ORIGINAL ARTICLE

MEDI0382, a GLP-1/glucagon receptor dual agonist, meets safety and tolerability endpoints in a single-dose, healthy-subject, randomized, Phase 1 study

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AIMS

MEDI0382 is a balanced glucagon-like peptide-1/glucagon receptor dual agonist under development for the treatment of type 2 diabetes mellitus and non-alcoholic steatohepatitis. The primary objective was to assess the safety of MEDI0382 in healthy subjects.

METHODS

In this placebo-controlled, double-blind, Phase 1 study, healthy subjects (aged 18–45 years) were randomized (3:1) to receive a single subcutaneous dose of MEDI0382 or placebo after ≥8 h of fasting. The study consisted of six cohorts that received study drug at 5 μg, 10 μg, 30 μg, 100 μg, 150 μg or 300 μg. The primary objective was safety and tolerability. Secondary endpoints included assessments of pharmacokinetics and immunogenicity. All subjects were followed for up to 28 days.

RESULTS

A total of 36 subjects received MEDI0382 (*n* = 6 per cohort) and 12 subjects received placebo (*n* = 2 per cohort). Treatment-emergent adverse events (TEAEs) occurred more frequently with MEDI0382 *vs.* placebo, which was mostly due to an increased occurrence at MEDI0382 doses ≥150 μg. All TEAEs were mild or moderate in severity. The most common TEAEs were vomiting, nausea and dizziness. There appeared to be a dose-dependent increase in heart rate with MEDI0382 treatment. MEDI0382 showed linear pharmacokinetic profile (time to maximum plasma concentration: 4.50–9.00 h; elimination half-life: 9.54–12.07 h). No immunogenicity was observed in the study.

CONCLUSIONS

In this single-dose, Phase 1 study in healthy subjects, the safety and pharmacokinetic profiles of MEDI0382 support once-daily dosing and further clinical development of MEDI0382.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- MEDI0382 is a balanced glucagon-like peptide-1 (GLP-1)/glucagon receptor dual agonist.
- MEDI0382 administration in mice and non-human primates resulted in robust glycaemic control and weight loss.

WHAT THIS STUDY ADDS
- In this first-in-human, single-dose study in healthy subjects, the safety and pharmacokinetic profile of MEDI0382 support once-daily dosing.
- Administration of MEDI0382 was associated with a dose-dependent reduction in glucose that was within the normal range and was not associated with a rise in blood glucose. This finding supports preclinical data suggesting that the glucagon and GLP-1 activity in MEDI0382 is adequately balanced.
- Further evaluation of MEDI0382 in patients with type 2 diabetes mellitus is warranted.

Introduction

Type 2 diabetes mellitus is characterized by insulin resistance, obesity and weight gain, which contribute to progressive beta-cell failure, ultimately resulting in steadily worsening glycaemic control [1]. Despite the variety of antihyperglycaemic agents approved for type 2 diabetes mellitus, none of them result in substantial weight loss at doses licensed for blood glucose reduction [2]. Weight loss, therefore, remains a significant unmet medical need in these patients [2]. Approximately 50% of patients with type 2 diabetes mellitus progress from oral monotherapy (usually metformin) for blood glucose level control to initiation of insulin within 10 years [3], often taking multiple oral combination therapies before initiating insulin. The use of insulin exacerbates weight gain, which can be as great as 6 kg in the first year after starting insulin therapy [4]. The overall weight gain, pre- and post-diagnosis of diabetes, can lead to increased insulin resistance, which is associated with hypertension, dyslipidaemia, and an increased risk of major adverse cardiovascular events, such as cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke [5, 6]. Significant weight loss (>5%) is the optimal intervention to reduce insulin resistance [7], although this can only be achieved reliably at present through intensive dietary and lifestyle interventions, and/or bariatric surgery [8, 9].

MEDI0382 is a synthetic oxyntomodulin-like peptide with balanced dual **glucagon-like peptide-1 (GLP-1)** and **glucagon** receptor agonist activity [10] that is under development for the treatment of type 2 diabetes mellitus and non-alcoholic steatohepatitis. In diet-induced obesity mouse models and nonhuman primates, MEDI0382 led to robust reductions in body weight, glucose levels, fasting insulin levels and hepatic fat content [10]. In the diet-induced obesity mouse model, greater weight loss was observed with MEDI0382 at lower molar doses compared with the approved GLP-1 agonist, liraglutide [10]. Moreover, in contrast to liraglutide, weight loss did not plateau with MEDI0382 over the course of the study [10]. This suggests that MEDI0382 could drive greater weight loss through dual agonism of GLP-1 and glucagon receptors compared with GLP-1 mono-agonists. This is supported by data with other dual agonist peptides as reviewed by Sánchez-Garrido et al. [11]. Preclinical data also suggest that, at least in the species studied, the balance of activity at the GLP-1 and glucagon receptors was considered to be optimal with regard to achieving both weight loss and glycaemic control [10]. These effects are thought to be mediated through stimulation of glucose-mediated insulin release (the incretin effect), delayed gastric emptying, and increased fatty acid oxidation [12, 13]. GLP-1 and glucagon receptor dual agonists may also exert central effects on appetite, and glucagon receptor agonism has been shown to drive increased energy expenditure in animal models and humans [12, 14]. Further, appetite suppression and increased energy expenditure in humans have been demonstrated with the use of oxyntomodulin, a weak GLP-1/glucagon receptor dual agonist [15]. Here, we report the results from a first-in-human, Phase 1, single-dose study of MEDI0382 in healthy subjects.

