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Single and Multiple Dose Evaluation of a Novel MetAP2 Inhibitor: Results of a Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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ABSTRACT

The methionine aminopeptidase 2 (MetAP2) inhibitor beloranib resulted in 13% weight loss and 2.0% reduction in A1C from baseline in obese T2DM subjects but development was halted due to its pro-thrombotic effect. Nonclinical studies of a 2nd generation MetAP2 inhibitor, ZGN-1061 (1061), showed a superior safety profile with a shorter half-life (t½) that is hypothesized to reduce endothelial cell exposure and limit thrombosis. This Phase 1 clinical trial of 1061 assessed safety, pharmacokinetics (PK), and preliminary efficacy. The clinical trial included a single ascending dose (SAD) phase in healthy subjects (BMI 23–<30) and a multiple ascending dose (MAD) phase in subjects with BMI 27–40. SAD phase doses were 0.2, 0.6, 1.2, 2.4, 3.6, and 4.8 mg, and MAD phase evaluated 0.2, 0.6, and 1.8 mg twice weekly for 4 wks. SAD included 39 subjects (1061 N=28, placebo N=11), 90% male and BMI 26. 1061 maximum plasma concentrations (Cmax) increased linearly with dose and occurred within 30 min, with t½ less than 1 hr. 1061 was well tolerated across all doses with most frequent adverse events of mild headache and procedural site irritation. There were no severe or serious events and no events of venous thromboembolism. MetAP2 binding and evidence of MetAP2 inhibition increased with dose; maximal values were observed at doses ≥1.2 mg. MAD included 29 subjects (1061 N=22, placebo N=7), 76% male and BMI 33. PK and target engagement results were consistent with SAD findings although Cmax, overall exposure, MetAP2 binding and MetAP2 inhibition increased after repeat dosing. Safety observations were comparable to the SAD phase. Efficacy measures indicated trends for greater weight loss and favorable biomarker changes with 1061 vs placebo. Safety results indicate that 1061 was well tolerated with no safety signals or venous thromboembolic events in all doses tested, together with the PK profile and efficacy trends, support the evaluation in larger and longer clinical trials.

INTRODUCTION

- Methionine aminopeptidase 2 inhibitors (MetAP2i) are a promising new therapeutic approach for the treatment of diabetes, obesity, and associated metabolic complications.
- A MetAP2i previously in development (beloranib) resulted in 13% weight loss and 2.0% reduction in HbA1c from baseline following 26 weeks of treatment in patients with obesity and type 2 diabetes. Beloranib development was discontinued due to an imbalance of venous thrombotic events in the treated groups compared to placebo (1-4).
- Nonclinical studies of the second generation MetAP2i, ZGN-1061, showed similar efficacy of ZGN-1061 and beloranib on body weight and glucose tolerance in vivo and an improved safety profile of ZGN-1061 with a shorter half-life compared to beloranib that is hypothesized to reduce endothelial cell exposure and limit thrombosis.

OBJECTIVE

- **This Phase 1 clinical trial of 1061 assessed safety, pharmacokinetics (PK), and preliminary efficacy of ZGN-1061**

METHODS

Table 1. Clinical Trial Design

ZAF-1061-101	Single Ascending Dose (SAD)	Multiple Ascending Dose (MAD)
Population	Healthy male and female volunteers aged 18–55 years	Healthy, overweight/obese male and female volunteers aged 18–55 years
Dosing cohorts	0.2, 0.6, 1.2, 2.4, 3.6, 4.8 mg	0.2, 0.6, 1.8 mg
Dosing schedule	Single dose SC	Twice-weekly SC dosing for 28 days (8 injections)
Randomization	3:1 (active/placebo)	3:1 (active/placebo)
Inpatient treatment	Domiciled days -1 through 4	Domiciled for the majority of the trial for safety monitoring: • No exercise allowed • Scheduled meals

Abbreviations: SC = subcutaneous.

