Diabetologia (2019) 62:373–386
https://doi.org/10.1007/s00125-018-4789-6

ARTICLE

Randomised, phase 1, dose-finding study of MEDI4166, a PCSK9 antibody and GLP-1 analogue fusion molecule, in overweight or obese patients with type 2 diabetes mellitus

Meena Jain[1] · Glenn Carlson[2] · William Cook[3] · Linda Morrow[4] · Marcella Petrone[1] · Nicholas E. White[1] · Tao Wang[3] · Jacqueline Naylor[1] · Philip Ambery[1] · Charles Lee[3] · Boaz Hirshberg[3]

Received: 8 June 2018 / Accepted: 31 October 2018 / Published online: 28 December 2018
© The Author(s) 2018

Abstract

Aims/hypothesis Cardiovascular disease is the leading cause of morbidity and mortality in people with type 2 diabetes. MEDI4166 is a proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody and glucagon-like peptide-1 (GLP-1) analogue fusion molecule designed to treat patients with type 2 diabetes who are at risk for cardiovascular disease. In this completed, first-in-human study, we evaluated the safety and efficacy of single or multiple doses of MEDI4166 in participants with type 2 diabetes.

Methods In this phase 1 study that was conducted across 11 clinics in the USA, eligible adults had type 2 diabetes, a BMI of ≥25 kg/m^2 to ≤42 kg/m^2, and LDL-cholesterol levels ≥1.81 mmol/l. Participants were randomised 3:1 to receive MEDI4166 or placebo using an interactive voice/web response system, which blinded all participants, investigators and study site personnel to the study drug administered. In 'Part A' of the study, five cohorts of participants received a single s.c. injection of MEDI4166 at 10 mg, 30 mg, 100 mg, 200 mg or 400 mg, or placebo. 'Part B' of the study consisted of three cohorts of participants who received an s.c. dose of MEDI4166 once weekly for 5 weeks at 50 mg, 200 mg or 400 mg, or placebo. The primary endpoint in Part A was safety. The co-primary endpoints in Part B were change in LDL-cholesterol levels and area under the plasma glucose concentration–time curve ($AUC_{0–4h}$) post-mixed-meal tolerance test (MMTT) from baseline to day 36. The pharmacokinetics and immunogenicity of MEDI4166 were also evaluated.

Results MEDI4166 or placebo was administered to $n = 30$ or $n = 10$ participants, respectively, in Part A of the study, and $n = 48$ or $n = 15$ participants, respectively, in Part B. The incidence of treatment-emergent adverse events (TEAEs) were comparable between MEDI4166 and placebo in both Part A (60% vs 50%) and Part B (79% vs 87%) of the study. Common TEAEs with MEDI4166 included injection-site reactions, diarrhoea and headache; there was no evidence for dose-related increases in TEAEs. In Part B of the study, at all tested doses of MEDI4166, there was a significant decrease in LDL-cholesterol levels vs placebo (least squares mean [95% CI]; MEDI4166 50 mg, −1.25 [−1.66, −0.84]; MEDI4166 200 mg, −1.97 [−2.26, −1.68]; MEDI4166 400 mg, −1.96 [−2.23, −1.70]; placebo, −0.03 [−0.35, 0.28]; all $p < 0.0001$). However, there were no clinically relevant reductions or significant differences between MEDI4166 vs placebo in glucose $AUC_{0–4h}$ post-MMTT (least squares mean [95% CI]; MEDI4166 50 mg, −10.86 [−17.69, −4.02]; MEDI4166 200 mg, −4.23 [−8.73, 0.28]; MEDI4166 400 mg, −2.59 [−7.14, 1.95]; placebo, −4.84 [−9.95, 0.28]; all $p > 0.05$). MEDI4166 was associated with a pharmacokinetic profile supportive of weekly dosing and an overall treatment-induced anti-drug antibody-positive rate of 22%.

Meena Jain and Glenn Carlson are joint first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-018-4789-6) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

✉ Meena Jain
JainM@MedImmune.com

[1] MedImmune Ltd, Milstein Building, Granta Park, Cambridge CB21 6GH, UK

[2] AstraZeneca, Gaithersburg, MD, USA

[3] MedImmune, Gaithersburg, MD, USA

[4] ProSciento Inc., Chula Vista, CA, USA

Research in context

What is already known about this subject?

