of severe symptomatic hypoglycemic and, therefore, cannot assess the effect of volagidemab therapy on hypoglycemia in that high-risk population. Glucagon is an important counterregulatory hormone in the treatment of severe hypoglycemia, however, this study did not address the question of how patients receiving volagidemab therapy would respond to exogenous glucagon administration in the event of a severe hypoglycemic reaction and no participants received glucagon rescue therapy during the study. A separate study is currently being designed to answer this clinical question. During the study, participants were seen weekly to provide careful monitoring of AEs. Weekly visits do not reflect real world care of patients with T1D, and it is possible this close monitoring could have affected the observed treatment effects.

Our study represents the largest cohort of individuals with T1D treated with a glucagon receptor antagonist to date. Although the primary endpoint of reductions in daily insulin dosing at 12 weeks was not met, we did observe reductions in HbA1c in patients with T1D treated with volagidemab. Once-weekly subcutaneous injections of volagidemab were safe and well tolerated, with adverse events being generally mild and dissipated. We believe that these data support the ongoing development of volagidemab as an adjunct to insulin for patients with T1D.

Online Methods

Study Design

This study (R477–202) was a randomized, placebo-controlled, double-blind study to evaluate the efficacy, safety, and PD of multiple doses of volagidemab in participants with T1D who had inadequate glycemic control with insulin treatment.

The primary endpoint was the change from baseline in daily insulin use at week 12. Secondary endpoints included change from baseline at in HbA1c week 13, the proportion of participants who achieved target HbA1c reduction (≥ 0.4%), time-in-range, incidence of hypoglycemic events, and safety/tolerability (incidence of adverse events and clinically relevant changes in medical history, physical examination, laboratory safety values, and ECGs). The proportion of participants who achieved HbA1c reduction to a target concentration of ≤7.0% and HbA1c reduction in the subset of participants with baseline HbA1c ≥7.5% were analyzed as post-hoc analyses.

The study was conducted at 11 sites in the United States from 23 January 2019 through 05 March 2021, at which time the study was complete. The study was conducted in

accordance with ICH guidelines, the principles of good clinical practice (GCP), and all applicable regulatory requirements. The protocol was approved by an institutional review board (IRB) for each study site: University of California, San Diego – Human Research Protections Program, Washington University Research Protection Office, WCG IRB (for University of Colorado), and Advarra IRB (for all other sites). No major protocol deviations occurred during the study. All participants provided written informed consent. Participants received compensation in the form of a travel stipend. The study was registered with ClinicalTrials.gov (NCT03117998).

Participants

This study was conducted in 79 patients with T1D who met the following eligibility criteria.

Inclusion criteria:

1. Men and women between the ages of 18 and 65 years old, inclusive, at the time of screening;
2. Females of non-childbearing potential must be ≥ 1 year post-menopausal (confirmed by a serum follicle-stimulating hormone (FSH) concentrations ≥ 40 IU/mL) or documented as being surgically sterile. Females of childbearing potential must agree to use two methods of contraception during the entire study and for an additional 3 months after the end of dosing with the investigational product;
3. Male participants must be willing to use clinically acceptable method of contraception during the entire study and for an additional 6 months after the end of the treatment period;
4. Body mass index between 18.5 and 32 kg/m2, inclusive, at screening (note that the subject's total daily insulin should be ≤ 1.0 unit/kg);
5. Diagnosed with Type 1 diabetes based on clinical history or as defined by the current American Diabetes Association (ADA) criteria;
6. HbA1c > 7% and < 10% at screening;
7. Fasting C-peptide < 0.7 ng/mL;
8. Treatment with a stable insulin regimen for at least 8 weeks before screening with MDI or CSII
9. Willing to use study-dedicated CGM system (e.g. DexCom) throughout the study, participants may continue to use personal CGM systems during the study but must be on stable use for at least 3 months prior to Screening;
10. ALT and/or AST ≤ 1.5x ULN at screening;
11. Able to provide written informed consent approved by an Institutional Review Board (IRB).

Exclusion criteria:

1. History or evidence of clinically-significant disorder or condition that, in the opinion of the Investigator, would pose a risk to participant safety or interfere with the study evaluation, procedures, or completion;
2. Significant organ system dysfunction (e.g., clinically significant pulmonary or cardiovascular disease, anemia [Hemoglobin < 10.0 g/dL], known hemoglobinopathies, and renal dysfunction [eGFR < 60 ml/min]);
3. Any severe symptomatic hypoglycemic event associated with a seizure or requiring help from other people or medical facility in the past 6 months;
4. Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident ≤ 12 weeks before screening;
5. History of New York Heart Association Functional Classification III-IV cardiac disease;
6. Current or recent (within 1 month of screening) use of diabetes medications other than insulin – participants on an SGLT2 inhibitor should discontinue the SGLT2 inhibitor during the Screening Period, at least 2 weeks prior to the start of the Lead-in Period;
7. Use of steroids and/or other prescribed or over-the-counter medications that are known to affect the outcome measures in this study or known to influence glucose metabolism;
8. Smokes > 10 cigarettes/day and/or is unwilling to abstain from smoking during the admission periods;
9. Known sensitivity to mammalian-derived drug preparations, recombinant protein-based drugs or to humanized or human antibodies;
10. History of illicit drug use or alcohol abuse within the last 6 months or a positive drug urine test result at screening;
11. History of pancreatitis, pancreatic neuroendocrine tumors or multiple endocrine neoplasia (MEN) or family history of MEN; 12. History of pheochromocytoma, or family history of familial pheochromocytoma;
12. Known or suspected susceptibility to infectious disease (e.g. taking immunosuppressive agents or has a documented inherited or acquired immunodeficiency);
13. Known history of positive for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HbsAg), or hepatitis C antibodies (HepC Ab);
14. Participation in an investigational drug or device trial within 30 days of screening or within 5 times the half-life of the investigational agent in the other clinical study, if known, whichever period is longer;
15. Blood donor or blood loss > 500 mL within 30 days of Day 1;