Outcome Measures:

- Primary outcome: Safety and tolerability
  - Adverse events (AEs), clinical laboratory measurements, vital signs, 12-lead electrocardiogram (ECG), local tolerability, physical examination, and other relevant parameters
  - Thrombosis risk was assessed by coagulation markers, lower extremity ultrasounds, and relevant AEs
- Secondary and exploratory outcomes
  - Pharmacokinetics: PK profile and PK parameters
  - Target engagement: ZGN-1061 binding to MetAP2 and evidence of MetAP2 enzymatic inhibition
  - Efficacy (MAD Phase): body weight, waist circumference, food intake (food consumption during a 30-minute test meal), lipids, and other cardiometabolic markers

Analysis:

- Analysis Populations: Safety analyses were conducted on all subjects who received at least 1 dose of study drug. PK and efficacy analyses were conducted on all subjects who received at least 1 dose of study drug and who provided adequate blood samples for bioanalysis (PK) or who were without major protocol violations (efficacy). Endpoints were analyzed based on observed values
- Safety and tolerability: Safety and tolerability parameters were summarized by treatment group
- Pharmacokinetics: PK parameters were calculated using noncompartmental analysis from the plasma concentration-time data
- Target engagement: Analyzed via ZGN-1061 bound to MetAP2 and evidence of MetAP2 inhibition (measured by thioredoxin substrate [thioredoxin 1-6]) in peripheral blood mononuclear cells (PBMCs)
- Exploratory efficacy (MAD Phase): Analyzed as absolute values and changes from baseline and summarized descriptively by treatment group

RESULTS

1) Subject Disposition and Baseline Demographics

SAD Phase:

- 39 subjects were randomized, 28 to ZGN-1061 and 11 to placebo. All subjects completed the assessment period. The majority of subjects (90%) were male and the mean BMI was 26 kg/m^2.

MAD Phase:

- 29 subjects were randomized, 22 to ZGN-1061 and 7 to placebo. 27 subjects completed clinical trial procedures; 2 withdrew consent (1 due to work schedule and 1 due to administrative reasons).

Table 1. Subject demographics and baseline characteristics (MAD Phase)

	ZGN-1061 0.2 mg (N=5)	ZGN-1061 0.6 mg (N=11)	ZGN-1061 1.8 mg (N=6)	ZGN-1061 Total (N=22)	Placebo (N=7)
Age (years)	32.6 ±7.5	45.1 ±7.6	37.0 ±12.7	40.0 ±10.3	38.9 ±13.3
Sex (% Male)	60	73	83	73	86
Race: (% White/Black/Asian)	40/60/0	91/9/0	83/17/0	77/23/0	86/0/14
Weight (kg)	104.1 ±19.0	105.0 ±18.0	107.6 ±11.0	105.5 ±15.9	95.2 ±20.7
BMI (kg/m^2)	32.7 ±2.0	34.4 ±4.1	34.6 ±3.3	34.1 ±3.5	31.6 ±3.6

Data are mean ±SD or percent of subjects. Total includes all ZGN-1061-treated subjects. Abbreviations: BMI=body mass index.

2) Pharmacokinetics of ZGN-1061

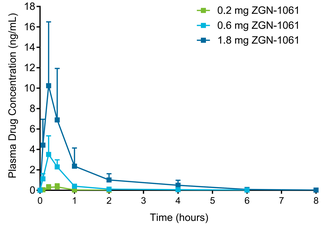
SAD Phase

- The mean maximal plasma concentration (C_{max}) of ZGN-1061 increased linearly with dose and ranged from 0.5 to 18.7 ng/mL
- Dose escalation was stopped at the 4.8 mg dose based on plasma concentrations in the predicted therapeutic range

MAD Phase

- The mean C_{max} of ZGN-1061 increased linearly with dose, with rapid absorption and a similarly rapid clearance over time, the time to C_{max} (T_{max}) occurred within 30 minutes of dosing, and half-life ($t_{1/2}$) occurred within 1 hour of dosing (Figure 1)
- ZGN-1061 was not detected at the 12 hour or later time points

Figure 1. Rapid absorption and clearance of ZGN-1061 meets prospectively established criteria (MAD Phase)



Data are mean and SD of plasma ZGN-1061 concentrations after the 5th dose.

