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# Pharmacodynamics, pharmacokinetics, safety and tolerability of the novel dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist RG7697 after single subcutaneous administration in healthy subjects

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**Aims:** To evaluate the pharmacodynamics, pharmacokinetics and safety of single subcutaneous (s.c.) injection of ascending doses of RG7697, a dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 agonist, in healthy subjects.

**Methods:** A total of 51 healthy volunteers were enrolled in this double-blind, placebo-controlled study investigating RG7697 doses ranging from 0.03 to 5 mg. Adverse events (AEs) were monitored and drug concentrations, fasting glycaemic variables, vital signs, ECG, antibody formation and routine laboratory variables were assessed. A meal tolerance test (MTT) was performed at the same time on day −1 (baseline) and day 1.

**Results:** RG7697 was generally well tolerated in healthy participants after s.c. injections up to 3.6 mg. Tolerability was limited by gastrointestinal AEs (nausea and vomiting) at the highest dose. There was a small dose-dependent increase in heart rate. No episodes of hypoglycaemia occurred. RG7697 concentrations peaked at 2 to 4 hours post-dose with a half-life of 19 to 25 hours. During MTT, RG7697 at doses ≥1.8 mg, reduced glucose maximum plasma concentration ($C_{max}$; −46%) without affecting overall glucose area under the curve (AUC). Its effect on insulin was more pronounced, with reductions in both $C_{max}$ (−64%) and AUC (−51%). Pharmacodynamic variables were well correlated to RG7697 average plasma concentration during MTT, with $IC_{50}$ (average concentration required for 50% reduction) values of 49 and 24.5 ng/mL for glucose and insulin, respectively.

**Conclusion:** Single s.c. injections of RG7697 up to 3.6 mg were generally well tolerated. Evidence of glycaemic effect and pharmacokinetic profiles consistent with once-daily dosing render this drug candidate suitable to be further tested in multiple-dose clinical trials in patients with type 2 diabetes.

KEYWORDS

diabetes, dual GIP/GLP-1 agonist, healthy volunteers, meal tolerance test, NNC0090-2746, RG7697, RO6811135, single ascending-dose study

## 1 | INTRODUCTION

The worldwide prevalence of diabetes has steadily increased in the last decades. The International Diabetes Federation reports that, as of 2013, there were more than 382 million people living with diabetes.[1] The World Health Organization estimates that, globally, 90% of patients with diabetes have type 2 diabetes mellitus (T2D).[2] T2D is a progressive heterogeneous metabolic disorder characterized by insulin resistance and β-cell failure. Obesity is a major risk factor for T2D,[3] and reduction of weight is associated with improvement of insulin resistance[4] and amelioration of diabetic symptoms; therefore, therapies which enhance both pancreatic

  

insulin secretion and weight loss will provide an improved therapeutic benefit.

The incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide (GIP) are naturally occurring peptide hormones. GLP-1 is a peptide hormone that is secreted from the L cells of the distal gut (distal ileum and colon) as a cleavage product of proglucagon, whereas GIP is a similarly sized peptide that is released from the epithelial K cells in the proximal small intestine (duodenum and jejunum).[5,6] GLP-1 and GIP are responsible for the incretin effect, ie, the enhanced secretion of insulin in response to nutrient or glucose ingestion.[7,8] This incretin effect accounts for ~50% to 70% of the total insulin secreted after oral glucose administration. Increases in GLP-1 and GIP secretion in response to oral glucose intake have been demonstrated in both healthy people and patients with T2D[9]; however only healthy people were completely able to enhance an insulinotropic response to oral glucose at progressively higher glucose loads.[10]

Glycaemic control is improved by GLP-1 through stimulating glucose-dependent insulin secretion in response to meals while suppressing glucagon secretion, and delaying gastric emptying. It also delays gastric acid secretion and suppresses appetite.[6] GIP improves glycaemic control by stimulation of insulin secretion in a glucose-dependent manner,[11] but does not slow gastric emptying.[12] Importantly, GIP is also reported pre-clinically to have direct anabolic effects on adipose tissue, including stimulation of glucose uptake, fatty acid synthesis, lipogenesis and inhibition of lipolysis.[13]

In patients with T2D, the incretin effect associated with GIP and GLP-1 is impaired. While secretion of GIP is maintained in those with T2D, the secretion of GLP-1 is diminished.[14,15] However, GLP-1 activity at the β cell remains less impaired than GIP in patients with T2D. Assessment of molecular signalling at the pancreatic β cell has been demonstrated to be differentially regulated for these two incretins.[16] GIP and GLP-1 constitute the two primary physiological incretins, but only one has progressed to development as registered medicine. We have previously published the scientific rationale for inclusion of GIP as a balanced, full potency complement to GLP-1 in a single molecule co-agonist to provide enhanced glycaemic control and body weight management.[17]

