# A Phase 1, Double-Blind, Placebo-Controlled Multiple Escalating Dose Study of RGT-075, a Novel Small-Molecule Oral GLP-1 Receptor Agonist in Adults with Type 2 Diabetes

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## SUMMARY

**Background:** RGT-075 is a small-molecule oral GLP-1 receptor agonist (GLP1RA) in clinical development for the treatment of type 2 diabetes (T2DM). Results from a phase 1 RGT-075 single-ascending dose study in healthy adults are presented in poster number 724-P in category 12-C Clinical Therapeutics/New Technology—Incretin-Based Therapies.[1] Here we present results from a phase 1, randomized, double-blind, placebo-controlled, multiple-ascending dose inpatient study in adults with T2DM (baseline HbA1c 6-10.5% and concomitant metformin ≥ 500 mg/d). RGT-075 or matching placebo (6 active/2 placebo per cohort) was administered for up to 28 days using an adaptive study design that permitted dose and titration adjustments between cohorts (see Figure 1). Assessments included safety (primary), PK (secondary), and exploratory efficacy variables including changes from baseline in HbA1c, fasting plasma glucose (FPG), continuous glucose monitoring time in range (CGM-TIR), body weight (BW) and mixed-meal tolerance test (MMTT) biomarkers.

**Results:** A total of 36 patients (56%F/44%M; mean age 55yF/61yM) were enrolled into 4 cohorts. [Starting Dose]→[Titration Duration]→[Target Dose] varied by Cohort as follows: Cohort 1 [60 mg][no titration][60 mg]; Cohort 2 [30 mg][9 d][120 mg]; Cohort 3 [15 mg][20 d][180 mg]; Cohort 4 [15 mg][14d][45 mg].

Safety: Treatment emergent adverse events (TEAEs) were reported by most subjects (100% C1 + C2; 88% C3; 83% C4; 78% pooled placebo) and incidence trended downward with lower starting doses and increased titration duration. TEAEs were predominantly GI-related and of mild severity; no serious AEs or deaths were reported; 3 subjects discontinued due to a TEAE. PK: RGT-075 plasma exposures increased as the dose levels increased. Exploratory Efficacy: baseline HbA1c was highly variable (7.2-9.0%); HbA1c mean changes from baseline up to 28 days ranged -0.6 to -1.2% with RGT-075 treatment compared with -0.37% with placebo. FPG, CGM-TIR changes from baseline correlated with HbA1c results. BW mean changes from baseline ranged -2.3 to -4.5 kg with RGT-075 treatment compared with -1.1 kg with placebo. MMTT results are presented.

**Conclusions:** Treatment with QD oral RGT-075 GLP1RA (15-180 mg/day) up to 28 days revealed a safety profile consistent with the GLP1RA peptide class and promising exploratory efficacy result trends despite high baseline variability and short treatment duration. RGT-075 plasma exposures increased as the dose levels increased. These results support advancement to phase 2 clinical development.

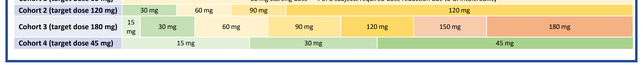
## STUDY DESIGN

- The study consisted of 4 cohorts (planned 6 active/2 placebo per cohort); a total of 36 subjects (56%F/44%M; mean age 55yF/61yM) were randomized to RGT-075 or placebo treatment for up to 28 days.
- An adaptive study design was planned to permit adjustments to starting dose and titration as needed during the study. A Safety Monitoring Committee reviewed all blinded aggregate safety and PK data after each cohort and adjusted dose designs between cohorts based on cumulative review of tolerability after each cohort was completed.
- Generally, as the study progressed the starting dose was decreased, and titration extended. See below Figure 1 for final dosing by cohort.