3) ZGN-1061 Target Engagement

- MetAP2 binding and evidence of MetAP2 inhibition in PBMCs increased with dose and with repeat dosing (MAD phase), confirming target engagement

4) Safety and Tolerability

- Single and repeat doses of ZGN-1061 were generally safe and well tolerated
- No severe AEs, no serious AEs (SAEs), and no AEs leading to early withdrawal from the clinical trial
- SAD Phase:
  - AEs were mild except 1 moderate AE of flank pain (0.6 mg ZGN-1061) and there were no noted trends by dose or type of AE
- MAD Phase:
  - AEs were mild except 1 moderate AE of toothache (0.6 mg ZGN-1061)
  - The most common AEs were mild gastrointestinal issues (similar incidence for ZGN-1061 and placebo), headache, and procedural-related irritation (Table 2)
- No meaningful changes observed among general safety laboratory measures, blood pressure, heart rate, or ECGs

Table 2. Adverse events in ≥3 subjects in the MAD Phase

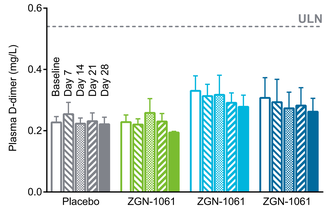
Data are n (% of subjects)	ZGN-1061 0.2 mg (N=5)	ZGN-1061 0.6 mg (N=11)	ZGN-1061 1.8 mg (N=6)	ZGN-1061 Total (N=22)	Placebo (N=7)
Any AE	3 (60.0)	9 (81.8)	5 (83.3)	17 (77.3)	5 (71.4)
Diarrhea	1 (20.0)	4 (36.4)	2 (33.3)	7 (31.8)	3 (42.9)
Headache	0	5 (45.5)	1 (16.7)	6 (27.3)	0
Catheter site pain	2 (40.0)	2 (18.2)	0	4 (18.2)	1 (14.3)
Application site irritation*	0	3 (27.3)	1 (16.7)	4 (18.2)	0
Abdominal pain	0	2 (18.2)	1 (16.7)	3 (13.6)	1 (14.3)
Erythema	0	0	2 (33.3)	2 (9.1)	1 (14.3)
Flatulence	0	1 (9.1)	1 (16.7)	2 (9.1)	1 (14.3)
Nausea	0	1 (9.1)	1 (16.7)	2 (9.1)	1 (14.3)

Data are for the Safety Population (N=29) by MedDRA preferred term. Adverse events with onset or worsening on or after the first randomized dose of trial medication are shown and are ordered by decreasing frequency in the Total ZGN-1061 group. Total includes all ZGN-1061-treated subjects. *Events involved irritation due to ECG stickers for electrode placement. Abbreviations: AE = adverse event; ECG = electrocardiogram.

Coagulation-related Safety: SAD and MAD Phase

- No venous thromboembolism (VTE) events
- No D-dimer elevations indicative of the presence of VTE. (D-dimer is a fibrin degradation product that is a conventional marker of clotting and becomes markedly elevated during periods of active clot formation and lysis)
- No meaningful elevations in mean D-dimer concentrations across the dosing groups compared to baseline or placebo (Figure 2)
  - There were 4 subjects (3 in the 0.6 mg ZGN-1061 group; 1 in the 1.8 mg ZGN-1061 group in the MAD phase) with D-dimer levels that exceeded the upper limit of normal (ULN) by 1.5-fold (>0.81 mg/L); none of these elevations were found to be indicative of a VTE event and were either associated with a single isolated measurement (during the follow-up period without ongoing study drug administrations), sampling from blocked catheter, tooth infection, or multiple hematomas at venipuncture sites
- No clinically meaningful changes in standard coagulation laboratory values or other coagulation parameters (eg, von Willebrand Factor [vWF], thrombomodulin)

Figure 2. No change in mean D-dimer levels with repeat dosing of ZGN-1061 for 28 days (MAD Phase)



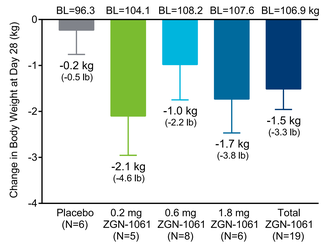
Data are mean and SEM at each timepoint. Dashed line represents the upper limit of normal range for the assay (0.54 mg/L). Abbreviations: ULN = upper limit of normal.