Methods

Study design

This randomized, placebo-controlled, double-blinded study, evaluated the safety, tolerability, pharmacokinetic and pharmacodynamic properties of single ascending doses of MEDI0382 *vs*. placebo, and was conducted at a single site in Berlin, Germany. The study protocol and amendments to the protocol were approved by the Berlin independent ethics committee (identification code/approval number: 14/0576-EK13). The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation Guidance for Good Clinical Practice, and all applicable local laws and requirements. All subjects provided written informed consent prior to initiating any study procedures. The trial was registered at ClinicalTrials.gov, NCT02394314.

The study was originally planned to evaluate the safety, tolerability, pharmacokinetic properties and immunogenicity of MEDI0382 up to single ascending doses of 2000 μg, with eight subjects per cohort and a total of eight or fewer cohorts (Figure 1). However, the 300 μg dose was not tolerated, as evidenced by events of significant vomiting (described in the Results section), and the dose was de-escalated to 150 μg for the final cohort. Thus, contrary to the initial plan, the study included six dosing cohorts for MEDI0382 at doses of 5 μg, 10 μg, 30 μg, 100 μg, 150 μg and 300 μg (Figure 1).

Study subjects

Eligible subjects were healthy volunteers, male or female (those who were not lactating and were not of childbearing potential), aged 18–45 years, with a body mass index (BMI)

Planned	**Actual**

| **Cohort 1 (*n* = 8)**
5 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 1 (*n* = 8)**
5 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 2 (*n* = 8)**
10 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 2 (*n* = 8)**
10 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 3 (*n* = 8)**
30 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 3 (*n* = 8)**
30 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 4 (*n* = 8)**
100 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 4 (*n* = 8)**
100 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 5 (*n* = 8)**
300 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 5 (*n* = 8)**
300 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 6 (*n* = 8)**
600 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | **Cohort 6 (*n* = 8)**
150 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) |

| **Cohort 7 (*n* = 8)**
1200 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | |

| **Cohort 8 (*n* = 8)**
2000 µg MEDI0382 (*n* = 6)
Placebo (*n* = 2) | |

Figure 1
Planned and actual study doses and cohort population sizes

between ≥ 22 kg m^{-2} and ≤ 30 kg m^{-2}, and body weight ≥ 70 kg. The BMI and weight criteria were chosen to approximate as closely as possible to a population of patients with type 2 diabetes mellitus, while minimizing the possibility for concomitant medical conditions. Subjects were required to have venous access suitable for multiple cannulations. Current or previous use (within 28 days of screening) of GLP-1 receptor agonists or systemic corticosteroids were not allowed. Use of any products licensed for control of body weight or appetite 7 days prior to screening were prohibited. Subjects with a history or presence of any condition that in the opinion of the investigator would interfere with the study were excluded.

Randomization and masking

Eligible subjects were randomized (3:1) to receive MEDI0382 or placebo using an interactive voice- or web-response system. Investigational products were supplied to the study site in vials of identical appearance in blinded coded kits. As such, the pharmacist, the subject, the investigator, staff and the Contract Research Organization personnel responsible for managing and monitoring the study were blinded to the treatment received. The study sponsor was not blinded to treatment allocation.

Procedures and materials

Subjects received a subcutaneous dose of the study drug within 24 h of randomization and following an overnight fast of ≥ 8 h. Subjects remained in the study facility for timed assessments and safety monitoring (including vital signs, pulse, blood pressure, cardiac telemetry and blood sample collections) until discharge from the unit on Day 3 post-dose to allow for extended monitoring of cardiovascular effects. Outpatient visits were scheduled for Days 4, 7 and 28 post-dose. A sentinel dosing approach was planned for each cohort. Two subjects in a given cohort were dosed on Day 1, and the randomization schedule ensured that these consisted of one active and one placebo subject. A time lag of 48 h occurred before additional subjects in the cohort were dosed and prior to dose escalations. Dosing was proposed to continue based on a lack of significant safety findings in the first two subjects who were dosed. The decision on whether to escalate the dose was based on review of the totality of unblinded safety and pharmacokinetic data by the dose-escalation committee. The dose-escalation committee consisted of the senior physician in charge of the MedImmune cardiovascular drug development group, the physician lead for MEDI0382, the clinical pharmacology lead for the study, and the principal investigator from the site. Dose escalation was not to proceed if moderate or severe adverse events (AEs) that were considered by the investigator to be related to the study drug occurred in >50% of MEDI0382-treated subjects in a cohort, or if any serious AE considered by the investigator to be related to MEDI0382 occurred in a MEDI0382-treated subject in a cohort.