RG7697 (also known as RO6811135 or NNC0090-2746) is a 40-amino-acid synthetic peptide analogue with homology to both GLP-1 and GIP, which is being developed for the treatment of T2D. The peptide is protected against dipeptidyl peptidase-4 proteolysis by an α-aminoisobutyric acid residue at position 2. It has been acylated at a C-terminal lysine with a saturated C16 lipid to extend its pharmacokinetic profile while preserving inherent *in vitro* potency and balanced selectivity at the GLP-1 and GIP receptors (concentration providing half of the maximum effect [$EC_{50}$] of 5 and 3 pM for GLP-1 and GIP, respectively). In a graded glucose infusion assay in monkeys, RG7697 reduced blood glucose and increased the insulin secretory response more effectively than liraglutide. In mice with diet-induced obesity, RG7697 decreased body weight, food intake and fat mass, improved glucose tolerance and lowered plasma insulin and cholesterol levels after chronic administration.[17] The present study, the first to test RG7697 in humans, was conducted to investigate the pharmacodynamics, pharmacokinetics and safety of RG7697 administered by single subcutaneous injection to healthy subjects.

## 2 | MATERIALS AND METHODS

This was a single ascending-dose study in healthy subjects, conducted at a single centre in the USA. The study was approved by the Western Institutional Review Board in Olympia (USA) and was performed in accordance with the Declaration of Helsinki, good clinical practice guidelines, and US law. It was registered at ClinicalTrials.gov (NCT01676584).

### 2.1 | Participants

Healthy men and women aged 18 to 45 years, with a body mass index (BMI) of 22 to 32 kg/m$^2$, participated in the study. Women had to be surgically sterile, postmenopausal or using an effective contraceptive method. Participants were fully informed of the purpose of the study and risks involved and gave written informed consent prior to enrolment. Participants with a history of diabetes, pancreatitis, reduced gastric motility, drug hypersensitivity or food allergies were excluded from the study. Exclusion criteria also included acute gastrointestinal symptoms, previous exposure to incretins, positive results for viral exposure (HIV and hepatitis B and C), a glomerular filtration rate <80 mL/min or required concurrent medication during the study.

### 2.2 | Study design

This single ascending-dose study was designed as a double-blind, randomized, placebo-controlled study. Participants in the first 2 cohorts were admitted to the clinic on the morning of day −1, while participants in the subsequent cohorts were admitted on the evening of day −2. Baseline assessments were conducted on day −1. Six cohorts were anticipated at the following dose levels: 0.03, 0.1, 0.3, 1, 3 and 6 mg. Within each cohort, 6 participants were to receive RG7697 and 2 to receive placebo. Study drug was injected s.c. into the abdomen on the morning of day 1, after participants had fasted for at least 8 hours. Participants in the first 2 cohorts remained hospitalized for ~96 hours after study drug injection, while participants in the later cohorts were discharged on the morning of day 4 (72 hours post injection). Participants returned to the clinic for a follow-up visit 2 to 3 weeks after dosing. Escalation to each new ascending dose was dependent on the complete review of safety (clinical laboratory tests including capillary blood glucose, vital signs, ECG), tolerability (adverse events [AEs], local tolerability), and pharmacokinetic data collected over 24 hours of preceding dose.

Dose escalation was stopped if 1 of the following criteria applied to participants on active treatment within the same dose group: a serious AE (SAE); severe treatment-related AEs of the same type observed in at least 2 participants; clinically significant drug-related laboratory abnormalities of the same type in at least 3 participants; clinically significant changes in vital signs or ECGs of the same type in at least 3 participants; documented hypoglycaemic episodes in at least 2 participants and plasma glucose levels ≤3.05 mmol/L (55 mg/dL), regardless of the presence of hypoglycaemic signs or symptoms

in at least 2 participants. Additionally, the dose was not escalated further if mean exposure was predicted to exceed the exposure cap ($AUC_{0\text{-}24}$ > 2000 ng × h/mL and/or a $C_{max}$ >150 ng/mL).

## 2.3 | Test compound

Clinical formulations of RG7697 were manufactured by Roche (Basel, Switzerland) as a solution for s.c. injection and packaged into vials of 1 mg/mL (batch GRD0683) or 5 mg/mL (batch GRD0680). Saline solution was used as placebo solution for s.c. injection and provided by the clinical site. Vials of 1 mg/mL of RG7697 were used for dose levels ≤1 mg, and vials of 5 mg/mL of RG7697 were used for dose levels >1 mg.

## 2.4 | Safety and tolerability

Safety and tolerability of RG7697 were assessed for up to 96 hours after receiving study drug in the 2 first dose cohorts and up to 72 hours in the subsequent dose cohorts, by monitoring of vital signs, ECGs and cardiac telemetry, clinical laboratory tests (haematology, biochemistry, urine analysis), capillary blood glucose, local tolerability, antidrug antibodies and AEs.

