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The methionine aminopeptidase 2 inhibitor ZGN-1061 improves glucose control and weight in overweight and obese individuals with type 2 diabetes: a randomized placebo-controlled trial.

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ABSTRACT

The methionine aminopeptidase 2 (MetAP2) inhibitor ZGN-1061 lowered weight and improved glucose in preclinical studies. We sought to determine its efficacy and safety by performing a multi-center Phase 2 randomized controlled trial involving overweight and obese adults with type 2 diabetes and HbA1c between 7 and 11% inclusive. Participants were randomized to receive subcutaneous treatment with placebo or 0.05mg, 0.3mg, 0.9mg or 1.8mg ZGN-1061 every 3rd day for 12 weeks. The primary outcome was Δ HbA1c at week 12. Relative to placebo, the 0.9mg and 1.8mg doses induced clinically meaningful reductions in HbA1c of 0.6% (95% CI 0.2 to 0.9; $p=0.0006$) and 1.0% (95% CI 0.6 to 1.4; $p<0.0001$) respectively. The 1.8mg dose also induced weight loss of 2.2% (95% CI 1.1 to 3.3; $p=0.0002$). The incidence of adverse events was balanced across the treatment groups. We conclude that MetAP2 inhibition with ZGN-1061 for 12 weeks improved glucose control and aided weight loss in overweight and obese people with type 2 diabetes. However, given safety issues, Zafgen has discontinued MetAP2 inhibitor development.

Registration

NCT03254368

Keywords

MetAP2, Methionine aminopeptidase 2 inhibitor, Obesity, Phase 2 clinical trial, Randomized controlled trial, Type 2 Diabetes, ZGN-1061.

INTRODUCTION

Methionine aminopeptidase 2 (MetAP2) inhibitors were developed by Zafgen to treat obesity and related metabolic diseases (1, 2). Beloranib was the first MetAP2 inhibitor to be trialled in people with obesity and diabetes (3, 4). It induced weight loss and improved glucose control, but also caused deep vein thrombosis. Zafgen then developed ZGN-1061, a second generation MetAP2 inhibitor that had a shorter half-life than beloranib and other different properties (5), which at the time were thought to contribute to the thrombotic risk of beloranib. Phase I testing of ZGN-1061 identified no safety concerns or thrombotic tendency in healthy volunteers who received single (0.2mg to 4.8mg) or multiple ascending (0.2mg to 1.8mg twice weekly) doses for up to 4 weeks (6). We now report outcomes of a Phase II clinical trial of ZGN-1061 in overweight and obese people with type 2 diabetes.

METHODS

This Phase 2 double-blind placebo-controlled randomized trial was sponsored by Zafgen (NCT03254368) and conducted in 22 sites in Australia and New Zealand. The trial was approved by the relevant human research ethics committee. All participants provided written informed consent.

Recruitment occurred in two phases. The first cohort (September 2017 to May 2018), was treated with placebo, 0.05mg, 0.3mg or 0.9mg ZGN-1061. After interim analysis indicated efficacy at the 0.9mg dose, a second cohort was recruited between June 2018 and February 2019. These participants were treated with placebo, 0.9mg or 1.8mg ZGN-1061.

Inclusion criteria were: Men and women aged 18 to 65 years; type 2 diabetes; HbA1c 7% to 11%; treatment with diet or any number of glucose-lowering medications other than insulin that had been stable over the preceding 6 months; body mass index $>27\text{kg/m}^2$. Exclusion criteria were: type 1 diabetes; significant hypoglycemia in the previous 6 months; bariatric surgery within the previous year; major surgery in the previous 6 months or planned to occur during the trial; risk of venous thrombosis based on clinical history, screening leg vein ultrasound or elevated plasma D-dimer; systolic or diastolic blood pressure greater than 160mmHg or 100mmHg respectively; psychiatric disorder associated with risk of suicide; prior alcohol abuse or illicit drug use; pregnancy, breast feeding or desire for pregnancy during the study; other comorbidity considered to pose a safety risk.

Eligible participants commenced a single-blind 2-week lead-in phase during which they self-administered 4 doses of placebo s/c every 3 days. If after review of treatment diaries and returned placebo vials adherence was confirmed, participants were randomized, stratified by HbA1c ($<8.5\%$, $\geq 8.5\%$), using a web-based tool (Endpoint Clinical, San Francisco, CA, USA). Cohort 1 (N=129) was randomized to placebo, 0.05mg, 0.3mg and 0.9mg doses in a 1:1:1:1 ratio. Cohort 2 (N=46) was randomized to placebo, 0.9 and 1.8mg in a 1:1:2 ratio.