MEDI0382 was provided as a sterile liquid drug product (nominal concentration of 2 mg ml^{-1}). Double-blind placebo, and open-label diluent were provided in 50 mM sodium phosphate buffer containing 1.85% weight per volume of propylene glycol, pH level of 7.8, intended for subcutaneous administration. MEDI0382 was supplied by MedImmune Ltd (Cambridge, UK) [10]. All doses were prepared by a treatment-blinded pharmacist.

Outcome measures

The primary endpoint was the safety of MEDI0382, as assessed by summary measures of treatment-emergent adverse events (TEAEs). Safety assessments also included electrocardiograms (ECGs), routine laboratory assessments, venous blood glucose and vital signs.

The secondary objectives were the pharmacokinetics and immunogenicity of MEDI0382. Pharmacokinetic analyses in ethylenediaminetetraacetic acid plasma were conducted using a liquid chromatography mass spectrometry method consisting of SCIEX API 5500 MS (SCIEX, Framingham, MA, USA) and Waters Acquity UPLC (Waters Corporation, Milford, MA, USA) systems. The assay method utilized an acetonitrile:water extraction (85:15 v/v) and a stable isotope-labelled version of MEDI0382, resulting in a validated method with a calibration range of 0.4–400 ng ml^{-1} MEDI0382 in neat plasma. All instrument control, data collection, peak area integration and storage were performed using SCIEX Analyst version 1.6.2 (SCIEX). The data and statistical analysis comply with recommendations on experimental design and analysis in pharmacology [16].

Standard hospital meals, as supplied by the Charité hospitals group, were given to all subjects. The exploratory endpoint of the effect of study drug administration on food intake was estimated by the study nurse who assessed the proportion of food remaining when the trays were returned at the end of the meal. The exploratory endpoint of glucose levels around mealtimes following study drug administration was assessed using venous blood glucose sampling.

Statistical analysis

The sample size of eight subjects per cohort (up to eight cohorts and 64 subjects total) for this single ascending-dose study was based on conventional study designs for first-in-human tolerance studies to obtain adequate safety, tolerability and pharmacokinetic data, and immunogenicity. All analyses were descriptive in nature; therefore, no formal hypothesis test-driven sample size calculations were performed.

All summaries, except for analyses of pharmacokinetic properties, used the as-treated population that included subjects who received investigational product, and were analysed as such. The pharmacokinetic population included all subjects who received any amount of investigational product and had at least one pharmacokinetic sample taken that was above the lower limit of quantitation.

Safety was monitored from the time of informed consent through Day 28. TEAEs were assessed by severity and relationship to the investigational product. TEAEs were coded by the most updated version of the Medical Dictionary for Regulatory Activities (MedDRA), and the type, incidence, severity and relationship to study investigational product was summarized by MedDRA system organ class and preferred term. Specific AEs were counted once for each subject for calculating percentages. In addition, if the same AE occurred multiple times within a particular subject, the highest severity and

level of relationship observed was reported. The adverse events of special interest (AESIs) were clinically significant arrhythmia, vomiting and hepatic function abnormality (defined as any increase in alanine aminotransferase or aspartate aminotransferase to at least three times the upper limit of normal, and concurrent increase in bilirubin to at least twice the upper limit of normal). GI tolerability and arrhythmia were selected as an AESI because of the known profile of GLP-1 or glucagon receptor agonists. As is typical for early-stage drug development, liver events were collected as AESIs. For the MEDI0382 group, TEAEs were summarized by each dosing cohort and by all cohorts combined. For the placebo group, TEAEs were summarized by all cohorts combined. The clinical laboratory parameters and other safety evaluations were summarized with descriptive statistics.

Pharmacokinetic parameters were assessed in subjects receiving MEDI0382. These included the maximum observed plasma concentration (C_{max}); time to C_{max} (t_{max}); apparent terminal elimination half-life ($t_{1/2}$; obtained as the ratio of $ln2/\lambda_z$, where λ_z is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration–time data); area under the concentration–time curve (AUC) to the last quantifiable concentration (AUC_{0-last}; determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations); and AUC extrapolated to infinity ($AUC_{0-\infty}$) was calculated where data permitted, as the sum of AUC_{0-t} and $C_{t/\lambda z}$, where C_t is the observed plasma concentration obtained from the log-linear regression analysis of the last quantifiable time-point and λz is the terminal phase rate constant. A maximum of 20% of extrapolation on the $AUC_{0-\infty}$ was considered acceptable. Missing data were not imputed. Summary statistics were calculated for each of these parameters. Actual time of sampling, rather than nominal (planned) sampling time, was used to derive pharmacokinetic parameters using noncompartmental model 200–202 for extravascular administration using Phoenix WinNonlin 6.3 (Pharsight Corporation, Mountain View, CA, USA).