- Despite the available therapies for managing hyperglycaemia and dyslipidaemia, cardiovascular disease remains the leading cause of morbidity and mortality in individuals with type 2 diabetes
- The combination of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition and glucagon-like peptide-1 (GLP-1) receptor activation is hypothesised to reduce the overall cardiovascular risk in patients with type 2 diabetes who require additional control of blood glucose and LDL-cholesterol levels

What is the key question?

- Will treatment with MEDI4166 (a PCSK9 antibody and GLP-1 peptide fusion molecule) be well tolerated and effectively decrease blood glucose and LDL-cholesterol levels in obese or overweight patients with type 2 diabetes?

What are the new findings?

- In this first-in-human phase 1 study, the safety and pharmacokinetic profiles of MEDI4166 supported once-weekly dosing
- Treatment with MEDI4166 resulted in a significant decrease in LDL-cholesterol level from baseline, compared with placebo, but had no clinically relevant impact on postprandial glucose levels

How might this impact on clinical practice in the foreseeable future?

- Based on these results, further clinical development of MEDI4166 was discontinued; however, this study illustrates the clinical application of a novel antibody–peptide platform, which combines distinct mechanisms of action of PCSK9 inhibitors and GLP-1 agonists, to help to achieve the goal of cardiovascular risk reduction in individuals with type 2 diabetes

Conclusions/interpretation MEDI4166 was associated with an acceptable tolerability profile and significantly decreased LDL-cholesterol levels in a dose-dependent manner in overweight or obese patients with type 2 diabetes. However, there were no significant reductions in postprandial glucose levels at any dose of MEDI4166.
Trial registration ClinicalTrials.gov NCT02524782
Funding This study was funded by MedImmune LLC, Gaithersburg, MD, USA.

Keywords First-in-human study · Glucagon-like peptide-1 analogue · Glucose · Low-density lipoprotein cholesterol · Multiple ascending dose · Pharmacokinetics · Phase 1 · Proprotein convertase subtilisin/kexin type 9 antibody · Single ascending dose · Type 2 diabetes mellitus

Abbreviations

CHO	Chinese hamster ovary
DPP-4	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1
HTRF	Homogenous time-resolved fluorescence
MMTT	Mixed-meal tolerance test
PCSK9	Proprotein convertase subtilisin/kexin type 9
TEAE	Treatment-emergent adverse event

Introduction

Diabetes is estimated to affect 425 million people and to cost US$727 billion in healthcare worldwide [1]. The growing pandemic of type 2 diabetes accounts for approximately 90% of this burden [1]. Type 2 diabetes is often associated with an increased risk for cardiovascular disease, which is the leading cause of morbidity and mortality in individuals with diabetes [2–5]. Other common coexisting conditions, such as hypertension, dyslipidaemia and obesity, further exacerbate the risk for cardiovascular disease [5]. Hence, guidelines for type 2 diabetes recommend that, in addition to controlling glucose levels, any risk factors for cardiovascular disease should be treated [5].

Blood glucose-lowering agents, in combination with lifestyle intervention, lipid-lowering drugs and/or antihypertensives, are often used to manage individuals with type 2 diabetes who are at risk for cardiovascular disease [5, 6]. More than 40% of patients receiving statin therapy for dyslipidaemia in type 2 diabetes fail to achieve a reduction in LDL-cholesterol levels by

a target decrease of 30–50% [5, 7, 8]. Similarly, more than 40% of patients with type 2 diabetes treated with blood glucose-lowering agents do not reach their glycaemic goals [9, 10]. Therefore, many individuals with type 2 diabetes have a residual risk for cardiovascular disease, despite receiving the recommended therapies for dyslipidaemia and hyperglycaemia.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an endogenous enzyme that promotes the degradation of LDL receptors on hepatocytes [11]. Inhibiting PCSK9 activity has been shown to maintain the expression of LDL receptors, which, in turn, decreases serum levels of LDL-cholesterol [11]. Currently, alirocumab and evolocumab are the only PCSK9 inhibitor antibodies approved for clinical use [12, 13]. In type 2 diabetes, PCSK9 inhibitors are recommended as adjuncts to maximally tolerated statin therapy in patients with atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol levels [5]. Moreover, inhibition of PCSK9 has been shown to significantly decrease cardiovascular outcomes in patients with type 2 diabetes and atherosclerotic disease [14]. Glucagon-like peptide-1 (GLP-1) is an endogenous hormone that stimulates insulin secretion in response to postprandial increases in glucose levels (i.e. the incretin effect) and slows gastric emptying [15]. Approved GLP-1 receptor agonists or GLP-1 analogues, such as liraglutide and exenatide, are resistant to degradation by dipeptidyl peptidase-4 (DPP-4) and thus provide robust and longer-acting efficacy [16]. GLP-1 receptor agonists or GLP-1 analogues are an attractive and recommended therapeutic option for type 2 diabetes because of their demonstrated effects on glycaemic control and weight loss, and positive impact on cardiovascular outcomes [6, 17–19].