**Key Study Endpoints:**
1. Safety (primary): TEAEs, laboratories, vital signs, ECG
2. PK (secondary): AUC, $C_{max}$, $T_{max}$, $t_{1/2}$, accumulation ratios, and urinary excretion
3. Exploratory Efficacy: HbA1c, FPG, CGM-TIR, BW, MMTT

**Key Eligibility Criteria at Screening:**
1. Adult with T2DM diagnosed ≥ 180 days; metformin ≥ 500 mg/day for at least 60 days; washout of oral anti-DM drugs was permitted between Screening and Randomization (at least 14 days); baseline HbA1c 6-10.5% inclusive at randomization.
2. BMI 25-45.4 kg/m2 inclusive; total BW<50 kg; stable BW (<5% change) in last 90 days prior to screening.
3. No history of malignancy not considered cured, GI surgery, CVD, current or recent tobacco use, substance abuse, etc.
4. Normal baseline labs, vital signs, and ECG intervals for age and sex.
5. Subjects without GLP-1RA treatment within the past 6 months prior to screening.
6. No self-report history of hypoglycemia requiring assistance or acute T2DM complications in last 6 months.
7. No personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2.
8. No history of clinically significant liver disease, acute or chronic renal disease.

### Figure 1 Study dosing by cohort




## RESULTS

### Disposition

- Thirty-one of 36 (86%) subjects completed the study.
- Subjects were not stratified by BW at baseline; mean BW trended higher for Cohort 3 (C3) and C4 compared with C1, C2, and pooled placebo.

### Table 1 Demographics and Baseline Characteristics by Cohort

| Characteristics | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| **Age at consent (years),** Mean (SD) | 61.0 (7.01) | 58.9 (6.84) | 55.0 (7.78) | 57.8 (6.88) | 55.9 (8.62) |
| **Sex,** n(%), Female | 5 (83%) | 3 (43%) | 4 (50%) | 3 (50%) | 5 (56%) |
| **Ethnicity,** n(%), Hispanic or Latino | 4 (67%) | 5 (71%) | 5 (63%) | 6 (100%) | 7 (78%) |
| **Race**[1], n(%) | | | | | |
| Asian | 1 (17%) | 1 (14%) | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 3 (38%) | 0 | 0 |
| White | 4 (67%) | 6 (86%) | 5 (63%) | 5 (83%) | 8 (89%) |
| Other | 2 (33%) | 0 | 0 | 1 (17%) | 1 (11%) |
| **Weight (kg),** Mean (SD) | 82.37 (12.12) | 88.80 (11.28) | 95.61 (19.63) | 100.60 (22.61) | 85.48 (12.22) |
| **Height (cm),** Mean (SD) | 155.13 (4.82) | 167.60 (11.22) | 166.95 (8.27) | 165.52 (11.20) | 162.29 (8.21) |
| **BMI (kg/m²),** Mean (SD) | 34.27 (5.10) | 31.79 (4.78) | 34.15 (5.52) | 36.60 (6.72) | 32.42 (3.83) |

SD, standard deviation; BMI, body mass index.
1. Patients were counted in more than one race category if multiple races were selected.

### Safety

- There were no reported serious adverse events (SAEs) or deaths.
- TEAEs leading to study discontinuation occurred in 4 subjects and 1 subject discontinued due to a worsening AE that started before first dose of the investigational product.
- The majority of TEAEs were mild or moderate (Grade 1 or 2).
- Most TEAEs were related to study treatment for subjects receiving RGT-075.

### Table 2 Overall Summary of Treatment-Emergent Adverse Events

| TEAE Category, Patients (%) | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| **Any TEAE** | 6 (100%) | 7 (100%) | 7 (88%) | 5 (83%) | 7 (78%) |
| Any Grade 1 TEAE[1] | 4 (67%) | 7 (100%) | 7 (88%) | 5 (83%) | 7 (78%) |
| Any Grade 2 TEAE[1] | 4 (67%) | 1 (14%) | 3 (38%) | 2 (33%) | 3 (33%) |
| Any Grade 3 TEAE[1] | 0 | 1 (14%) | 0 | 0 | 1 (11%) |
| Any Grade 4 TEAE[1] | 0 | 0 | 0 | 0 | 0 |
| Any Serious TEAE | 0 | 0 | 0 | 0 | 0 |
| **Any TEAE Related to Study Drug** | 6 (100%) | 7 (100%) | 7 (88%) | 5 (83%) | 4 (44%) |
| **Any TEAE Leading to Study Discontinuation** | 1 (17%) | 3 (43%) | 1 (13%) | 0 | 0 |