16. Women who are pregnant or lactating/breastfeeding;
17. Unable or unwilling to follow the study protocol or who are non-compliant with screening appointments or study visits;
18. Any other condition(s) that might reduce the chance of obtaining study data, or that might cause safety concerns, or that might compromise the ability to give truly informed consent.

Study Treatment

Enrolled participants were randomized 1:1:1 into one of three treatment groups: placebo, 35 mg volagidemab, or 70 mg volagidemab. Participants were randomized in a double-blind fashion based on the sequential order in which they met eligibility using a randomization block size of 3. A blinded central randomizer was used assign a unique subject randomization number for each subject randomized into this study. Randomization was based on a randomization schedule prepared by the contract research organization's designated unblinded biostatistician and provided to the unblinded site pharmacist or designee before the start of the study. Participants, study investigators, and all staff associated with the study conduct were blinded, with the exception of the unblinded pharmacist at each site and the biostatistician preparing the randomization schedule.

Prior to initiating study treatment, a minimum 1-week Lead-In period was required for all participants, during which participants were required to wear a CGM device and to record daily insulin use. Study-provided CGM devices were "blinded" (i.e., CGM data was not available to participants or Investigators). All participants could monitor glucose values by fingerstick or their own CGM, if these modalities were part of their usual care before the study.

Following the Lead-In Period, participants received once weekly subcutaneous (SC) injections of placebo, 35 mg volagidemab, or 70 mg volagidemab for 12 weeks (12 total doses). All visits were outpatient. Each dose was divided into two blinded 0.5 mL volume SC injections administered to the subject's anterior abdominal wall, for a total dose volume of 1 mL. Participants randomized to placebo received two 0.5 mL SC injections of blinded placebo on each scheduled day of dosing; participants randomized to 35 mg volagidemab received one 0.5 mL SC injection of 70 mg/mL volagidemab and one 0.5 mL SC injection of placebo on each scheduled day of dosing; participants randomized to 70 mg volagidemab received two 0.5 mL SC injections of 70 mg/mL volagidemab on each scheduled day of dosing. To mitigate a potential risk of hypoglycemia, participants with HbA1C ≤ 8.0% at screening, could reduce their total insulin dose by 10–20% on the day of randomization, at the discretion of the investigator.

After completion of the 12-week dosing, participants were followed for an additional 12 weeks during washout in the Safety Follow-up Period.

Study Assessments

Participants were evaluated for daily insulin requirements, measures of glycemic control, and safety at baseline and regularly throughout the treatment period and during the 12-

week Safety Follow-up Period. Daily insulin requirements were assessed through the use of dosing diaries. Measurements of blood HbA1c concentrations, CGM, and seven-point glucose profiles were conducted to assess the effect of volagidemab versus placebo on glucose variability and metabolic control. Blood samples were collected on Days 1, 8, 29, 57, 85, and 106 and assayed for volagidemab serum concentration. Anti-volagidemab antibody samples were collected pre-dose on Days 1, 85, and at the End of Study Visit (Day 162). Safety assessments included physical examinations, measurement of vital signs, clinical laboratory tests, and electrocardiograms (ECG). Participants were assessed for adverse events and event severity was graded by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Medidata Rave EDC version 2016.4.1 was used for electronic data capture and review.

Statistical Analyses

Statistical analyses were performed using Statistical Analysis Software (SAS®) version 9.4.