MEDI4166 is an antibody–peptide fusion molecule comprised of a PCSK9 antibody and a GLP-1 analogue linked to the N-terminus of the antibody light chain using a peptide linker (M. Chodorge, MedImmune, Cambridge, UK, personal communication). MEDI4166 was designed to combine the mechanisms of action of PCSK9 inhibitors and GLP-1 agonists/analogues, described above, to treat patients with type 2 diabetes who require additional control of blood glucose and LDL-cholesterol levels, with the goal of reducing overall cardiovascular risk. Here, we report results from a phase 1, first-in-human, combined single ascending dose and multiple ascending dose study that evaluated the safety, efficacy, pharmacokinetics and immunogenicity of MEDI4166 in overweight or obese participants with type 2 diabetes.

Methods

Study design and procedures This was a phase 1, randomised, placebo-controlled, double-blind, combined single ascending dose ('Part A') and multiple ascending dose ('Part B') study conducted in overweight or obese participants with type 2 diabetes (ClinicalTrials.gov registration no. NCT02524782). All participants provided written, informed consent prior to participation in the study. The trial was conducted across 11 study sites in the USA and was approved by each respective institutional review board. The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidance for Good Clinical Practice.

Eligible participants were randomised 3:1, using an interactive voice/web response system (PAREXEL International, Billerica, MA, USA), to receive MEDI4166 or placebo. The study drug/placebo were identical in appearance and all participants, investigators and study site personnel were blinded to the investigational product. Part A of the study consisted of five cohorts of participants who received a single s.c. administration of MEDI4166 (10 mg, 30 mg, 100 mg, 200 mg or 400 mg) or placebo (Fig. 1a). Part B of the study consisted of three cohorts of participants who received once-weekly s.c. administration of MEDI4166 for 5 weeks (50 mg, 200 mg or 400 mg) or placebo (Fig. 1b). A dose-escalation committee, which was not blinded to treatment allocation, reviewed all safety data and made decisions on escalating to the next dose level. For safety, all participants were followed for ≥6 weeks after the last dose was administered.

Participants Eligible participants (aged 18–65 years) presented with type 2 diabetes and had a BMI of ≥25 kg/m^2 to ≤42 kg/m^2 and LDL-cholesterol level ≥1.81 mmol/l at screening. Metformin monotherapy was allowed during Part A and was required during Part B of the study. Participants who were taking sulfonylureas, DPP-4 inhibitors, α-glucosidase inhibitors or sodium–glucose cotransporter-2 inhibitors as adjuncts to metformin were eligible for the study after a washout period of 28 days. Statin therapy was allowed but it could not be initiated or adjusted within 6 weeks of screening. Individuals were excluded if they received a GLP-1 receptor agonist within 3 months prior to screening or they had taken a PCSK9 inhibitor at any time. Individuals with major complications of type 2 diabetes or who displayed evidence of cardiovascular disease were also excluded.

Study assessments The primary endpoint of Part A was safety. The incidence of treatment-emergent adverse events (TEAEs) and serious adverse events was recorded. Analyses of TEAEs included the type, severity and relationship to the study drug as summarised by the Medical Dictionary for Regulatory Activities, version 19.1 (www.meddra.org). The co-primary endpoints of Part B were change from baseline (day 1 pre-dose) to day 36 in LDL-cholesterol levels and glucose area under the plasma concentration–time curve from 0 h to 4 h ($AUC_{0–4h}$) post-mixed-meal tolerance test (MMTT).