During the 12-week treatment phase, participants self-administered study drug every 3 days and were assessed every 2 weeks. HbA1c and other biochemistry were performed every 4 weeks and lower limb venous ultrasound was performed at week 12. Participants were required to continue constant doses of their usual diabetes, lipid and blood pressure medication. The study protocol required intensification of glucose-lowering therapy if HbA1c increased by 1% or exceeded 11.5%.

Sonic Clinical Trials (Sydney, NSW, Australia) performed laboratory tests, BioClinica (Audubon, PA, USA) managed study data and Pharmapace (San Diego, CA, USA) performed statistical analyses.

The primary outcome was change in HbA1c from week 0 to week 12. Key secondary endpoints included adverse events, weight, lipid profile and plasma concentrations of leptin, adiponectin and D-dimer.

The primary efficacy analysis was conducted using combined data for both study cohorts, representing 175 randomized participants who received at least one dose of study drug. Treatment groups were compared using a mixed effects model for repeated measures, which included treatment group, HbA1c stratum ($<8.5\%$, $\geq 8.5\%$), visit week and treatment-by-visit interaction as fixed effects, baseline HbA1c as a covariate, and subject as a random effect. Each comparison of placebo to the 4 different ZGN-1061 doses was not adjusted for multiple comparisons.

The sample size of 30/arm for the first cohort was expected to provide 90% power to detect a difference of 1.0 HbA1c percentage units between the 0.9mg ZGN-1061 group and placebo, based on a 2-sided, 2-sample comparison of means at the 5% significance level and assuming a SD of 1.0 and a withdrawal rate of 15%. In the second cohort, 10, 10 and 20

participants in the placebo, 0.9mg and 1.8mg groups respectively were expected to provide 90% power to detect a difference of 0.8 between the combined placebo groups from both cohorts and the 1.8mg group based on a SD of 0.8 and otherwise identical assumptions.

RESULTS

Of 188 participants enrolled, 175 completed the placebo run-in phase and were randomized to treatment with subcutaneous injections of ZGN-1061 (0.05mg, 0.3mg, 0.9mg or 1.8mg doses) or placebo every 3 days for 12 weeks. Their baseline characteristics are presented in Table 1. The mean $\pm$ SD age, weight, BMI, HbA1c and disease duration of the study population were 54 $\pm$ 8 years, 107 $\pm$ 21kg, 37 $\pm$ 7kg/m², 8.6 $\pm$ 1.1% and 8 $\pm$ 6 years respectively, and 48% were men. The rate of adherence to study drug was $\geq$ 90% in all groups. During the 12-week treatment phase, 2, 2, 1, 2 and 3 participants in the 0.05mg, 0.3mg, 0.9mg, 1.8mg and placebo groups, respectively, increased their glucose-lowering medication. Six participants (0, 1, 2, 2 and 1 from each of the aforementioned treatment groups, respectively) withdrew from the study before week 12 for personal reasons including family illness and unwillingness to travel to study sites. A participant from the 0.05mg group was withdrawn by the sponsor due to prolonged overseas travel during the study, and 2 participants from the 1.8mg group were withdrawn by their investigator because they were either unreliable or commenced a low-calorie diet in preparation for bariatric surgery.

The change in HbA1c at 8 and 12 weeks for the 0.9mg and 1.8mg groups differed significantly from the corresponding values for the placebo group (Figure 1A). Both of these doses met the primary outcome. At week 12, relative to placebo, HbA1c decreased 0.6% (95% CI 0.2 to 0.9; $p=0.0006$) in the 0.9mg group and 1.0% (95% CI 0.6 to 1.4; $p<0.0001$) in the 1.8mg group. When compared to placebo, significantly more participants in the 1.8mg group attained HbA1c $<$ 7% at week 12 (1 (2%) v 5 (22%) respectively; $p=0.0225$). Significant weight loss was only observed with 1.8mg ZGN-1061 (Figure 1B). At week 12, relative to placebo, this group lost 2.2% (95% CI 1.1 to 3.3; $p=0.0002$) or 2.3kg (95% CI 1.1 to 3.4; $p=0.0002$).