5) Efficacy: MAD Phase

Body Weight

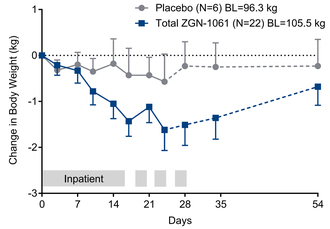
- All doses of ZGN-1061 resulted in weight loss from baseline to Day 28 of approximately 1 to 2 kg (Figure 3)
- After the last dose of study drug, ZGN-1061-treated subjects generally experienced weight regain (Figure 4)

Figure 3. Body weight change shows impact at all dose levels of ZGN-1061



Data are mean and SEM (change from baseline) or mean (baseline). Total includes all ZGN-1061-treated subjects. Abbreviation: BL=baseline.

Figure 4. Body weight loss was steady and progressive during treatment with ZGN-1061 and rebounded post-treatment, supporting a drug effect

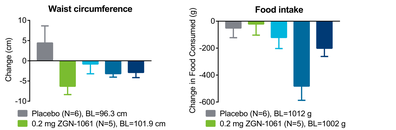


Data are mean and SEM (change from baseline) or mean (baseline). Total includes all ZGN-1061-treated subjects. Dashed line indicates washout period during which no treatments were administered. Abbreviation: BL=baseline weight.

Trends for Improvement Across Multiple Cardiometabolic Measures Supportive of ZGN-1061 Activity

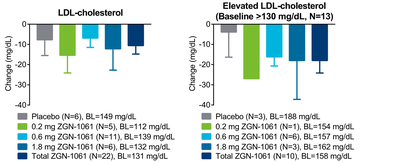
- ZGN-1061 produced improvements in waist circumference relative to placebo (Figure 5)
- ZGN-1061 also produced a trend for reduced food intake (Figure 5)
- There were trends for reductions in LDL-cholesterol and high-sensitivity C-reactive protein (hsCRP; Figure 6). Notably, there were greater reductions in mean LDL-cholesterol and hsCRP in ZGN-1061-treated subjects with abnormally elevated LDL-cholesterol or hsCRP at baseline (Figure 6)
- There was also a trend for reductions in leptin and increases in adiponectin with ZGN-1061 compared to placebo (data not shown)
- There was no change in blood pressure or heart rate (data not shown)

Figure 5. Reduction in waist circumference and food intake with ZGN-1061



Data are mean and SEM (change from baseline to Day 28) or mean (baseline). Food intake was assessed by measuring weight of food consumption during a 30-minute test meal. Abbreviations: BL = baseline.

Figure 6. Improvement in LDL-cholesterol and hsCRP ZGN-1061



Data are mean and SEM (change from baseline to Day 28) or mean (baseline). Abbreviations: BL = baseline; hsCRP = high sensitivity C-reactive protein, LDL = low density lipoprotein.

CONCLUSION

- **In this first-in-human clinical trial of single and multiple ascending doses of ZGN-1061 for up to 28 days:**
  - **There were no notable safety signals or tolerability issues**
  - **There was no evidence of prothrombotic effects**
  - **The brief exposure profile of ZGN-1061 enables rapid target engagement without long-term exposure**
  - **Efficacy data trends support a favorable effect of ZGN-1061 on body weight and cardiometabolic measures. Further titration of the dose-response and evaluation of the full extent of weight loss and other efficacy parameters is needed**
- **These data support evaluation in larger and longer Phase 2 studies; a Phase 2 study of ZGN-1061 in patients with obesity and type 2 diabetes is planned**

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