For the analysis of the primary endpoint, a sequential stepwise hypothesis and a Hochberg testing procedure were used to allow for multiple testing while preserving the overall significance level of the trial. A repeated measures analysis of covariance (ANCOVA) was used to compare the changes (as the primary analysis) and percentage changes (as a sensitivity analysis) from baseline in daily insulin use between treatment groups for each timepoint. The LS mean for each treatment and the difference between treatments was presented for each timepoint with 95% CIs and p-values as applicable based on following sequential testing methods:

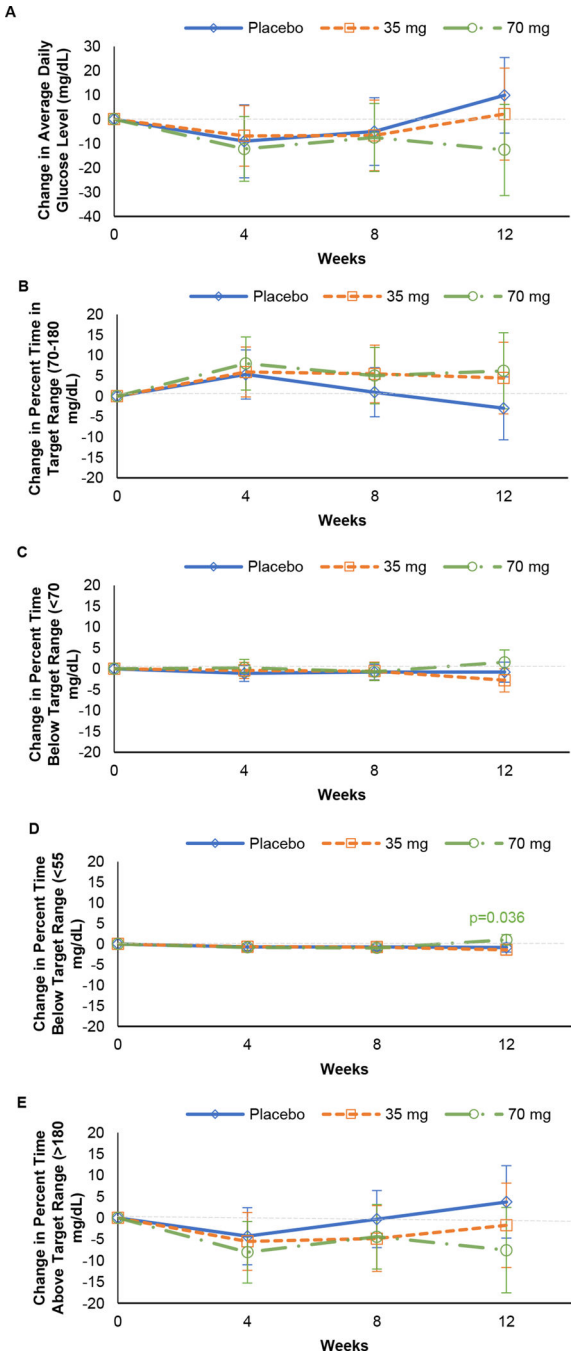
- *Step 1: Effect of Volagidemab.* The Hochberg procedure was used to assess (1) the superiority of 70 mg volagidemab compared to placebo and (2) the superiority of 35 mg volagidemab compared placebo. If the larger of the two p-values was less than the significance level (ie, 0.05), then both tests were considered to have reached statistical significance. Otherwise, if the smaller of the two p-values was less than half of the significance level (ie 0.025), then the corresponding test was considered to have reached statistical significance.
- Step 2: *Dose Comparison.* If at least one of the two doses of volagidemab was found to be superior to placebo, then the two doses of volagidemab were to be compared using the same significance level as that used to claim significance of either dose of volagidemab.

The power calculation for the primary endpoint (difference in the change from baseline in daily insulin use) was based on the assumption that daily insulin requirement would not change in the placebo group and would decrease in the volagidemab treatment group. Based on expected coefficient of variation of the daily insulin requirement of ~36%, it was estimated that ≥ 22 subjects in each group (treatment and placebo) would be sufficient to detect a difference of at least 30% with a power of 0.8, and an alpha value of 0.05. To ensure statistical power, and to avoid inadequacy due to unanticipated subject dropout, enrollment of 25 participants per group was planned.

Descriptive statistics (including means, medians, standard deviations, and/or ranges for continuous data and frequency counts for categorical data) are provided for selected demographics, safety and PD data.

For selected measures of glycemic control, least squares means with standard error are provided and nominal P-values were calculated based on differences between each volagidemab group versus the placebo group. For comparison of proportion of subjects that achieve HbA1c reduction of ≥ 0.4% in the volagidemab and placebo groups, a chi-square test was conducted. All statistical tests were 2-sided.

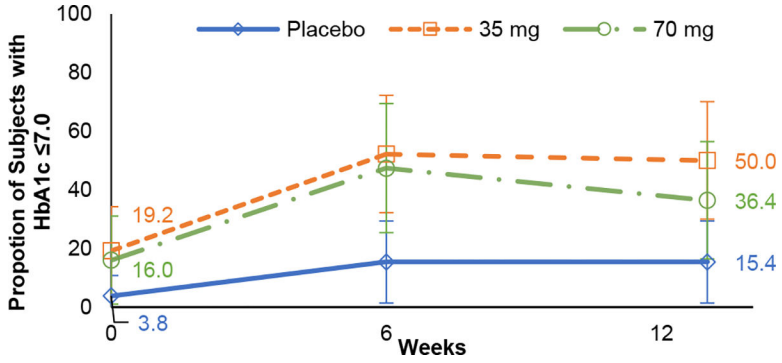
Extended Data



Extended Data Figure 1. Blood glucose concentrations from continuous glucose monitoring