## 2.5 | Pharmacokinetic analysis

Blood samples for pharmacokinetic determination of plasma concentrations of RG7697 were collected in EDTA-containing tubes initially at predose, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 48, 60, 72 and 96 hours post dose, and at follow-up visit (first 2 cohorts). In later cohorts, additional time points were collected at 2.5, 3 and 3.5 hours post dose, while the 96-hour sample was deleted. Aprotinin solution was added immediately after collection and samples were centrifuged at 1500 *g* for 15 minutes at 4°C within 30 minutes of collection. Plasma samples were stored below −20°C until analysis. Plasma concentrations of RG7697 were measured by a specific and validated liquid chromatography tandem mass spectrometry method. The analysis was performed by Nuvisan GmbH (Neu-Ulm, Germany). The lower limit of quantification in human plasma was 0.05 ng/mL, and the calibration range was 0.05 to 10 ng/mL. Samples with results above the upper limit of quantification were reanalysed after appropriate dilution. The precision and accuracy of the assay, ranged from 2.8% to 5.5% and 94.5% to 96.7%, respectively. Pharmacokinetic variables were derived from the concentration–time data by non-compartmental methods with the aid of Phoenix WinNonlin 6.2 (Pharsight, Mountain View, California).

## 2.6 | Pharmacodynamic analyses

Daily fasting plasma glucose and insulin samples were collected during hospitalization. A standardized meal tolerance test (MTT) was conducted on day −1 and day 1 at the same time, corresponding to 10 hours post-dose (first 2 cohorts) or 3 hours post-dose (later cohorts). Blood samples were collected before and at 20 and 40 min, 1, 1.5, 2, 2.5, 3, 3.5 and 4 hours after test meal ingestion, for the measurement of glucose, insulin, glucagon and C-peptide concentrations. Analyses of glucose, insulin, C-peptide and glucagon were carried out by Covance Central Laboratory (Indianapolis, Indiana and Geneva, Switzerland). Maximum plasma concentration ($C_{max}$) and area under the curve ($AUC_{0\text{-}4h}$) of all 4 glycaemic markers were derived from the concentration–time data during MTT using a non-compartmental method, as described for pharmacokinetics. $C_{max}$ and $AUC_{0\text{–}4h}$ ratios for day 1/day −1 were also calculated.

## 2.7 | Statistical analysis

Safety data were summarized descriptively. Pharmacokinetic and pharmacodynamic data were summarized using descriptive statistics including arithmetic means, standard deviation (s.d.), geometric means, medians, coefficients of variation and ranges.

Statistical analyses were performed using PROC GLM from SAS software version 9.2 (SAS Institute, Cary, North Carolina). To investigate possible deviations from dose proportionality, an analysis of variance model, with fixed effects for dose and random effects for participants, was applied to the dose-normalized and logarithmically transformed values of maximum concentration ($C_{max}$) and area under the concentration–time curve from time zero to infinity ($AUC_{0\text{-}inf}$) of RG7697.

## 2.8 | Pharmacokinetic/pharmacodynamic relationships

Exploratory analyses were performed to investigate the pharmacokinetic/pharmacodynamic relationships between RG7697 exposure and glycaemic variables (glucose $C_{max}$, insulin $C_{max}$ and $AUC_{0\text{-}4h}$). The data on all participants from all dose groups were pooled and analysed together (naïve pooling). Pharmacokinetic/pharmacodynamic relationships were analysed using Phoenix WinNonlin 6.2 (Pharsight, Mountain View, California). To reduce noise attributable to inter-participant variability, intra-participant ratios for day 1/day −1 of $C_{max}$ and $AUC_{0\text{-}4h}$ of glycaemic variable were used. Ratios of glycaemic markers were plotted as a function of RG7697 average concentrations measured during the MTT (ie, $AUC_{0\text{-}4h}$/4 h). Direct effect between RG7697 exposure and glycaemic variables was assumed. Different inhibitory maximum effect ($E_{max}$) models were tested for best fit, and selection was made on the basis of the Akaike information criterion. Model diagnosis was also performed by visual analysis of the weighted residual plots and by observation of the relative standard error of the estimated variables. The estimates and associated relative standard error were reported. All three relationships between RG7697 average concentration during the MTT and glucose $C_{max}$, insulin $C_{max}$ and insulin $AUC_{0\text{-}4h}$ were well described by an inhibitory $E_{max}$ model:

$$Glycaemic\ C_{max}\ \text{or}\ AUC_{0-4h}\ \text{ratio} = E_0 \cdot \left(1 - \left[\frac{C}{C + IC_{50}}\right]\right)$$

where $E_0$ is the glucose or insulin $C_{max}$ or $AUC_{0\text{-}4h}$ ratio value at RG7697 average concentration (C) equal to 0 (ratio for placebo group) and $IC_{50}$ the RG7697 concentration causing half of the maximal effect.

# 3 | RESULTS

A total of 51 healthy volunteers (33 men, 18 women) were enrolled in the study. Demographic characteristics are provided in Table 1.