In Part A, secondary efficacy endpoints included LDL-cholesterol levels and glucose $AUC_{0–4h}$ post-MMTT. In Part B, drug safety and the change in fructosamine levels from

baseline were evaluated as secondary objectives. The pharmacokinetics and immunogenicity of MEDI4166 were assessed as secondary objectives in both parts of the study. The following pharmacokinetic variables were assessed: maximum observed plasma concentration (C_{max}); time to C_{max} (T_{max}); terminal phase elimination half-life ($T_{½}$); AUC from time 0 extrapolated to infinity ($AUC_{0–inf}$); AUC from time 0 to the last measurable plasma concentration (Part A) or the end of the dosing interval (Part B) and apparent clearance (Part A) or apparent clearance at steady state (Part B). A sequential flow-through sandwich method on the Gyrolab System (Gyros Protein Technologies, Uppsala, Sweden), validated to current regulatory guidelines, was used to quantify serum levels of MEDI4166 in participants with type 2 diabetes. The method was specific and selective for MEDI4166, using anti-idiotype antibodies to MEDI4166 to capture and detect the analyte. Immunogenicity was evaluated by the incidence of treatment-emergent anti-drug antibodies to MEDI4166, which was defined as the sum of treatment-induced and treatment-boosted anti-drug antibody-positive responses. To test immunogenicity, blood samples were collected on days 1, 15, 29 and 43 in Part A and on days 1, 15, 29, 43 and 71 in Part B.

Safety was analysed in a subgroup of participants who had LDL-cholesterol levels <0.65 mmol/l at any point during either portion of the study. Exploratory endpoints assessed in Part B included free PCSK9 levels, fasting GLP-1 activity, insulin AUC post-MMTT, HbA_{1c} levels, fasting blood glucose levels, body weight and other lipid variables (total cholesterol, HDL-cholesterol, triacylglycerols, lipoprotein[a] and apolipoproteins A_1 and B).

Fasting GLP-1 activity was determined ex vivo against a human GLP-1 receptor-expressing Chinese hamster ovary (CHO) cell line (AstraZeneca, Cambridge, UK; mycoplasma free) in serum samples following an overnight fast of ≥8 h. Using a competitive homogenous time-resolved fluorescence (HTRF) assay (Cisbio, Codolet, France), changes in CHO intracellular cAMP levels resulting from MEDI4166-receptor interaction, were assessed following cellular lysis. Within the assay, unlabelled cAMP produced from the CHO cell line competes with a known concentration of cAMP–d2 to bind to anti-cAMP–cryptate. The level of HTRF between the d2 and cryptate molecules was indirectly proportional to the concentration of intracellular cAMP and, therefore, MEDI4166 levels. Unknown levels of MEDI4166 in samples were then quantified from a MEDI4166–agonist curve. This validated method [20, 21] was selective and specific for MEDI4166 and presented acceptable accuracy (within 25%) and precision (with 30%) for cell-based bioassays (MedImmune, data not shown).

Experiments in cells were replicated more than 5 times. No randomisation was carried out and experimenters were not blinded.

Statistical analyses A sample size of 40 individuals was planned for use in Part A. Participants were randomised 3:1 to receive MEDI4166 ($n = 6$ per cohort) or placebo ($n = 2$ per cohort). For all analyses in Part A, the respective placebo arm was pooled. This sample size is consistent with those typically used for first-in-human studies and was empirically determined as sufficient to obtain initial safety and pharmacokinetic data.

In Part B, individuals were randomised 3:1 to receive MEDI4166 or placebo. Accounting for a dropout rate of 20%, a sample size of 12 participants for the 50 mg dose level (MEDI4166, $n = 9$; placebo, $n = 3$) was required to sufficiently assess safety. A sample size of 24 participants per cohort was required for the 200 mg (MEDI4166, $n = 18$; placebo, $n = 6$) and 400 mg (MEDI4166, $n = 18$; placebo, $n = 6$) dose levels. Accounting for a dropout rate of 20%, the planned sample

Fig. 1 Study design for (**a**) Part A and (**b**) Part B of the study. The dose-escalation committee reviewed all safety data and made decisions on escalating to the next dose level. DEC, dose escalation committee

sizes (MEDI4166, $n = 14$ per cohort; placebo, $n = 7$ per cohort) provided a two-sided significance level of 0.05 with 80% power to detect a 25% relative decrease in glucose AUC (assuming CV 0.2) and 85% power to detect a 50% relative decrease in LDL-cholesterol levels (assuming CV 0.5) at week 5 between treatment groups. For all analyses in Part B, data from the respective placebo arms were pooled.