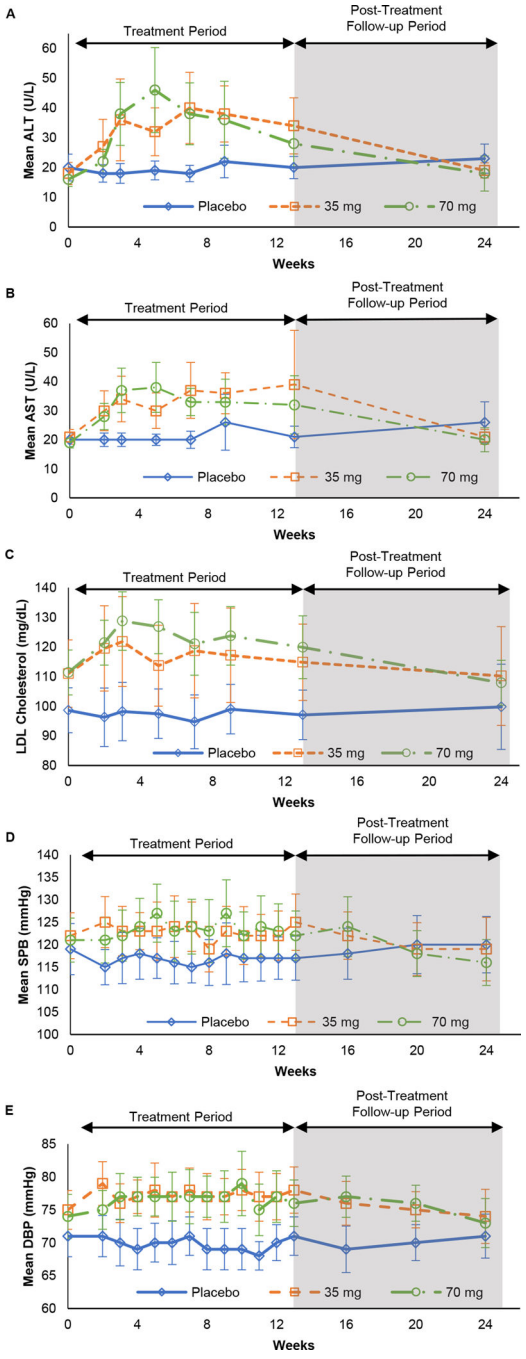
Blood glucose concentration data from available continuous glucose monitoring data are presented as least square means with error bars representing 95% confidence intervals for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=25). Change in a, average daily glucose; b, percent of samples in target range (70–180

mg/dL); c, percent of samples below target range (<70 mg/dL); d, percent of samples below target range (<55 mg/dL); e, percent samples above target range (>180 mg/dL).



Extended Data Figure 2. Proportion of patients who reached target hemoglobin A1c ≤7.0

The proportion of patients who reached a target HbA1c level of ≤7.0 are presented for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=25). Error bars represent 95% confidence intervals.



Extended Data Figure 3. Adverse events of special interest

Adverse event data are presented as arithmetic means with error bars representing 95% confidence intervals for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=26). Change in a, serum alanine aminotransferase (ALT); b, serum aspartate aminotransferase (AST); c, low-density lipoprotein (LDL) cholesterol; d, systolic blood pressure (SBP); and e, diastolic blood pressure (DBP).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was sponsored and funded by REMD Biotherapeutics. REMD Biotherapeutics was directly involved in the design, conduct, analysis, and reporting of the study. Research reported in this publication was also supported by the National Institute Of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health under Award Number R44DK108305. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Medical writing support, under the direction of the authors, was provided by Janis Leonoudakis, PhD and was funded by REMD Biotherapeutics in accordance with Good Publication Practice guidelines.

Data Availability Statement

Data from these analyses cannot be made publicly available due to the sponsor's contractual obligations. We encourage researchers or parties interested in collaboration for non-commercial use to apply to the corresponding author (jpettus@health.ucsd.edu). Applications should outline specifically what data they are interested in receiving and how the data will be used. All data shared will be de-identified and will be made available 2 years after the date of publication. A signed data access agreement with the sponsor is required before accessing the shared data.