**TABLE 1** Baseline demographic characteristics

| | Placebo | 0.03 mg | 0.07 mg | 0.2 mg | 0.6 mg | 1.8 mg | 3.6 mg | 5 mg | Total |
|---|---|---|---|---|---|---|---|---|---|
| Participants, n | 13 | 6 | 7 | 6 | 6 | 5 | 6 | 2 | 51 |
| Gender, n (%) | | | | | | | | | |
| Men | 7 (54) | 3 (50) | 6 (86) | 3 (50) | 6 (100) | 4 (80) | 3 (50) | 1 (50) | 33 (65) |
| Women | 6 (46) | 3 (50) | 1 (14) | 3 (50) | 0 (0) | 1 (20) | 3 (50) | 1 (50) | 18 (35) |
| Race, n (%) | | | | | | | | | |
| Black | 7 (54) | 3 (50) | 4 (57) | 5 (83) | 6 (100) | 3 (60) | 2 (33) | 1 (50) | 31 (61) |
| White | 6 (46) | 3 (50) | 3 (43) | 1 (17) | 0 (0) | 2 (40) | 4 (67) | 1 (50) | 20 (39) |
| Age, years | 30.0 (6.1) | 34.2 (6.2) | 28.9 (5.7) | 24.7 (8.5) | 30.2 (10.2) | 25.0 (6.0) | 29.3 (5.2) | 26.5 (0.7) | 29.0 (6.9) |
| Weight, kg | 83.1 (14.6) | 80.0 (8.2) | 85.1 (18.9) | 79.8 (11.7) | 85.9 (10.9) | 72.3 (2.6) | 73.6 (4.9) | 90.2 (11.4) | 81.1 (12.5) |
| BMI, kg/m$^2$ | 27.9 (3.2) | 28.0 (2.2) | 27.7 (4.0) | 28.5 (2.6) | 28.4 (3.2) | 24.2 (1.7) | 26.0 (3.3) | 30.4 (1.3) | 27.5 (3.2) |

Mean (s.d.).

Mean age, body weight and BMI were 29 years, 81.1 kg and 27.5 kg/m$^2$, respectively. All but 2 participants completed the study per protocol. One participant (cohort 2) withdrew consent on day 1 and was replaced. Another participant (cohort 6) completed in-clinic assessment but was lost to follow-up (Figure S1). All 51 participants were included in the safety analyses. One participant vomited the content of the test meal and was excluded from the pharmacodynamic analysis (5-mg dose group).

The anticipated dose for the second cohort was 0.1 mg; however, because of the occurrence of mild gastrointestinal-related AEs (expected AEs for GLP-1 analogues) after s.c. injection of the starting dose of 0.03 mg in 2 participants, a reduced escalation step was imposed with a dose of 0.07 mg administered to the second cohort. As a consequence, the actual escalation scheme was revised as follows: 0.03, 0.07, 0.2, 0.6, 1.8, 3.6 and 5 mg. Furthermore, design and sampling schemes were adapted after the pharmacokinetic results of the first 2 cohorts indicated earlier time to maximum drug concentration ($t_{max}$) and shorter elimination half-life than initially anticipated. Notably, the 5-mg cohort was stopped after dosing of the first 3 participants (2 active, 1 placebo) because of the occurrence of drug-related gastrointestinal serious AEs in a participant dosed with 5 mg.

The mean pharmacokinetic profiles of RG7697 are shown in Figure 1. After single s.c. injection, maximum plasma concentrations were achieved at ~2 to 3 hours post-dose with doses up to 0.6 mg, while time to $C_{max}$ was slightly delayed up to 4 hours in the higher dose groups. Unexpected pharmacokinetic profiles were observed at 5 mg, with flat and sustained high plasma concentration for almost 24 hours post dose, although lower than maximum concentrations achieved with 3.6 mg dose. RG7697 elimination was biphasic with a terminal half-life in the range of 19 to 25 hours (disregarding apparent terminal half-life [$t_{½β}$] values at low doses rather representing distribution half-life). Excluding the 5-mg data, exposures ($AUC_{inf}$ and $C_{max}$) increased with increasing doses in the dose range of 0.03 to 3.6 mg. $AUC_{inf}$ increased in a slightly greater than dose-proportional manner ($P < .0001$), while $C_{max}$ did not deviate from dose-proportionality ($P < .3805$; Table 2).