After 12 weeks of treatment, the 1.8mg dose decreased triglycerides by 0.7mmol/l (95% CI 0.2 to 1.3mmol/l; $p=0.0073$) without causing significant changes in total or HDL cholesterol.

Each of the 0.3mg, 0.9mg and 1.8mg doses decreased leptin relative to placebo by 4.3ng/ml (95% CI 1.9 to 6.8; $p=0.0005$), 4.2ng/ml (95% CI 1.9 to 6.5; $p=0.0004$) and 4.7ng/ml (95% CI 1.8 to 7.5; $p=0.0016$) respectively. The 0.9mg and 1.8mg doses also increased adiponectin by 0.34 μ g/ml (95% CI 0.02 to 0.66; $p=0.0389$) and 0.44 μ g/ml (95% CI 0.07 to 0.87; $p=0.0221$) respectively.

A summary of treatment-emergent adverse events (TEAEs) is provided in Supplemental Tables 1 and 2. The most frequent TEAEs ($\geq 10\%$ in any group) were upper respiratory tract infection, contusion, injection site bruising, diarrhea, headache, nasopharyngitis, and pain in extremity, which were generally comparable across the groups. At least one AE was reported by 81% of placebo participants and by 63%, 82%, 80% and 91% of ZGN-1061 participants in the 0.05mg, 0.3mg, 0.9mg and 1.8mg groups respectively. Most AEs were mild or moderate in severity (Supplemental Table 3). Three serious AEs (SAEs) were reported in 3 participants from the 0.9mg group: upper abdominal pain (moderate); skin ulcer (severe); and anaphylactic reaction to antibiotic (severe). None of these events were attributed to study drug by the investigator. AEs deemed to be related to study drug by the investigator generally had a similar incidence across all treatment groups. One participant (3%) in the 0.05 mg group, 1 (2%) in the 0.9 mg group, and 1 (4%) in the 1.8 mg group stopped study drug after reporting sensory disturbance, abdominal pain and injection site urticaria respectively. There were no deaths.

There were no significant changes in blood pressure or heart rate and no major adverse cardiovascular events. No confirmed venous thrombosis was evident at week 12 on lower limb venous ultrasound. During the 12-week randomized treatment period, mean D-dimer concentrations were measured every 2 weeks and were normal ($<0.5\text{mg/l}$) at all timepoints in all groups, with no significant change over time or between groups. No meaningful changes were observed in other physical examination results, ECGs, or safety questionnaires for sleep latency and suicidality.

CONCLUSIONS

Self-administration of 0.9mg or 1.8mg ZGN-1061 every 3 days for 12 weeks delivered progressive and clinically meaningful reductions in HbA1c in overweight and obese people with type 2 diabetes. The 1.8mg dose also induced clinically meaningful weight loss. ZGN-1061 was generally well-tolerated and there were no instances of confirmed venous thrombosis or of sleep disturbance.

A previous trial of beloranib in obese people with type 2 diabetes (3) reported 8% weight loss relative to placebo after 12 weeks of treatment with 0.9mg or 1.8mg s/c twice weekly, and a corresponding reduction in HbA1c of ~1.5% at the expense of an increased risk of venous thrombosis and sleep disturbance. Caution is advised when comparing across studies given differences in study populations, designs and treatment regimens.

Mechanisms linking MetAP2 inhibition to improved glucose control and weight loss are poorly understood. The observation that the 0.9mg dose improved HbA1c in the absence of weight loss contrasts with results of the beloranib trial (3). The relevance of this is unknown but could potentially relate to differences in pharmacokinetics or other properties of the drugs. The observation that all doses of ZGN-1061 significantly decreased circulating leptin concentrations implicates adipose tissue as key therapeutic target, with improved HbA1c observed in the 0.9mg and 1.8mg groups potentially related to increased adiponectin concentration. Recent reports demonstrating increased adipocyte glucose uptake (7) and energy consumption (8) following MetAP2 inhibition suggest other possible mechanisms.

While ZGN-1061 was well tolerated, the short duration of ZGN-1061 therapy in this study limits the conclusions that can be drawn about its safety in humans. In addition, the metabolic outcomes need to be interpreted in the knowledge that diabetes therapy was held constant in most participants. Other add-on glucose-lowering medication or lifestyle intervention may have enabled similar or even greater reductions in HbA1c. Finally, the

applicability of these findings to the general type 2 diabetes population is questioned by the relatively high body mass index and baseline HbA1c of the study population, and the exclusion of participants treated with insulin and those with risk factors for thrombosis and major depression.