Immunogenicity of MEDI0382 was assessed on Days 1 (pre-dose), 7 and 28, and at early discontinuation. A screening assay, in the form of a traditional ligand-binding 'bridging' assay using electrochemiluminescence, was used to determine antidrug antibody-positive samples. Any positive samples were confirmed as either positive or negative with respect to MEDI0382. Cross-reactivity of antidrug antibody-positive samples to GLP-1 and glucagon may also have been assessed in the confirmatory assay, should the sample confirm a specific response for MEDI0382. Titre evaluation was performed on samples that were confirmed positive for antidrug antibody. The number and percentage of subjects in each treatment group showing an immunological response to MEDI0382 were summarized by study visit, for the as-treated population and by cohort. All valid assay results from subjects who received any investigational product were included in immunogenicity summaries. Study discontinuation blood samples were summarized at the closest nominal time-point that did not already have a value. Descriptive statistics were generated for the levels of glucose by treatment group at each specified time-point.

Overall, the placebo groups were pooled together across all cohorts for analyses and presentation of results. Categorical data were summarized by the number and percentage of subjects in each category. Continuous variables were summarized by descriptive statistics, including mean, standard deviation, median, minimum and maximum. Baseline values were defined as the last valid assessment prior to the first administration of investigational product. All analyses were based on available data, and missing data were not imputed. Data analyses were conducted using the SAS® System version 9.3 or higher (SAS Institute Inc., Cary, NC, USA).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [17], and are
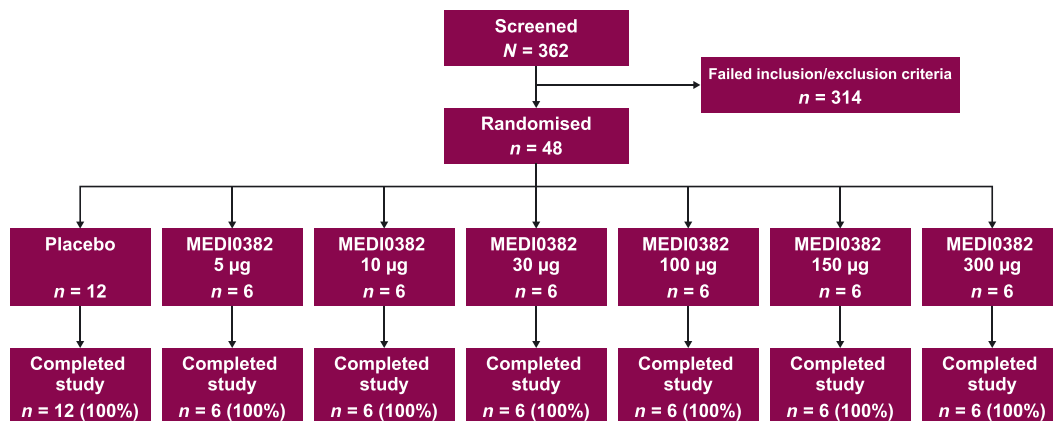
Figure 2
Subject disposition

Table 1

Subject demographics and baseline characteristics

	MEDI0382 (*n* = 6 per cohort)						Pooled MEDI0382 (*n* = 36)	Pooled placebo (*n* = 12)	Total population (*N* = 48)
	5 μg	10 μg	30 μg	100 μg	150 μg	300 μg			
Mean age, years (SD)	37.3 (6.4)	31.8 (6.8)	33.2 (10.4)	27.8 (4.3)	34.5 (6.5)	28.3 (5.9)	32.2 (7.3)	32.8 (9.1)	32.3 (7.7)
Male, *n* (%)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	36 (100)	12 (100)	48 (100)
Race, *n* (%)									
White	6 (100)	5 (83.3)	6 (100)	6 (100)	5 (83.3)	6 (100)	34 (94.4)	11 (91.7)	45 (93.8)
Other	0	1 (16.7)	0	0	1 (16.7)	0	2 (5.6)	1 (8.3)	3 (6.3)
Mean BMI, kg m^{-2} (SD)	27.6 (2.3)	24.5 (1.6)	24.7 (1.9)	26.1 (1.6)	26.4 (2.2)	27.4 (2.8)	26.1 (2.3)	25.7 (2.4)	26.0 (2.3)