RG7697 had no detectable effect on fasting plasma glucose and fasting plasma insulin in healthy participants. After ingestion of the standardized meal, glucose concentrations were not affected by RG7697 doses up to 0.6 mg (Figure 2A). There was, however, a decrease in maximum plasma concentration of glucose compared with baseline at doses of 1.8 mg (−25%) and 3.6 mg (−46%). Glucose $C_{max}$ was reduced by 30% in the single evaluable participant dosed at 5 mg. These reductions in glucose $C_{max}$ did not result in reductions for the overall glucose $AUC_{0\text{-}4h}$ (Figure 2B). Similarly, RG7697 doses up to 0.6 mg had no effect on insulin levels during the MTT, while higher doses decreased both $C_{max}$ and $AUC_{0\text{-}4h}$. Insulin $C_{max}$ decreased by 38% and 64% at doses of 1.8 and 3.6 mg, respectively

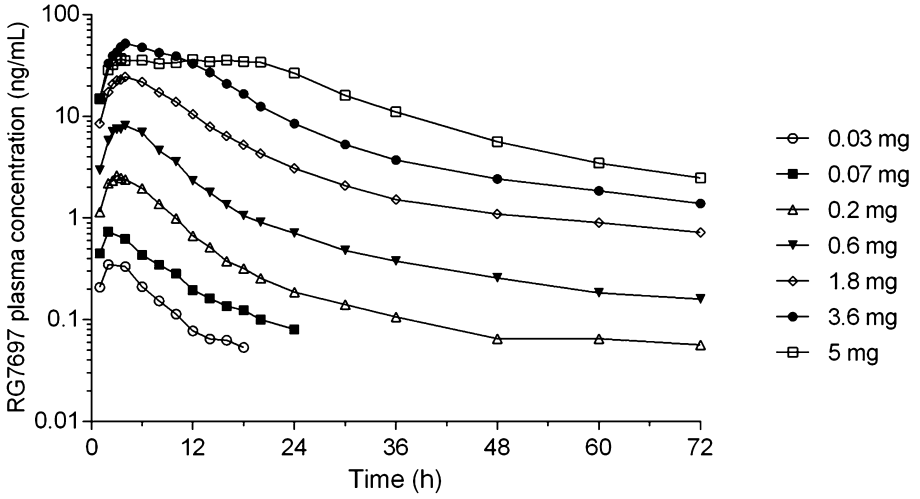


**FIGURE 1** Plasma concentration–time profiles of RG7697 after single s.c. administration (semi-log scale)

**TABLE 2** Summary of RG7697 pharmacokinetic parameters after single s.c. injections in healthy participants

| Variable[a] | 0.03 mg (n = 6) | 0.07 mg (n = 7) | 0.2 mg (n = 6) | 0.6 mg (n = 6) | 1.8 mg (n = 5) | 3.6 mg (n = 6) | 5 mg[b] (n = 2) |
|---|---|---|---|---|---|---|---|
| $C_{max}$, ng/mL | 0.353 (15.5) | 0.642 (74.9) | 2.49 (43.9) | 8.12 (17.7) | 24.3 (13.7) | 49.7 (42.9) | 38.0 / 47.1 |
| $t_{max}$, h | 3.00 (2.00-4.00) | 2.00 (2.00-400) | 2.82 (2.80-6.00) | 3.43 (2.82-4.02) | 4.00 (4.00-6.00) | 4.00 (4.00-6.00) | 3.42 / 20.0 |
| $AUC_{inf}$, ng h/mL | 3.10 (13.5) | 7.26 (32.0) | 28.0 (24.4) | 95.5 (7.87) | 353 (24.9) | 828 (35.4) | 1220 / 1240 |
| $t_{½β}$, h | 5.14 (22.6) | 7.38 (33.9) | 19.3 (24.9) | 23.2 (15.3) | 25.4 (10.2) | 19.9 (5.39) | 15.3 / 15.7 |
| CL/F, L/h | 9.66 (13.5) | 9.64 (32.0) | 7.15 (24.4) | 6.28 (7.87) | 5.10 (24.9) | 4.35 (35.4) | 4.04 / 4.10 |

Abbreviation: $AUC_{inf}$: area under the concentration-time curve extrapolated to infinity; CL/F: apparent total clearance after extravascular administration; $C_{max}$: maximum observed drug concentration; $t_{½β}$: apparent terminal half-life; $t_{max}$: time to maximum drug concentration.

[a] Median (range) for $t_{max}$, geometric mean (coefficient of variation %) for all other variables.

[b] Individual values.