In summary, this Phase 2 study demonstrated ZGN-1061 treatment for 12 weeks was well-tolerated and improved weight and glucose control in overweight and obese people with type 2 diabetes. However, given unresolved safety issues (9), Zafgen has discontinued the development of MetAP2 inhibitors.

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Guarantor Statement

John Wentworth is the guarantor of this work and takes full responsibility for the work as a whole. He had full access to study data, and took the decision to submit the manuscript for publication.

Data availability

The study protocol and data are available from Zafgen Inc. upon reasonable request.

Funding

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Duality of interest

JMW, PGC and the other clinical investigators received institutional grant support from Zafgen.

Contribution statement

The trial was designed and sponsored by Zafgen Inc. JMW, PGC and the other clinical investigators were responsible for consenting, screening and enrolling participants. All clinical investigators were responsible for acquisition of data. JMW and PGC wrote the manuscript. Both authors had full access to all clinical trial data and take responsibility for the integrity of the work. Both authors critically reviewed and revised the manuscript and have read and approved the final version.

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Figure 1. Effects of ZGN-1061 on HbA1c and body weight

Least squares mean $\pm$ sem for the change from baseline in HbA1c (A) and weight (B) for placebo (N=42, open circles), 0.05mg ZGN-1061 (N=32, inverted triangles), 0.3mg ZGN-1061 (N=34, upright triangles), 0.9mg ZGN-1061 (N=44, diamonds) and 1.8mg ZGN-1061 (N=23, squares). •• and •••: $p<0.01$ and $p<0.001$ for 0.9mg v placebo; ** and ***: $p<0.01$ and $p<0.001$ for 1.8mg v placebo.

Table 1. Baseline characteristics

Treatment arm	0.05 mg N=32	0.3 mg N=34	0.9 mg N=44	1.8 mg N=23	Placebo N=42	Total N=175
Age (years)	56±8	54±9	55±7	54±8	53±8	54±8
Duration of type 2 diabetes (years)	8±6	7±6	8±5	9±6	8±6	8±6
Percent male	56	38	50	44	50	48
Race (n (%))						
White	25 (78)	23 (68)	34 (77)	18 (78)	34 (81)	134 (77)
Black	0	0	0	1 (4)	0	1 (1)
Asian	2 (3)	2 (6)	0	0	0	3 (2)
Pacific islander	0	1 (3)	0	1 (4)	0	2 (1)
Other	6 (19)	8 (24)	10 (23)	3 (13)	8 (19)	28 (16)
Percent smoking	13	15	7	9	11	11
Weight (kg)	106±23	107±22	107±24	106±21	106±15	107±21
BMI (kg/m ²)	36±7	38±7	38±8	36±6	37±5	37±7
HbA1c (%)	8.6±1.0	8.7±1.1	8.5±1.1	8.3±1.0	8.7±1.2	8.6±1.1
Fasting glucose (mmol/l)	10.9±2.8	10.9±3.4	10.3±2.7	10.2±3.2	10.9±2.8	10.7±2.9

Number of glucose-lowering medications	1.6±0.9	1.6±0.8	1.6±0.8	1.8±0.9	1.5±0.9	1.6±0.8
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Continuous data are mean±SD

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RESULTS

Of 188 participants enrolled, 175 completed the placebo run-in phase and were randomized to treatment with subcutaneous injections of ZGN-1061 (0.05mg, 0.3mg, 0.9mg or 1.8mg doses) or placebo every 3 days for 12 weeks. Their baseline characteristics are presented in Table 1. The mean $\pm$ SD age, weight, BMI, HbA1c and disease duration of the study population were 54 $\pm$ 8 years, 107 $\pm$ 21kg, 37 $\pm$ 7kg/m², 8.6 $\pm$ 1.1% and 8 $\pm$ 6 years respectively, and 48% were men. The rate of adherence to study drug was $\geq$ 90% in all groups. During the 12-week treatment phase, 2, 2, 1, 2 and 3 participants in the 0.05mg, 0.3mg, 0.9mg, 1.8mg and placebo groups, respectively, increased their glucose-lowering medication. Six participants (0, 1, 2, 2 and 1 from each of the aforementioned treatment groups, respectively) withdrew from the study before week 12 for personal reasons including family illness and unwillingness to travel to study sites. A participant from the 0.05mg group was withdrawn by the sponsor due to prolonged overseas travel during the study, and 2 participants from the 1.8mg group were withdrawn by their investigator because they were either unreliable or commenced a low-calorie diet in preparation for bariatric surgery.