References

1. Janah L et al. Glucagon Receptor Signaling and Glucagon Resistance. Int J Mol Sci 20, 3314 (2019). [PubMed: 31284506]
2. Fredheim S et al. The influence of glucagon on postprandial hyperglycaemia in children 5 years after onset of type 1 diabetes. Diabetologia 58, 828–34 (2015). [PubMed: 25541633]
3. Gelling RW et al. Lower blood glucose, hyperglucagonemia, and pancreatic α cell hyperplasia in glucagon receptor knockout mice. Proc Natl Acad Sci USA 100, 1438–1443 (2003). [PubMed: 12552113]
4. Wang M et al. Glucagon receptor antibody completely suppresses type 1 diabetes phenotype without insulin by disrupting a novel diabetogenic pathway. Proc Natl Acad Sci U S A 112, 2503–8 (2015). [PubMed: 25675519]
5. Gu W et al. Long-term inhibition of the glucagon receptor with a monoclonal antibody in mice causes sustained improvement, with reversible alpha-cell hyperplasia and hyperglucagonemia. J Pharmacol Exp Ther 331, 871–81 (2009). [PubMed: 19720878]
6. Yan H et al. Fully human monoclonal antibodies antagonizing the glucagon receptor improve glucose homeostasis in mice and monkeys. Pharmacol Exp Ther 329, 102–11 (2009).
7. Pettus J et al. Effect of a glucagon receptor antibody (REMD-477) in type 1 diabetes: A randomized controlled trial. Diabetes Obes Metab 20, 1302–1305 (2018). [PubMed: 29283470]
8. Althunian TA et al. Assessment of the Regulatory Dialogue Between Pharmaceutical Companies and the European Medicines Agency on the Choice of Noninferiority Margins. Clin. Ther. 42, 1588–1594 (2020). [PubMed: 32782135]
9. Navarro V & Senior J Drug-related hepatotoxicity. N Engl J Med 354, 731–9 (2006). [PubMed: 16481640]
10. Van der Schueren B et al. Obesity in people living with type 1 diabetes. Lancet Diabetes Endocrinol 9, 776–785 (2021). [PubMed: 34600607]
11. Gregory JM et al. Iatrogenic hyperinsulinemia, not hyperglycemia, drives insulin resistance in type 1 diabetes as revealed by comparison with GCK-MODY (MODY2). Diabetes 68, 1565–1576 (2019). [PubMed: 31092478]

12. Arcaro G et al. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 105, 576–82 (2002). [PubMed: 11827922]
13. Unger RH & Cherrington AD Glucagonocentric restructuring of diabetes: A pathophysiologic and therapeutic makeover. J Clin Invest 122, 4–12 (2012). [PubMed: 22214853]
14. Wang MY et al. Glucagon blockade restores functional β-cell mass in type 1 diabetic mice and enhances function of human islets. Proc Natl Acad Sci U S A 118, 1–8 (2021).
15. Levetan C & Pierce S Distinctions between the islets of mice and men: implications for new therapies for type 1 and 2 diabetes. Endocr Pr. 19, 301–12 (2013).
16. Cabrera O et al. The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc Natl Acad Sci U S A 103, 2334–2339 (2006). [PubMed: 16461897]
17. Brissova M et al. Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy. J Histochem Cytochem 53, 1087–97 (2005). [PubMed: 15923354]
18. Holt R et al. The Management of Type 1 Diabetes in Adults. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 44, 2589–2625 (2021). [PubMed: 34593612]
19. Garg S et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. N Engl J Med 377, 2337–2348 (2017). [PubMed: 28899222]
20. Dandona P et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 5, 864–876 (2017). [PubMed: 28919061]
21. Mathieu C et al. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care. Diabetes Care 39, 1702–10 (2016). [PubMed: 27506222]
22. Kazda C et al. Evaluation of Efficacy and Safety of the Glucagon Receptor Antagonist LY2409021 in Patients With Type 2 Diabetes: 12- and 24-Week Phase 2 Studies. Diabetes Care 39, 1241–9 (2016). [PubMed: 26681715]
23. Guzman C et al. Treatment with LY2409021, a glucagon receptor antagonist, increases liver fat in patients with type 2 diabetes. Diabetes Obes Metab 19, 1521–1528 (2017). [PubMed: 28371155]
24. Engel S et al. Efficacy and tolerability of MK-0893, a glucagon receptor antagonist (GRA), in patients with type 2 diabetes (T2DM). Diabetes 60, A85 (2011).
25. Guan H et al. Glucagon receptor antagonism induces increased cholesterol absorption. J Lipid Res 56, 2183–95 (2015). [PubMed: 26373568]
26. Kazda C et al. Treatment with the glucagon receptor antagonist LY2409021 increases ambulatory blood pressure in patients with type 2 diabetes. Diabetes Obes Metab 19, 1071–1077 (2017). [PubMed: 28191913]
27. Murtagh J, Binnion P, Lal S, Hutchison K & Fletcher E Haemodynamic effects of glucagon. Br Hear. J 32, 307–315 (1970).
28. Lucas MB & Yu VE Mahvash Disease: Pancreatic Neuroendocrine Tumor Syndrome Caused by Inactivating Glucagon Receptor Mutation. J Mol Genet Med 07, 1000084 (2013).
29. Wiebkin P, Dees J, JM M & Prough R Drug metabolism by isolated fetal human hepatocytes in suspension and primary culture. Drug Metab Dispos 13, 163–8 (1985). [PubMed: 2859163]
30. Wewer Albrechtsen N et al. Evidence of a liver-alpha cell axis in humans: hepatic insulin resistance attenuates relationship between fasting plasma glucagon and glucagonotropic amino acids. Diabetologia 61, 671–680 (2018). [PubMed: 29305624]
31. Dejgaard T et al. Efficacy and safety of liraglutide in type 1 diabetes by baseline characteristics in the ADJUNCT ONE and ADJUNCT TWO randomized controlled trials. Diabetes Obes Metab 23, 2752–2762 (2021). [PubMed: 34463425]
32. Petrie J et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol 5, 597–609 (2017). [PubMed: 28615149]
33. Edelman S et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 29, 2189–2195 (2006). [PubMed: 17003291]