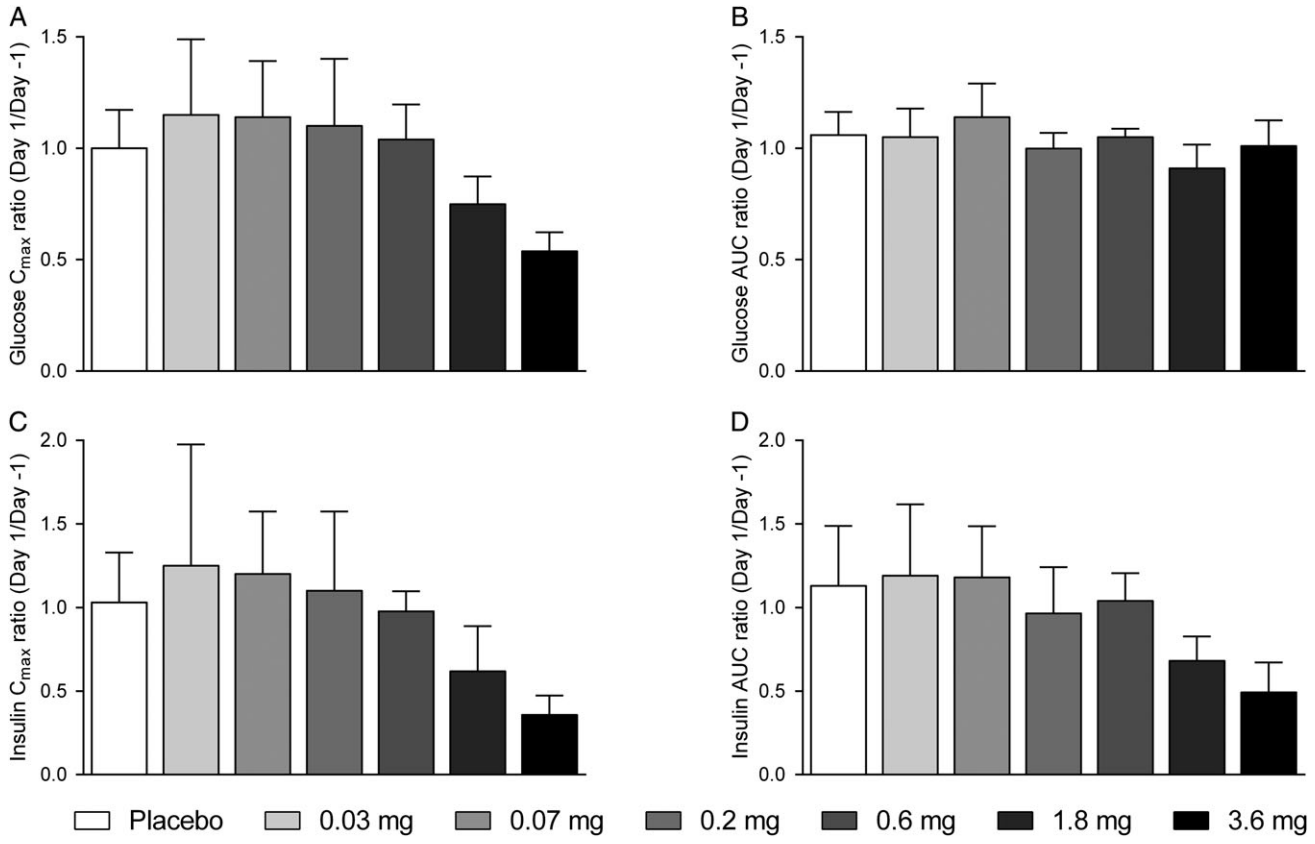


**FIGURE 2** Effect of RG7697 on glucose and insulin levels after a standardized MTT. A, Glucose $C_{max}$ ratio (day 1/day −1); B, glucose $AUC_{0\text{-}4h}$ ratio; C, insulin $C_{max}$ ratio; D, insulin $AUC_{0\text{-}4h}$ ratio. Data are represented as geometric mean (+ geometric s.d.)

(Figure 2C). This was accompanied by a corresponding decrease in insulin $AUC_{0\text{-}4h}$ of 32% and 51%, respectively (Figure 2D). Insulin $C_{max}$ and $AUC_{0\text{-}4h}$ decreased by 61% and 24%, respectively, in the participants dosed with 5 mg. In line with the effect on insulin, a reduction in C-peptide exposure was also observed (not shown). In contrast, RG7697 had no detectable effect on plasma glucagon levels, even at the highest doses (not shown).

RG7697 average concentrations during MTT were linked to glucose and insulin $C_{max}$ ratios using an inhibitory $E_{max}$ model (Figure 3). The same model also adequately described the relationship between RG7697 average concentrations and insulin $AUC_{0\text{-}4h}$ ratio (not shown). All three glycaemic measurements correlated well with RG7697 average concentrations. The average concentration required to reduce by 50% ($IC_{50}$) glucose $C_{max}$, insulin $C_{max}$ and $AUC_{0\text{-}4h}$ after the MTT, similarly, ranged between 25 and 50 ng/mL (Table 3).