TEAE, treatment-emergent adverse event.
1. Grade 1 = mild severity, did not interfere with daily activity; Grade 2 = moderate severity, interfered with daily activity; Grade 3= severe, prevents daily activity and/or requires significant medical intervention; Grade 4 = a potentially life-threatening or fatal event.

- The most frequently reported TEAEs included GI disorders (nausea, diarrhea, and vomiting), metabolism and nutrition disorders (decreased appetite), and nervous system disorders (headache); TEAE incidence may have trended downward with lower starting dose and extended titration in the later cohorts.
- No hypoglycemia TEAEs were reported.
- Changes in other clinical laboratory evaluations, vital signs, ECG, and physical examination were clinically unremarkable and similar between treatment groups.

### Table 3 TEAEs by System Organ Class

| System Organ Class, n (%) | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| Subjects with at least one TEAE | 6 (100%) | 7 (100%) | 7 (88%) | 5 (83%) | 7 (78%) |
| Gastrointestinal disorders | 6 (100%) | 7 (100%) | 7 (88%) | 5 (83%) | 5 (56%) |
| Metabolism and nutrition disorders | 1 (17%) | 4 (57%) | 4 (50%) | 4 (67%) | 1 (11%) |
| Nervous system disorders | 3 (50%) | 4 (57%) | 2 (25%) | 2 (33%) | 2 (22%) |
| General disorders and administration site conditions | 1 (17%) | 2 (29%) | 2 (25%) | 2 (33%) | 2 (22%) |
| Musculoskeletal and connective tissue disorders | 1 (17%) | 1 (14%) | 1 (13%) | 1 (17%) | 3 (33%) |
| Skin and subcutaneous tissue disorders | 0 | 0 | 2 (25%) | 0 | 2 (22%) |
| Infections and infestations | 1 (17%) | 0 | 1 (13%) | 0 | 1 (11%) |
| Renal and urinary disorders | 0 | 0 | 2 (25%) | 0 | 1 (11%) |
| Blood and lymphatic system disorders | 0 | 0 | 0 | 1 (17%) | 1 (11%) |
| Investigations | 0 | 1 (14%) | 1 (13%) | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 1 (17%) | 0 | 0 | 0 | 1 (11%) |
| Vascular disorders | 0 | 1 (14%) | 0 | 0 | 1 (11%) |
| Psychiatric disorders | 0 | 1 (14%) | 0 | 0 | 0 |

## RESULTS

### Exploratory Efficacy: HbA1c, FPG, BW

- Mean baseline values for HbA1c, FPG, and BW were variable between the cohorts and pooled placebo group.
- RGT-075 QD dosing showed promising exploratory efficacy trends despite high baseline variability and short treatment duration in mean changes for FPG, HbA1c, and BW.