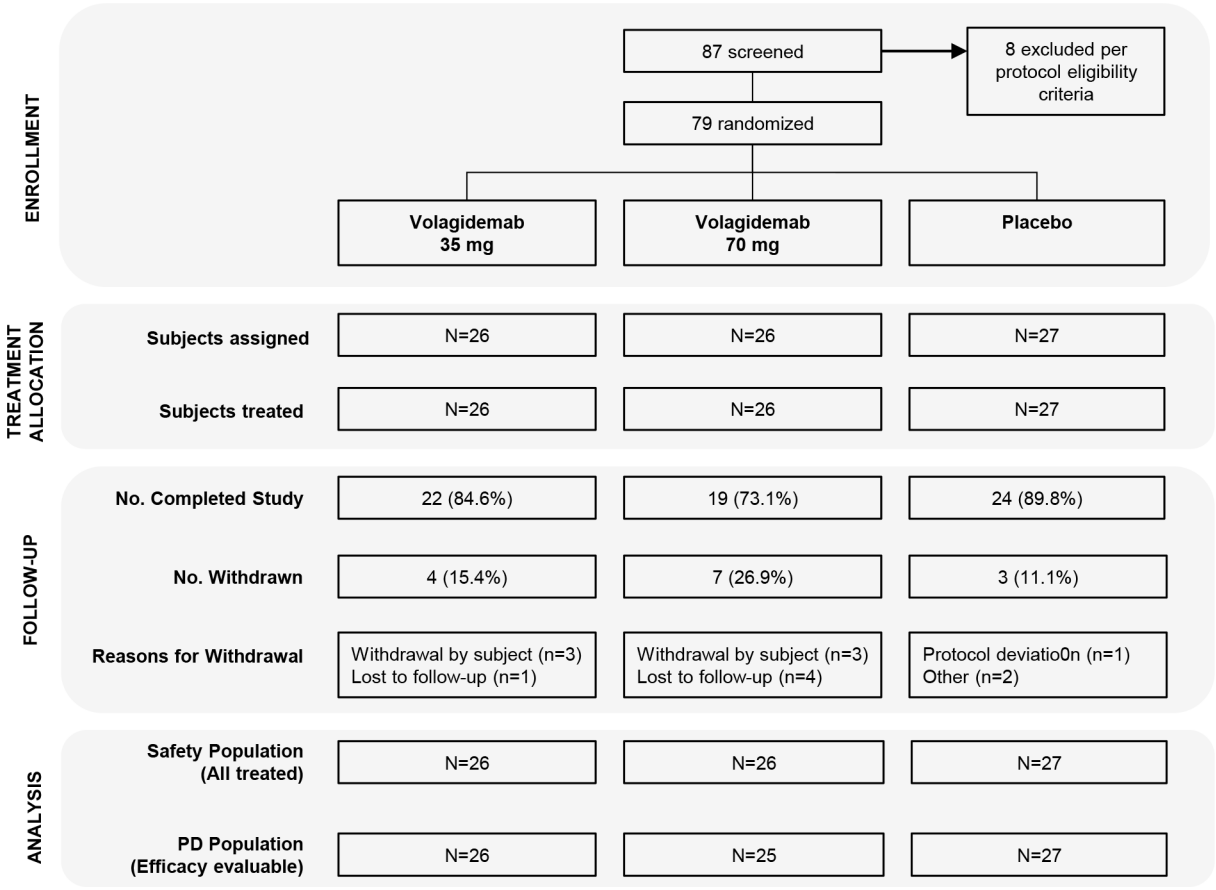


Figure 1. Patient disposition

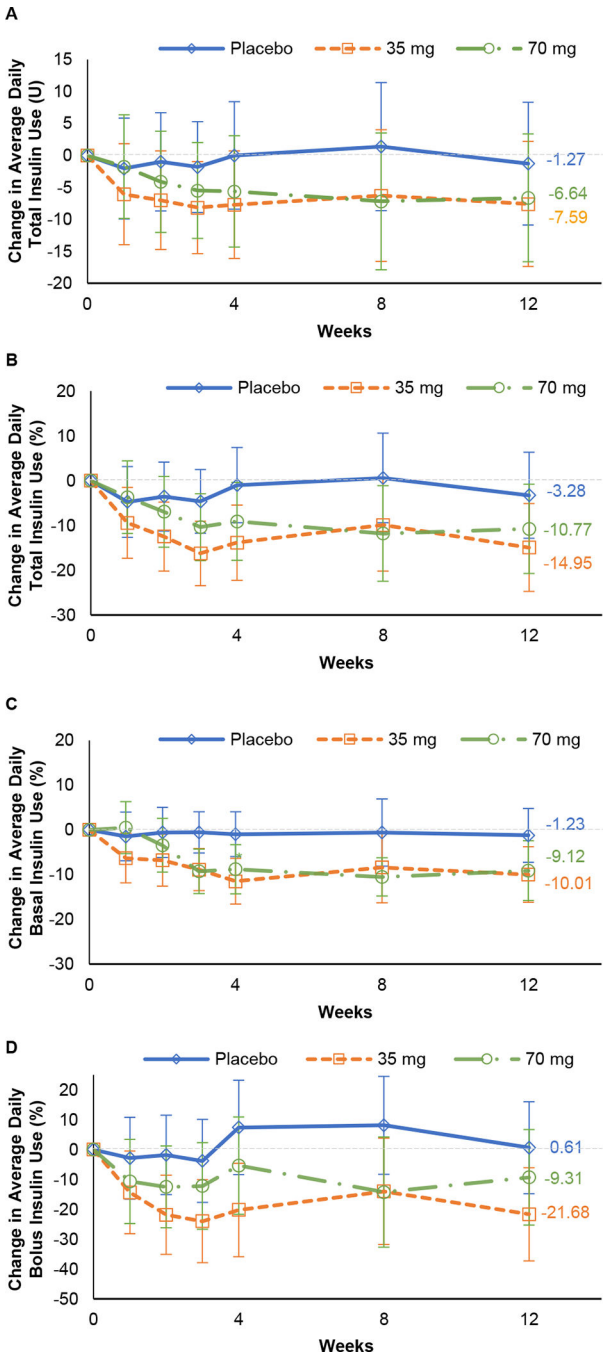


Figure 2. Daily insulin use

Daily insulin use data are presented as change or percent change from baseline in least square means with error bars representing 95% confidence intervals for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=25). a, Change in average daily total; b, percent change in average daily total; c, percent change basal and; d, percent change bolus insulin dose.