BMI, body mass index; SD, standard deviation

Table 2

Summary of safety and TEAEs by MedDRA, SOC and PT

	MEDI0382 (*n* = 6 per cohort)						Pooled MEDI0382 (*n* = 36)	Pooled placebo (*n* = 12)
	5 μg	10 μg	30 μg	100 μg	150 μg	300 μg		
TEAEs, *n* (%)	2 (33.3)	3 (50.0)	4 (66.7)	2 (33.3)	5 (83.3)	5 (83.3)	21 (58.3)	2 (16.7)
TEAEs by SOC and PT, *n* (%)								
Cardiac disorders	0	1 (16.7)	0	1 (16.7)	0	1 (16.7)	3 (8.3)	0
Arrhythmia	0	0	0	1 (16.7)	0	0	1 (2.8)	0
AV block, second degree	0	1 (16.7)	0	0	0	0	1 (2.8)	0
Ventricular extrasystoles	0	0	0	0	0	1 (16.7)	1 (2.8)	0
GI disorders	0	1 (16.7)	0	1 (16.7)	5 (83.3)	5 (83.3)	12 (33.3)	1 (8.3)
Abdominal distension	0	0	0	0	2 (33.3)	0	2 (5.6)	0
Abdominal pain	0	1 (16.7)	0	0	0	0	1 (2.8)	0
Diarrhoea	0	1 (16.7)	0	0	0	0	1 (2.8)	0
Nausea	0	0	0	1 (16.7)	4 (66.7)	3 (50.0)	8 (22.2)	1 (8.3)
Vomiting	0	0	0	1 (16.7)	4 (66.7)	5 (83.3)	10 (27.8)	0
General disorders and administration site conditions	0	0	1 (16.7)	0	0	1 (16.7)	2 (5.6)	0
Application site erosion	0	0	1 (16.7)	0	0	0	1 (2.8)	0
Device-associated injury	0	0	0	0	0	1 (16.7)	1 (2.8)	0
Immune system disorders	0	0	1 (16.7)	0	0	0	1 (2.8)	0
Seasonal allergies	0	0	1 (16.7)	0	0	0	1 (2.8)	0
Infections and infestations	1 (16.7)	0	0	0	0	0	1 (2.8)	1 (8.3)
Nasopharyngitis	1 (16.7)	0	0	0	0	0	1 (2.8)	1 (8.3)
Injury, poisoning, and procedural complications	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Procedural dizziness	0	0	0	1 (16.7)	0	0	0	1 (2.8)

(continues)

Table 2

(Continued)

	MEDI0382 (*n* = 6 per cohort)						Pooled MEDI0382 (*n* = 36)	Pooled placebo (*n* = 12)
	5 µg	10 µg	30 µg	100 µg	150 µg	300 µg		
Musculoskeletal and connective tissue disorders	0	0	1 (16.7)	0	0	0	1 (2.8)	0
Musculoskeletal chest pain	0	0	1 (16.7)	0	0	0	1 (2.8)	0
Nervous system disorders	1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	7 (19.4)	0
Dizziness	0	1 (16.7)	1 (16.7)	0	2 (33.3)	1 (16.7)	5 (13.9)	0
Headache	1 (16.7)	0	1 (16.7)	1 (16.7)	1 (16.7)	0	4 (11.1)	0
Respiratory, thoracic, and mediastinal disorders	0	0	0	0	1 (16.7)	0	1 (2.8)	0
Oropharyngeal pain	0	0	0	0	1 (16.7)	0	1 (2.8)	0

AV, atrioventricular; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, systems organ class; TEAE, treatment-emergent adverse event

permanently archived in the Concise Guide to PHARMA-COLOGY 2017/18.

Results

Between 26 February 2015 and 12 August 2015, 48 subjects were randomized to receive MEDI0382 (*n* = 36; six subjects per cohort) or placebo (*n* = 12; two subjects per cohort). All subjects completed the study as planned and were included in the as-treated population (Figure 2). A total of 33 of 36 subjects who received MEDI0382 had evaluable post-dose pharmacokinetic data and were included in the pharmacokinetic population; only three subjects from the 5 µg cohort could not be included because of a lack of evaluable post-dose pharmacokinetic data. Demographic characteristics were generally balanced across treatment groups. The mean age of subjects in the as-treated population was 32.3 years,

all subjects were male, and the majority were white (93.8%; Table 1).