Subcutaneous administration of RG7697 at single doses up to 3.6 mg was generally well tolerated in healthy participants. The incidence of AEs was higher among RG7697-treated participants (39%) than placebo-treated participants (8%). The majority of AEs were of mild intensity, with AEs of moderate or severe intensity reported for participants in the two highest dose groups. The most commonly reported AEs were nausea, vomiting, dizziness and vasovagal episode. Most of the AEs reported during the study were of gastrointestinal origin. These gastrointestinal AEs have been observed at almost all dose levels including placebo. Frequency of nausea increased with doses (Table 4). Two SAEs of nausea and vomiting occurred in one participant dosed with 5 mg of RG7697 and were considered drug-related by the investigator. Another SAE of acute appendicitis (not drug-related) occurred between discharge and follow-up examination in a participant dosed with 3.6 mg of RG7697. No AEs of

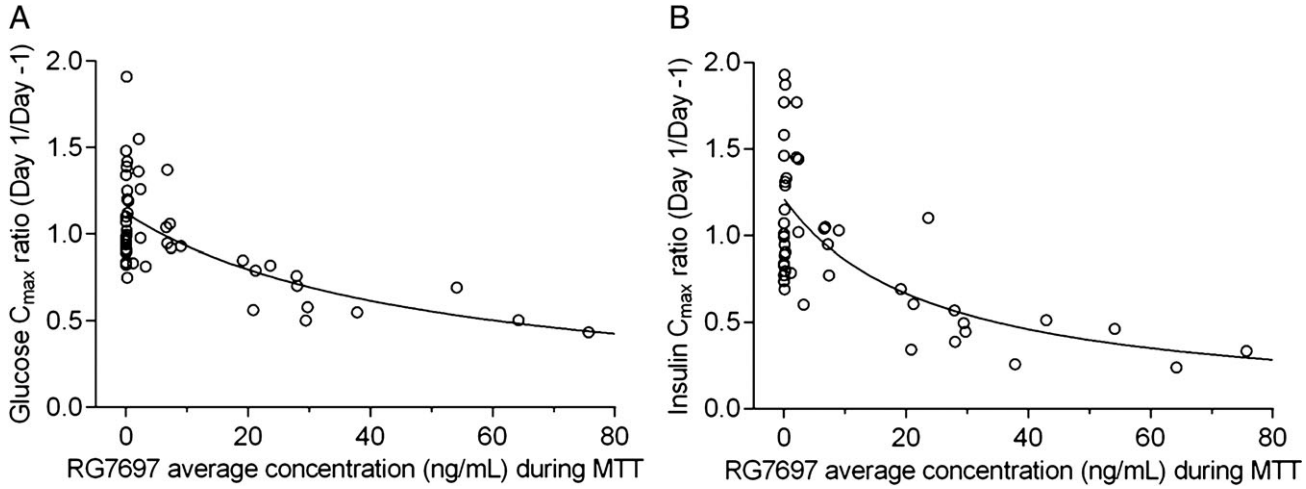


**FIGURE 3** Relationship between $C_{max}$ ratios (day 1/day −1) of glucose (A) and insulin (B) after a standardized MTT and average RG7697 concentration during the MTT on day 1

**TABLE 3** Pharmacokinetic/pharmacodynamic parameter estimates

| | Glucose $C_{max}$ ratio | | Insulin $C_{max}$ ratio | | Insulin $AUC_{0\text{-}4h}$ ratio | |
|---|---|---|---|---|---|---|
| **Variable** | **Estimates** | **RSE (%)** | **Estimates** | **RSE (%)** | **Estimates** | **RSE (%)** |
| $E_0$ (−) | 1.12 | 3.65 | 1.21 | 6.22 | 1.19 | 4.8 |
| $IC_{50}$, ng/mL | 49.0 | 27.1 | 24.5 | 39.5 | 35.0 | 11.5 |

Abbreviations: $E_0$, baseline effect; $IC_{50}$, RG7697 average concentration during MTT causing half of the maximum effect; RSE, relative standard error.

**TABLE 4** Adverse event summary

| | Placebo (n = 13) | 0.03 mg (n = 6) | 0.07 mg (n = 7) | 0.2 mg (n = 6) | 0.6 mg (n = 6) | 1.8 mg (n = 5) | 3.6 mg (n = 6) | 5 mg (n = 2) | All RG7697 (n = 38) |
|---|---|---|---|---|---|---|---|---|---|
| Participants with any AE, n (%) | 1 (8) | 3 (50) | 3 (43) | 1 (17) | 1 (17) | 1 (20) | 4 (67) | 2 (100) | 15 (39) |
| Participants with following AE, n (%) | | | | | | | | | |
| Nausea | 1 (8) | 1 (17) | 1 (14) | 1 (17) | – | 1 (20) | 2 (33) | 2 (100) | 8 (21) |
| Vomiting | – | 1 (17) | – | – | – | – | – | 1 (50) | 2 (5) |
| Dizziness | 1 (8) | – | – | – | 1 (17) | – | 1 (17) | – | 2 (5) |
| Vasovagal episode | – | 1 (17) | – | – | – | – | 1 (17) | – | 2 (5) |

AEs reported in ≥2 participants.

hypoglycaemia were reported. Overall, no clinically relevant changes in vital signs, laboratory variables, or ECGs were reported; however, an increase in heart rate was observed with doses of ≥1.8 mg. At the highest doses tested (3.6 and 5 mg), pulse rate was increased by ~6 to 20 beats/min compared with placebo. No changes with treatment in capillary blood glucose were observed. No injection site reactions were reported. All participants tested negative for treatment-emergent anti-RG7697 antibodies.