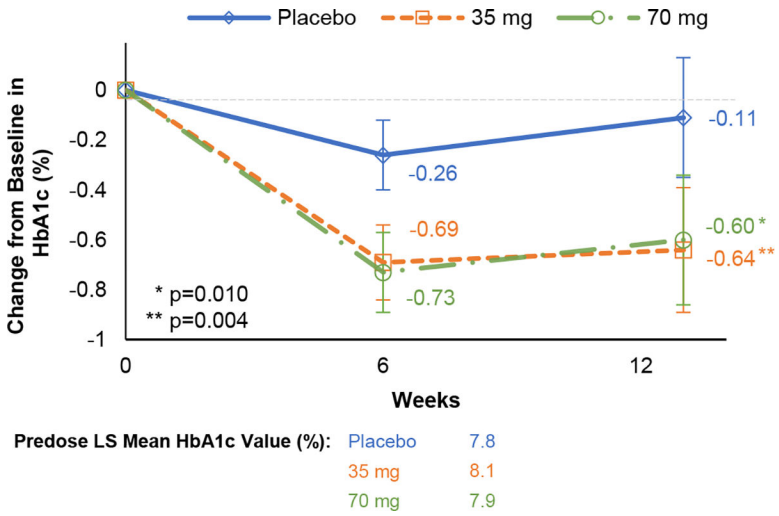


Figure 3. Hemoglobin A1c over time

Percent HbA1c data are presented as change from baseline in least square means with error bars representing 95% confidence intervals for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=25).Two-sided p-values are indicated for differences at Week 13, as assessed by a repeated measures analysis of covariance (ANCOVA) test.