Overall, the incidence of TEAEs was higher in the MEDI0382 groups compared with the placebo group, and was highest in the 150 µg and 300 µg groups (Table 2). The majority of TEAEs were considered related to the investigational product, and related TEAEs were also more frequent in the highest MEDI0382 dose groups. At the preferred-term level, the most frequent TEAEs were vomiting and nausea (Table 2). The onset of these TEAEs approximated to the t_{max} (3–4 h post-dose) and subsided approximately 12 h post-dose. There was a total of 40 vomiting episodes for the 10 subjects who experienced vomiting. Of these subjects, 30 episodes were from five subjects at the MEDI0382 300 µg dose. With the exception of one event of vomiting in the MEDI0382 150 µg group, all events were considered related to the investigational product. All events resolved at the time of reporting and no event of vomiting led to withdrawal from the study or was classed as serious. However, because of the number of
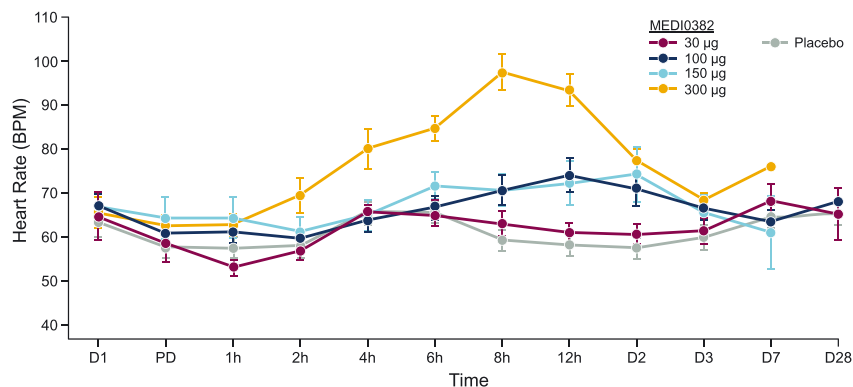

Figure 3

Effect of study drug treatment on heart rate (mean ± SEM) BPM, beats per minute; D, Day; h, hour; PD, pre-dose

Table 3

Pharmacokinetic parameters of MEDI0382 (all data are geometric mean [95% CI], unless otherwise specified)

Parameter	MEDI0382					
	5 µg (n = 3)	10 µg (n = 6)	30 µg (n = 6)	100 µg (n = 6)	150 µg (n = 6)	300 µg (n = 6)
C_{max}, ng ml^{-1}	0.47 (0.44–0.50)	0.80 (0.62–1.03)	3.00 (2.59–3.47)	6.19 (4.29–8.92)	8.97 (6.20–12.97)	20.98 (16.21–27.14)
t_{max}, h[a]	7.00 (5.88–10.00)	6.94 (4.00–13.50)	9.00 (4.50–10.02)	7.53 (4.50–10.00)	9.00 (4.00–12.00)	4.50 (4.00–5.88)
AUC_{0-last}, ng.h ml^{-1}	1.96 (0.58–6.64)	9.97 (7.01–14.17)	51.99 (44.55–60.67)	137.33 (106.15–177.67)	194.60 (162.84–232.56)	364.47 (298.50–445.02)
$AUC_{0-\infty}$, ng.h ml^{-1}	NC	NC	63.10[b] (51.49–77.33)	150.03 (118.44–190.04)	209.03 (178.45–244.86)	379.12 (310.26–463.25)
$t_{1/2}$, h	NC	NC	11.43[a] (8.42–15.50)	12.07 (9.58–15.20)	10.97 (8.60–13.99)	9.54 (8.63–10.56)

[a]Median (range)
[b]$n = 4$

AUC_{0-last}, area under the concentration–time curve from time zero to the last quantifiable concentration; $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; C_{max}, maximum observed plasma concentration; NC, not calculated; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to maximum observed plasma concentration

clinically significant events of vomiting observed at the 300 µg dose, the dose of MEDI0382 was de-escalated to 150 µg for the final cohort.

All TEAEs were grade 1 (mild) or grade 2 (moderate) in severity. There was one serious AE in the MEDI0382 10 µg group (atrioventricular block, second degree) that was considered unrelated to the investigational product and did not result in withdrawal from the study. There were no deaths or TEAEs that led to withdrawal from the study and, overall, there were no serious AEs related to the investigational product. No hepatic function abnormalities (an AESI) were observed, and no abnormalities in clinical laboratory or vital sign parameters were reported as TEAEs. Increased heart rate (Figure 3) and increased systolic blood pressure were observed with the MEDI0382 300 µg group. No trends were observed in vital sign parameters for any other treatment group.