The change in HbA1c at 8 and 12 weeks for the 0.9mg and 1.8mg groups differed significantly from the corresponding values for the placebo group (Figure 1A). Both of these doses met the primary outcome. At week 12, relative to placebo, HbA1c decreased 0.6% (95% CI 0.2 to 0.9; $p=0.0006$) in the 0.9mg group and 1.0% (95% CI 0.6 to 1.4; $p<0.0001$) in the 1.8mg group. When compared to placebo, significantly more participants in the 1.8mg group attained HbA1c $<$ 7% at week 12 (1 (2%) v 5 (22%) respectively; $p=0.0225$). Significant weight loss was only observed with 1.8mg ZGN-1061 (Figure 1B). At week 12, relative to placebo, this group lost 2.2% (95% CI 1.1 to 3.3; $p=0.0002$) or 2.3kg (95% CI 1.1 to 3.4; $p=0.0002$).

After 12 weeks of treatment, the 1.8mg dose decreased triglycerides by 0.7mmol/l (95% CI 0.2 to 1.3mmol/l; $p=0.0073$) without causing significant changes in total or HDL cholesterol. Each of the 0.3mg, 0.9mg and 1.8mg doses decreased leptin relative to placebo by 4.3ng/ml (95% CI 1.9 to 6.8; $p=0.0005$), 4.2ng/ml (95% CI 1.9 to 6.5; $p=0.0004$) and 4.7ng/ml (95% CI 1.8 to 7.5; $p=0.0016$) respectively. The 0.9mg and 1.8mg doses also increased adiponectin

by 0.34 μ g/ml (95% CI 0.02 to 0.66; p=0.0389) and 0.44 μ g/ml (95% CI 0.07 to 0.87; p=0.0221) respectively.

A summary of treatment-emergent adverse events (TEAEs) is provided in Supplemental Tables 1 and 2. The most frequent TEAEs ($\geq 10\%$ in any group) were upper respiratory tract infection, contusion, injection site bruising, diarrhea, headache, nasopharyngitis, and pain in extremity, which were generally comparable across the groups. At least one AE was reported by 81% of placebo participants and by 63%, 82%, 80% and 91% of ZGN-1061 participants in the 0.05mg, 0.3mg, 0.9mg and 1.8mg groups respectively. Most AEs were mild or moderate in severity (Supplemental Table 3). Three serious AEs (SAEs) were reported in 3 participants from the 0.9mg group: upper abdominal pain (moderate); skin ulcer (severe); and anaphylactic reaction to antibiotic (severe). None of these events were attributed to study drug by the investigator. AEs deemed to be related to study drug by the investigator generally had a similar incidence across all treatment groups. One participant (3%) in the 0.05 mg group, 1 (2%) in the 0.9 mg group, and 1 (4%) in the 1.8 mg group stopped study drug after reporting sensory disturbance, abdominal pain and injection site urticaria respectively. There were no deaths.

There were no significant changes in blood pressure or heart rate and no major adverse cardiovascular events. No confirmed venous thrombosis was evident at week 12 on lower limb venous ultrasound. During the 12-week randomized treatment period, mean D-dimer concentrations were measured every 2 weeks and were normal ($<0.5\text{mg/l}$) at all timepoints in all groups, with no significant change over time or between groups. No meaningful changes were observed in other physical examination results, ECGs, or safety questionnaires for sleep latency and suicidality.

CONCLUSIONS

Self-administration of 0.9mg or 1.8mg ZGN-1061 every 3 days for 12 weeks delivered progressive and clinically meaningful reductions in HbA1c in overweight and obese people with type 2 diabetes. The 1.8mg dose also induced clinically meaningful weight loss. ZGN-1061 was generally well-tolerated and there were no instances of confirmed venous thrombosis or of sleep disturbance.

A previous trial of beloranib in obese people with type 2 diabetes (3) reported 8% weight loss relative to placebo after 12 weeks of treatment with 0.9mg or 1.8mg s/c twice weekly, and a corresponding reduction in HbA1c of ~1.5% at the expense of an increased risk of venous thrombosis and sleep disturbance. Caution is advised when comparing across studies given differences in study populations, designs and treatment regimens.