Safety data were summarised in each category and treatment group. The co-primary endpoints and exploratory endpoints in Part B were analysed using ANCOVA adjusted for baseline and treatment group, with a two-sided significance level of 0.05. There was no pre-specified plan to split the α or test the two primary endpoints in a hierarchical manner. Pharmacokinetic variables were evaluated by non-compartmental analysis using Phoenix WinNonlin 6.3 (Certara USA, Princeton, NJ, USA). Anti-drug antibody responses to MEDI4166 were assessed using tiered analysis to include screening, confirmatory and titre assay components. The positive and negative cut points were statistically determined from drug-naive validation samples taken from a population with type 2 diabetes (validation study: 2016-MEDI4166-0116 [data not shown]) [22]. Data analyses were conducted using SAS 9.3, or higher, software (SAS Institute, Cary, NC, USA). Data are expressed as mean ± SEM.

Results

Participants Between 7 October 2015 and 14 April 2017, 458 individuals were assessed for eligibility. Of those screened, 40 participants were randomised in Part A (consisting of five cohorts) to receive MEDI4166 ($n = 30$) or placebo ($n = 10$) and 63 participants were randomised in Part B (consisting of three cohorts) to receive MEDI4166 ($n = 48$) or placebo ($n = 15$) (Fig. 2). Participant demographics and baseline characteristics were well balanced between treatment groups and among dosing levels in Part A (Table 1) and Part B (Table 2) of the study.

Safety In Part A, the incidence of TEAEs were comparable at all tested doses of MEDI4166 vs placebo (primary endpoint; Table 3). The most common TEAEs in participants treated with MEDI4166 in Part A were nausea and headache. Most TEAEs were mild to moderate in severity and none led to treatment discontinuations in Part A of the study. There were no serious adverse events or deaths in either part of the study.

In Part B, the incidence of TEAEs was comparable at all tested doses of MEDI4166 vs placebo (Table 4). Injection-site reaction and diarrhoea were the most common TEAEs observed with MEDI4166 in Part B. Most events were mild or