Plasma concentrations of MEDI0382 were measurable until 16–24 h in all subjects in the MEDI0382 5 µg and 10 µg groups. Plasma concentrations of MEDI0382 were measurable until 48 h in all subjects in the MEDI0382 100 µg and 300 µg groups. No subject had quantifiable plasma concentrations of MEDI0382 at 72 h post-dose. The t_{max} was estimated to be between 4.50 and 9.00 h, with $t_{1/2}$ estimated to be between 9.54 and 12.07 h (Table 3). MEDI0382 was associated with linear pharmacokinetic profiles for $AUC_{0-\infty}$ and C_{max}
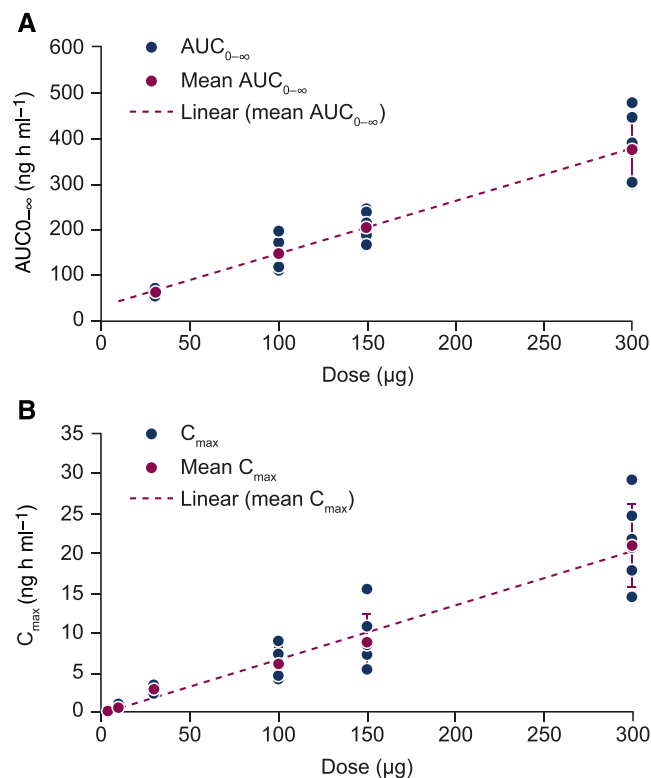
Figure 4

Dose proportionality of $AUC_{0-\infty}$ (A) and C_{max} (B) observed with MEDI0382 treatment $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; C_{max}, maximum observed plasma concentration

(Figure 4). No subjects tested positive for anti-drug antibodies following administration of MEDI0382 (data not shown).

A trend indicating a dose-dependent effect on glucose levels was observed even at low doses, especially after breakfast (2.0–4.5-h intervals post-dose) and dinner (13.0–14.5-h intervals post-dose; Figure 5). A dose-dependent reduction in food intake was also observed following single doses of MEDI0382 (Table 4).

Discussion

In this single-dose, Phase 1 study, MEDI0382 was generally well tolerated at doses ≤100 μg in healthy subjects. MEDI0382 showed a linear pharmacokinetic profile and no subjects tested positive for anti-drug antibodies. There was a trend towards dose-dependent reduction in glucose levels with MEDI0382 even at the lowest dose of 10 μg. Moreover, a step-wise reduction in food intake was observed with MEDI0382 compared with placebo.

Increases in oxyntomodulin, a naturally occurring GLP-1/glucagon receptor dual agonist, and GLP-1 are often observed following bariatric surgery [18, 19]. These increases in endog-

enous incretin levels are generally associated with rapid improvements in the control of blood glucose levels and marked weight reduction [15, 20]. Subcutaneous delivery of oxyntomodulin in overweight and obese subjects is associated with weight loss over a 4-week period [21]. Because of its short half-life, however, native oxyntomodulin does not represent an appropriate therapeutic option for the treatment of type 2 diabetes mellitus and obesity [22].

MEDI0382 is designed as a once-daily, synthetically produced oxyntomodulin-like peptide. By mimicking incretin changes observed after bariatric surgery, it is anticipated that GLP-1/glucagon receptor dual agonists, such as MEDI0382, will result in superior weight reduction and glucose level control compared with GLP-1 mono-agonist therapy [11]. As a step in this direction, this first-in-human study evaluated the safety, tolerability and pharmacokinetic properties of a single subcutaneous dose of MEDI0382 in healthy subjects.

With regard to safety, a higher proportion of TEAEs were observed in subjects receiving MEDI0382 compared with placebo. This difference in the proportion of TEAEs was largely driven by events of the system organ class of gastrointestinal disorders and nervous system disorders observed in the MEDI0382 group. Importantly, no event of vomiting led to
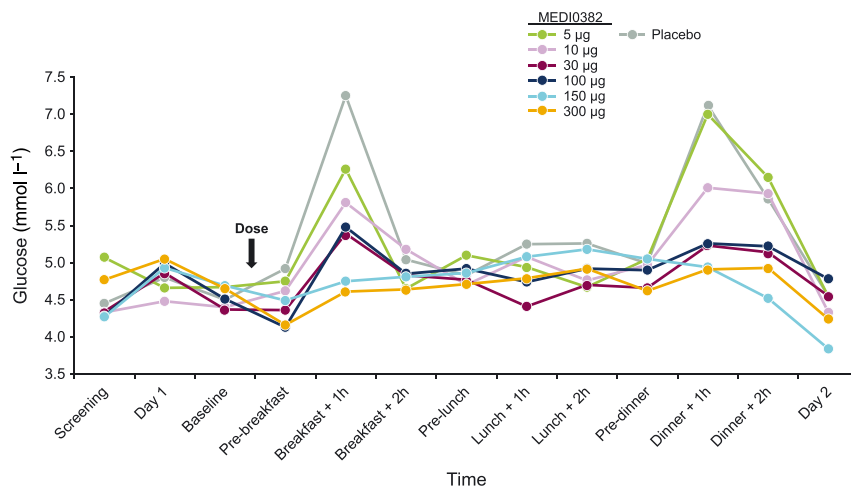
Figure 5