## 4 | DISCUSSION

In this first-in-humans study, RG7697 was administered to healthy volunteers in single ascending s.c. doses ranging from 0.03 to 5 mg. Its pharmacodynamics, pharmacokinetics, general safety, local tolerability and immunogenicity were investigated.

RG7697 pharmacokinetics were characterized by rapid s.c. absorption ($t_{max}$ ~ 2 to 4 hours), relatively long elimination ($t_{½\beta}$ 19.3 to 25.4 hours), and minor non-linearity (over-proportionality in $AUC_{inf}$). The flat pharmacokinetic profile observed at the highest dose (5 mg) may indicate saturation of absorption. Moderate to high inter-participant variability was seen in exposure variables ($AUC_{inf}$ and $C_{max}$). Pharmacokinetic characteristics of RG7697 support once daily dosing in subsequent clinical studies.

RG7697 showed a dose-dependent reduction of glucose concentrations after the ingestion of a test meal. At doses ≥1.8 mg, RG7697 reduced glucose $C_{max}$ (up to −46%) and delayed $t_{max}$ without affecting the overall exposure to glucose. The effect on plasma glucose was accompanied by a reduction of exposure to insulin (up to −64% for $C_{max}$ and −51% for AUC). A dual agonist, such as endogenous GIP and GLP-1, would be expected to stimulate insulin secretion in a glucose-dependent manner, as previously observed in a graded glucose infusion assay with RG7697 in monkeys and with a PEGylated dual GIP/GLP-1 agonist in healthy subjects.[17] Although not investigated in the present study, it cannot be excluded that delay of gastric emptying occurred with high doses of RG7697, which would have

slowed glucose absorption after test meal ingestion and consequently decreased insulin requirement. The dose-dependent reduction of insulin during MTT may also reflect a unique feature in the mechanism of action of dual agonists, consistent with previously reported observations when studied in rodents and non-human primates.[17] This would need to be further investigated in patient trials. Overall, the pharmacological effects of RG7697 on glucose and insulin were dose- and concentration-dependent, with an $IC_{50}$ of the same order (25-50 ng/mL). This provides direction to the plasma concentration to target in patients.

RG7697 doses up to 3.6 mg were generally safe and well tolerated in healthy participants. Tolerability was limited at high doses by gastrointestinal-related AEs. While the proportion of participants with nausea, the most commonly reported AE in this study, was overall similar to that of placebo (8%) for the dose groups up to 1.8 mg (0%-20%), it increased with higher doses. One third of participants (2/6) dosed with 3.6 mg and both participants (2/2) dosed with 5 mg experienced nausea. For doses up to 1.8 mg, all nausea events were mild in intensity and of short duration. Intensity and duration of nausea increased thereafter with the highest dose. Dose escalation was *de facto* stopped after 1 participant experienced a drug-related SAE of nausea and vomiting. The maximum dose of 5 mg was determined to be not tolerated and was not further evaluated. Gastrointestinal side effects, including nausea, vomiting and diarrhoea, are commonly reported after initiation of therapy with GLP-1 receptor agonists.[18] They have also been reported to be dose-dependent, transient and mitigated by slow dose escalation.[19] The present finding of gastrointestinal AEs occurring with high doses of RG7697 is consistent with the GLP-1 agonism of the compound. The risk of hypoglycaemia is expected to be low with RG7697 as insulinotropic activity of both GLP-1 and GIP is glucose-dependent.[6] Consistent with its mechanism of action, no AEs of hypoglycaemia were reported. Additionally, no changes in capillary blood glucose measurements were observed.

An increase in heart rate was observed for doses ≥1.8 mg. Although similar increases in heart rate have been reported with GLP-1 agonists in studies with similar conditions of intensive heart monitoring,[20,21] additional data in a larger number of participants are needed to evaluate the clinical effect of RG7697 on heart rate.

The present study showed that RG7697, a dual GIP/GLP-1 analogue, is safe and well tolerated after the administration of single s.c. injections up to 3.6 mg in healthy participants. RG7697 lowered plasma glucose and decreased insulin requirement in response to an MTT in a dose-dependent manner. In addition, its elimination half-life supports a once-daily dosing regimen. Together, these data suggest that RG7967 should provide good glycaemic control as a once-daily therapy for the treatment of T2D.

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## Conflict of interest

This study was sponsored by Roche. A. P., S. J., N. S. and C. S. are employees of Roche. R. D. M. is an employee of Novo Nordisk. The authors report no other conflicts of interest in this work.

## Author contributions

C. S. designed the study. A. P., C. S., N. S. analysed the data. A. P. wrote the manuscript. A. P., C. S., N. S., S. J., R. D. M. contributed to interpretation of the data and critical revision of the manuscript.

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## SUPPORTING INFORMATION

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