### Table 4 HbA1c, FPG, and BW Results by Treatment

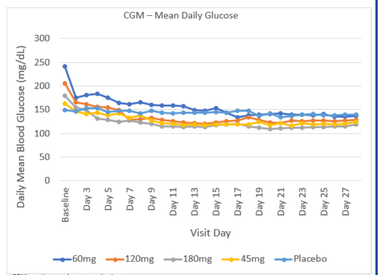
| | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| **HbA1c** | | | | | |
| Baseline[1] | 9.02 (0.97)[e] | 7.74 (0.76)[e] | 7.62 (1.25)[f] | 7.27 (1.04) | 7.16 (0.76) |
| Change from Baseline to Day 28 | -1.22 (0.41)[e] | -0.84 (0.48)[e] | -0.85 (0.43)[f] | -0.63 (0.22) | -0.37 (0.28) |
| **HbA1c Subgroup – Baseline < 8.0%** | | | | | |
| Baseline | 7.50[a] | 7.23 (0.40)[c] | 7.18 (0.73)[e] | 6.68 (0.57)[d] | 7.00 (0.65)[g] |
| Change from Baseline to Day 28 | -0.90[a] | -0.50 (0.17)[c] | -0.70 (0.26)[e] | -0.58 (0.22)[d] | -0.34 (0.29)[g] |
| **HbA1c Subgroup – Baseline ≥ 8.0%** | | | | | |
| Baseline | 9.40 (0.53)[d] | 8.50 (0.28)[b] | 9.80[a] | 8.45 (0.50)[b] | 8.40[a] |
| Change from Baseline to Day 28 | -1.30 (0.42)[d] | -1.35 (0.07)[b] | -1.60[a] | -0.75 (0.21)[b] | -0.60[a] |
| **FPG (mg/dL)** | | | | | |
| Baseline | 190.0 (30.91)[f] | 150.0 (33.04) | 157.3 (44.59) | 147.7 (38.56) | 122.5 (23.73) |
| Change from Baseline to Day 28 | -82.6 (31.03)[e] | -49.2 (41.08)[e] | -57.9 (35.13)[f] | -42.0 (18.12) | -10.7 (23.98) |
| **Body Weight (kg)** | | | | | |
| Baseline | 82.37 (12.12) | 88.80 (11.28) | 95.61 (19.63) | 100.60 (22.61) | 85.48 (12.22) |
| Change from Baseline to Day 28 | -2.32 (1.12)[e] | -4.54 (0.96)[e] | -4.13 (2.34)[f] | -3.18 (2.24) | -1.11 (1.21) |

HbA1c, hemoglobin A1c; FPG, fasting plasma glucose.
Data are shown as Mean (SD). [a]n=1, [b]n=2, [c]n=3, [d]n=4, [e]n=5, [f]n=6, [g]n=8.
1. Baseline was defined as the last non-missing value collected prior to or on the treatment start date and time, if applicable.

### Exploratory Efficacy: Continuous Glucose Monitoring

- CGM mean daily blood glucose decreased, and TIR increased over time for all RGT-075 treatment groups relative to pooled placebo.

### Figure 2 Daily Mean Blood Glucose (mg/dL) Results




CGM, continuous glucose monitoring.

### Table 5 Time in Range 70-180 mg/dL[1] (%) Results and Change from Baseline to Day 28

| | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| Baseline[2] | 12.50 (13.69) | 41.67 (39.97) | 56.25 (36.80) | 69.44 (25.78) | 77.24 (20.12) |
| Change from Baseline to Day 28 | 87.60 (12.11)[a] | 60.27 (39.01)[a] | 36.80 (28.69)[b] | 27.43 (21.26) | 9.66 (24.57) |

Data are shown as Mean (SD). [a]n=5, [b]n=6.
1. Time in range was calculated as (number of blood glucose measurements 70-180 mg/dL within a day/number of intervals collected) × 100.
2. Baseline was defined as the last 24-hour period prior to first dose.

## RESULTS

### Exploratory Efficacy: MMTT

- MMTT mean clinical chemistry values and change from baseline to Day 28 (240 minutes) by treatment are summarized below.
- Changes reflect improvement in metabolic parameters consistent with GLP1RA activity and the observed changes in FPG, HbA1c, and CGM TIR results with RGT-075 treatment (all groups) compared with placebo.