Effect of study drug treatment and food intake on median glucose levels over time

Table 4

Mean percentage reduction in food intake and median percentage of peak glucose levels following single doses of study drug treatment

Parameter, %	MEDI0382						Pooled placebo
	5 μg	10 μg	30 μg	100 μg	150 μg	300 μg	
Reduction in food intake	0	0	4.1	17.8	40.0	76.6	0
Median peak glucose level[a]	86	80	74	76	66	64	100

[a]After breakfast

withdrawal from the study or was classified as serious. Because significant increases in pulse rate have been observed with GLP-1 agonists after single-dose administration, including studies in healthy volunteers, as well as nausea and vomiting [23–25], these events were identified as AESIs [26]. A rise in systolic blood pressure was observed at the 300 μg dose. Although direct effects on blood pressure have been observed with administration of high-dose glucagon (3 mg), the relative glucagon agonist activity of a single 300 μg dose of MEDI0382 is unlikely to lead to a clinically significant rise in systolic blood pressure. The authors hypothesize that at least some of the rise in systolic blood pressure observed here may be due to profuse vomiting, driving anxiety in the highest dose cohort. In general, GLP-1 agonists have not been shown to increase blood pressure [27].

Even though this was a first-in-human study only evaluating single doses, a pharmacological effect on both plasma glucose and food intake was reported. Effects on mealtime glucose excursions were observed with doses as low as 10 μg, while there were also significant effects on food intake from 100 μg. Both observations are suggestive of the high potency of MEDI0382 in humans, supporting the pre-clinical evidence [10]. The observed glucose reduction also suggests that the effects of glucagon receptor agonism with MEDI0382, do not lead to hyperglycaemia.

After administration of increasing single subcutaneous doses (5 μg, 10 μg, 30 μg, 100 μg, 150 μg and 300 μg), MEDI0382 appeared to be moderately absorbed with a median peak plasma concentration observed between 4.50 and 9.00 h post-dose. The median $t_{1/2}$ of approximately 9.54 and 12.07 h could not be estimated accurately in the lowest MEDI0382 dose groups (5 μg and 10 μg) but was comparable across the other dose groups (30–300 μg).

As is common with approved GLP-1 mono-agonists [28, 29], tachyphylaxis, a reduction in gastrointestinal effects with multiple dosing, is expected with repeat administration of MEDI0382. Furthermore, dose titrations of GLP-1 mono-agonists such as semaglutide, have been shown to improve tolerability [30]. Gastrointestinal effects of MEDI0382 at a single dose of ≤150 μg occurred without any major changes in pulse or blood pressure. Thus, a 'tolerability window' exists in which MEDI0382 can be safely administered to subjects with type 2 diabetes mellitus at a dose expected to improve glycaemic control and drive weight reduction, without a negative impact on the cardiovascular risk profile. Such doses could also be used as a starting point for dose up-titrations. The results from this study indicate that commencing dosing of MEDI0382 up to 150 μg is acceptable with respect to initiating a multi-dose clinical study. This conclusion is further supported by the pharmacokinetic and pharmacodynamic data observed in this study.

Overall, these data were consistent with a predictable pharmacokinetic profile amenable to once-daily dosing, minimal accumulation of the compound in plasma after repeat dose, and steady-state achievement within 4–7 days. Exploratory endpoints suggested that a lowering of blood glucose levels and a reduction in food intake were observed after administration of a single dose of MEDI0382 to healthy volunteers. A limitation to this study is that the method used to assess food intake (proportion of serving returned to the nurse after a meal) may be subject to bias.

In conclusion, the safety and pharmacokinetic profile of MEDI0382 support a once-daily dosing regimen at doses less than 150 μg, followed by an up-titration to higher doses. Multiple dosing studies will further inform the profile of MEDI0382 with respect to optimal titration regimen and the relative clinical effects of GLP-1 and glucagon agonism in patients with type 2 diabetes mellitus.

Competing Interests

Contributors

All authors contributed to drafting this manuscript by providing critical revisions and important intellectual content, and all approved the final version for submission. P.D.A was the medical monitor of this study. P.D.A., W.P., C.R. and M.P. were involved in the conception and design of the study.S.K. and M.P. were involved in the acquisition of data. P.D.A., S.K., C.R., L.J. and W.P. were involved in data analysis and interpretation. S.K. was the principal investigator.

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