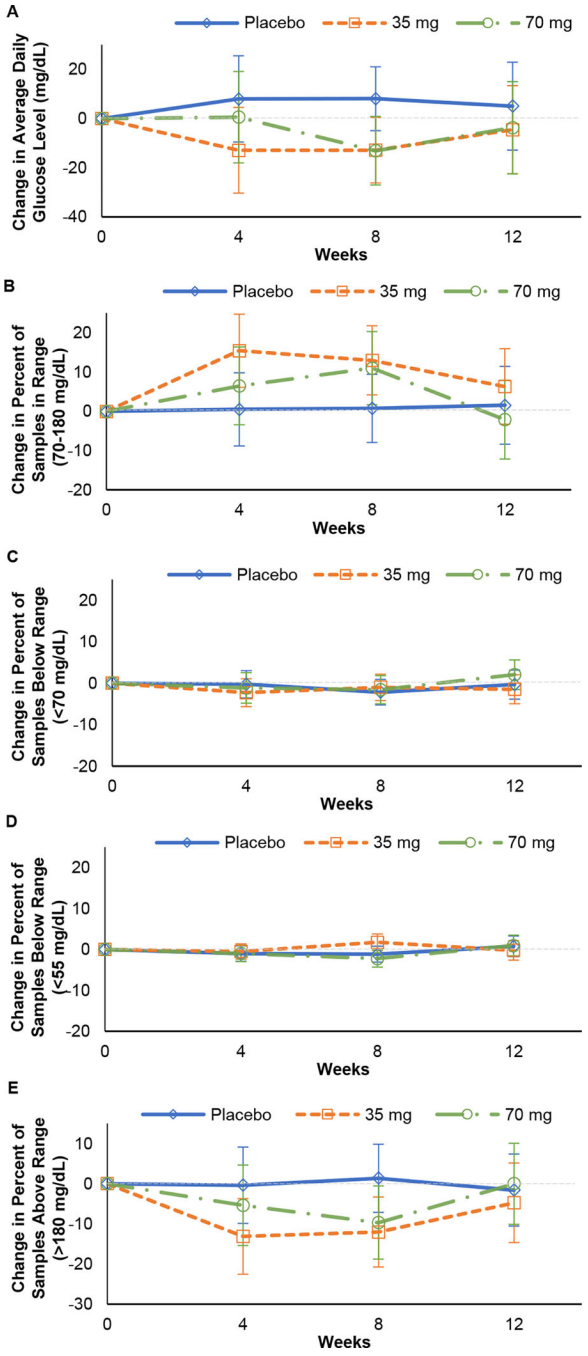


Figure 4. Blood glucose concentrations from 7-point profile

Blood glucose concentration data from 7-point profiles are presented as change from baseline in least square means with error bars representing 95% confidence intervals for participants treated with placebo (n=27), 35 mg volagidemab (n=26), or 70 mg volagidemab (n=25).Change in a, average daily glucose; b, percent of samples in target range (70–180 mg/dL); c, percent of samples below target range (<70 mg/dL); d, percent of samples below target range (<55 mg/dL); e, percent samples above target range (>180 mg/dL).

Table 1.

Baseline characteristics of study participants

	Volagidemab		Placebo (N=27)	Overall (N=79)
	35 mg (N=26)	70 mg (N=26)		
Age, years				
Median (IQR)	45 (31–51)	40 (23–48)	44 (28–57)	42 (28–52)
Min, max	18, 64	19, 65	20, 65	18, 65
Sex, n (%)				
Male	11 (42.3)	9 (34.6)	15 (55.6)	35 (44.3)
Female	15 (57.7)	17 (65.4)	12 (44.4)	44 (55.7)
Race, n (%)				
White	21 (80.8)	23 (88.5)	27 (100)	71 (89.9)
Black or African American	3 (11.5)	2 (7.7)	0	5 (6.3)
Asian	0	0	0	0
Native Hawaiian or other Pacific Islander	1 (3.8)	0	0	1 (1.3)
Other	1 (3.8)	1 (3.8)	0	2 (2.5)
Mean BMI (SD), kg/m^2	25.9 (3.38)	26.8 (3.39)	25.9 (3.34)	26.2 (3.35)
Time since T1D diagnosis, years				
Median (IQR)	22.4 (9.4–32.2)	16.7 (11.4–29.7)	23.0 (13.2–35.6)	19.5 (11.4–33.5)
Min, max	2.2, 38.5	2.7, 48.4	1.9, 54.6	1.9, 54.6
Mean (SD) average daily insulin use, U				
Basal	23.7 (12.3)	25.9 (10.4)	23.4 (10.0)	--
Bolus	19.9 (8.3)	21.4 (9.5)	26.3 (12.4)	--
Total	42.6 (15.4)	47.1 (17.1)	50.0 (17.9)	--
Mean (SD) HbA1c, %	8.1 (0.92)	7.9 (0.80)	7.8 (0.60)	--

Abbreviations: BMT, body mass index; HbA1c, hemoglobin A1c; SD, standard deviation; T1D, Type 1 diabetes; U, units.

Note: An analysis of variance test was used to compare baseline patient characteristics across treatment groups in a post-hoc analysis. P-values were >0.05 for all between-group differences.

Table 2.

Most common treatment-emergent adverse events (occurring in ≥3% of participants overall)

Participants with Adverse Event, n (%)	Volagidemab		Placebo (N=27)	Total (N=79)
	35 mg (N=26)	70 mg (N=26)		
Any adverse event	18 (69.2)	18 (69.2)	20 (74.1)	56 (70.9)
Upper respiratory tract infection	2 (7.7)	6 (23.1)	---	8 (10.1)
Nausea	3 (11.5)	3 (11.5)	---	6 (7.6)
Dizziness	2 (7.7)	2 (7.7)	1 (3.7)	5 (6.3)
Hypoglycemia	2 (7.7)	1 (3.8)	2 (7.4)	5 (6.3)
Headache	2 (7.7)	2 (7.7)	---	4 (5.1)
Food poisoning	1 (3.8)	---	2 (7.4)	3 (3.8)
Hyperglycemia	---	2 (7.7)	1 (3.7)	3 (3.8)
Hypertension	2 (7.7)	1 (3.8)	---	3 (3.8)
Pain in extremity	---	1 (3.8)	2 (7.4)	3 (3.8)
Rash	1 (3.8)	1 (3.8)	1 (3.7)	3 (3.8)
Viral upper respiratory tract infection	---	1 (3.8)	2 (7.4)	3 (3.8)