### Table 6 MMTT Area Under the Concentration Curve Results and Change from Baseline to Day 28

| | Cohort 1 RGT-075 60 mg (N=6) | Cohort 2 RGT-075 120 mg (N=7) | Cohort 3 RGT-075 180 mg (N=8) | Cohort 4 RGT-075 45 mg (N=6) | Placebo (All Cohorts) (N=9) |
|---|---|---|---|---|---|
| **Glucose (mg hr/dL)** | | | | | |
| Baseline | 1076.57 (198.38) | 914.31 (198.82)[d] | 874.52 (207.76)[d] | 747.08 (241.84) | 774.48 (162.28) |
| **Change from Baseline to Day 28** | **-599.10 (219.69)[c]** | **-466.76 (236.48)[c]** | **-450.39 (232.06)[d]** | **-256.79 (134.40)[b]** | **-81.48 (125.03)** |
| **C-Peptide (ng hr/mL)** | | | | | |
| Baseline | 30.97 (8.14) | 29.97 (7.63)[d] | 31.89 (4.19)[d] | 42.08 (16.02)[d] | 42.51 (19.69) |
| **Change from Baseline to Day 28** | **-4.75 (5.12)[c]** | **-14.12 (3.28)[c]** | **-6.77 (11.42)[d]** | **-12.94 (16.32)[b]** | **-3.23 (10.74)** |
| **GLP-1 Active (pg hr/mL)** | | | | | |
| Baseline | 35.09 (16.10) | 44.87 (33.07)[d] | 30.22 (25.70)[d] | 30.63 (21.08) | 27.82 (18.80)[e] |
| **Change from Baseline to Day 28** | **-19.94 (20.94)[c]** | **-19.64 (29.16)[c]** | **-19.33 (25.40)[d]** | **-6.64 (8.88)[b]** | **2.59 (17.34)[e]** |
| **GIP Total (pmol hr/L)** | | | | | |
| Baseline | 241.10 (49.84) | 228.02 (56.26) | 197.88 (59.61)[d] | 285.51 (107.52) | 211.93 (92.24)[e] |
| **Change from Baseline to Day 28** | **-79.14 (41.16)[c]** | **-114.80 (93.18)[c]** | **-53.38 (116.51)[d]** | **-110.81 (35.36)[b]** | **-35.51 (59.65)[e]** |
| **Glucagon (pmol hr/L)** | | | | | |
| Baseline | 63.21 (20.53) | 72.21(21.49)[b] | 111.38 (58.10)[d] | 82.20 (51.51) | 61.70 (23.52)[e] |
| **Change from Baseline to Day 28** | **-44.98 (12.04)[c]** | **-34.74 (15.11)[a]** | **-71.49 (53.14)[d]** | **-27.03 (28.69)[b]** | **-3.43 (18.14)[e]** |

GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory peptide.
Data are shown as Mean (SD). [a]n=3, [b]n=4, [c]n=5, [d]n=6, [e]n=8.

### Pharmacokinetics

- All the subjects showed exposures of RGT-075 after single or multiples doses of RGT-075 from 15 to 180 mg, with $t_{max}$ between 1.0 to 4.0 hours.
- The $t_{1/2}$ ranged from 6.2 to 10.0 hours.
- Dose proportionality for $C_{max}$ and AUC were observed on Day 1 and Day 1 of target dose from 15 to 180 mg, but these parameters were less than dose-proportional on day 28.
- No significant accumulations for RGT-075 exposures were observed after multiple doses.
- The apparent clearance (CL/F) suggested RGT-075 is a low clearance drug, with a very minimal amount (<0.01%) excreted through urine.

## CONCLUSIONS

- **RGT-075 administered up to 180 mg/day including titration for up to 28 days was safe in adult subjects with T2DM receiving concomitant metformin.**
- **Despite high baseline variability and relatively short treatment duration, promising exploratory efficacy trends were observed with once-daily oral RGT-075 treatment compared with placebo and reflect improvement in metabolic parameters consistent with GLP1RA activity.**
- **No significant accumulations for RGT-075 exposures after multiple doses were observed.**
- **A phase 2 study of RGT-075 in adults with T2DM is currently open and recruiting patients.**

### References

1. Pirner M; Lin J; Liu F; et al. A First-in-Human Study of RGT-075, a Novel, Orally Bioavailable, Small-Molecule GLP-1 Receptor Agonist, in Healthy Adult Subjects. *ADA*, 2022, 724-P in category 12-C Clinical Therapeutics/New Technology—Incretin-Based Therapies.