Mechanisms linking MetAP2 inhibition to improved glucose control and weight loss are poorly understood. The observation that the 0.9mg dose improved HbA1c in the absence of weight loss contrasts with results of the beloranib trial (3). The relevance of this is unknown but could potentially relate to differences in pharmacokinetics or other properties of the drugs. The observation that all doses of ZGN-1061 significantly decreased circulating leptin concentrations implicates adipose tissue as key therapeutic target, with improved HbA1c observed in the 0.9mg and 1.8mg groups potentially related to increased adiponectin concentration. Recent reports demonstrating increased adipocyte glucose uptake (7) and energy consumption (8) following MetAP2 inhibition suggest other possible mechanisms.

While ZGN-1061 was well tolerated, the short duration of ZGN-1061 therapy in this study limits the conclusions that can be drawn about its safety in humans. In addition, the metabolic outcomes need to be interpreted in the knowledge that diabetes therapy was held constant in most participants. Other add-on glucose-lowering medication or lifestyle intervention may have enabled similar or even greater reductions in HbA1c. Finally, the applicability of these findings to the general type 2 diabetes population is questioned by the relatively high body mass index and baseline HbA1c of the study population, and the exclusion of participants treated with insulin and those with risk factors for thrombosis and major depression.

In summary, this Phase 2 study demonstrated ZGN-1061 treatment for 12 weeks was well-tolerated and improved weight and glucose control in overweight and obese people with type 2 diabetes. However, given unresolved safety issues (9), Zafgen has discontinued the development of MetAP2 inhibitors.

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Guarantor Statement

John Wentworth is the guarantor of this work and takes full responsibility for the work as a whole. He had full access to study data, and took the decision to submit the manuscript for publication.

Data availability

The study protocol and data are available from Zafgen Inc. upon reasonable request.

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Contribution statement

The trial was designed and sponsored by Zafgen Inc. JMW, PGC and the other clinical investigators were responsible for consenting, screening and enrolling participants. All clinical investigators were responsible for acquisition of data. JMW and PGC wrote the manuscript. Both authors had full access to all clinical trial data and take responsibility for the integrity of the work. Both authors critically reviewed and revised the manuscript and have read and approved the final version.

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Figure 1. Effects of ZGN-1061 on HbA1c and body weight

Least squares mean $\pm$ sem for the change from baseline in HbA1c (A) and weight (B) for placebo (N=42, open circles), 0.05mg ZGN-1061 (N=32, inverted triangles), 0.3mg ZGN-1061 (N=34, upright triangles), 0.9mg ZGN-1061 (N=44, diamonds) and 1.8mg ZGN-1061 (N=23, squares). •• and •••: $p<0.01$ and $p<0.001$ for 0.9mg v placebo; ** and ***: $p<0.01$ and $p<0.001$ for 1.8mg v placebo.

Table 1. Baseline characteristics

Treatment arm	0.05 mg N=32	0.3 mg N=34	0.9 mg N=44	1.8 mg N=23	Placebo N=42	Total N=175
Age (years)	56±8	54±9	55±7	54±8	53±8	54±8
Duration of type 2 diabetes (years)	8±6	7±6	8±5	9±6	8±6	8±6
Percent male	56	38	50	44	50	48
Race (n (%))						
White	25 (78)	23 (68)	34 (77)	18 (78)	34 (81)	134 (77)
Black	0	0	0	1 (4)	0	1 (1)
Asian	2 (3)	2 (6)	0	0	0	3 (2)
Pacific islander	0	1 (3)	0	1 (4)	0	2 (1)
Other	6 (19)	8 (24)	10 (23)	3 (13)	8 (19)	28 (16)
Percent smoking	13	15	7	9	11	11
Weight (kg)	106±23	107±22	107±24	106±21	106±15	107±21
BMI (kg/m ²)	36±7	38±7	38±8	36±6	37±5	37±7
HbA1c (%)	8.6±1.0	8.7±1.1	8.5±1.1	8.3±1.0	8.7±1.2	8.6±1.1
Fasting glucose (mmol/l)	10.9±2.8	10.9±3.4	10.3±2.7	10.2±3.2	10.9±2.8	10.7±2.9
Number of glucose-lowering medications	1.6±0.9	1.6±0.8	1.6±0.8	1.8±0.9	1.5±0.9	1.6±0.8

Continuous data are mean±SD

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