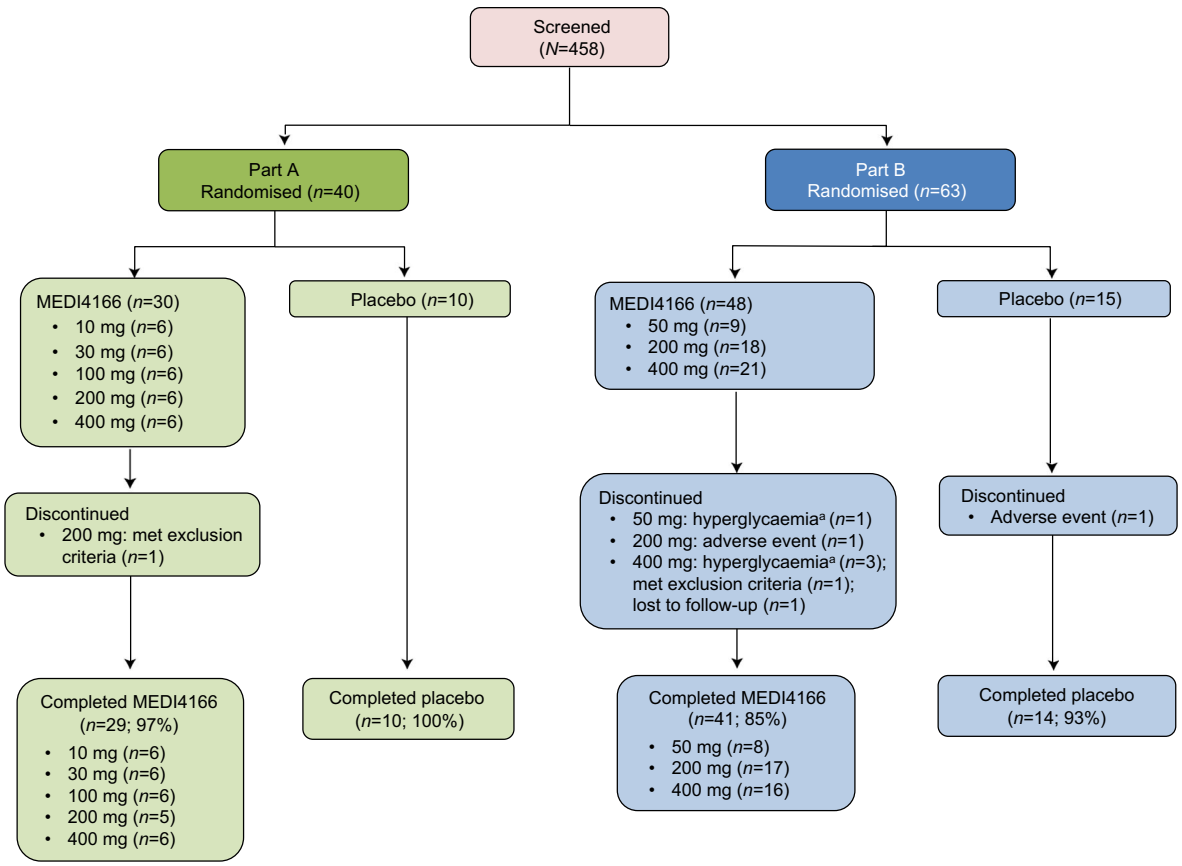

Fig. 2 Participant disposition. [a]Not considered to be an adverse event

Table 1 Participant demographics and baseline characteristics in Part A of the study

Variable	MEDI4166					Placebo
	10 mg ($n = 6$)	30 mg ($n = 6$)	100 mg ($n = 6$)	200 mg ($n = 6$)	400 mg ($n = 6$)	($n = 10$)
Age, years	54.3 (6.4)	58.7 (5.2)	55.2 (7.9)	55.7 (6.4)	57.3 (5.0)	58.7 (3.8)
Sex, *n* (%)						
Male	3 (50)	2 (33)	5 (83)	1 (17)	4 (67)	4 (40)
Female	3 (50)	4 (67)	1 (17)	5 (83)	2 (33)	6 (60)
Race, *n* (%)						
Black	3 (50)	0	0	1 (17)	0	3 (30)
White	3 (50)	6 (100)	6 (100)	5 (83)	6 (100)	7 (70)
BMI, kg/m^2	32.5 (4.1)	31.5 (2.0)	31.0 (3.2)	32.7 (3.5)	31.6 (3.1)	33.0 (3.7)
Heart rate, bpm	73.8 (6.8)	69.5 (5.3)	64.2 (9.5)	71.0 (11.0)	58.5 (7.7)	71.9 (9.5)
BP, mmHg						
Systolic	129.8 (8.7)	123.8 (9.6)	123.0 (3.4)	121.5 (17.4)	121.3 (11.2)	124.8 (7.8)
Diastolic	81.8 (4.3)	71.0 (6.9)	71.3 (8.6)	75.0 (6.4)	75.3 (5.9)	77.1 (5.9)
Duration of T2DM, years	11.8 (10.0)	8.8 (6.4)	8.2 (2.9)	9.3 (4.0)	12.2 (4.4)	7.8 (5.7)
HbA_{1c}						
mmol/mol	66.8 (7.7)	65.7 (5.6)	61.8 (9.6)	64.2 (11.4)	68.7 (10.4)	60.2 (6.9)
%	8.3 (0.7)	8.2 (0.5)	7.8 (0.9)	8.0 (1.0)	8.4 (1.0)	7.7 (0.6)
Fasting glucose, mmol/l	11.8 (3.2)	10.2 (2.0)	11.7 (3.1)	10.4 (5.5)	12.3 (2.8)	9.3 (3.2)
Fasting insulin, pmol/l	278.1 (144.6)	157.2 (47.0)	183.9 (79.1)	168.5 (158.1)	118.1 (56.3)	208.9 (109.5)
LDL-cholesterol, mmol/l	2.52 (0.53)	2.41 (0.81)	3.39 (1.65)	3.41 (0.95)	2.71 (0.53)	3.17 (0.61)
Concomitant medications, *n* (%)						
Metformin	6 (100)	6 (100)	5 (83)	6 (100)	6 (100)	10 (100)
Statins	6 (100)	3 (50)	1 (17)	2 (33)	1 (17)	6 (60)

Data are shown as mean (SD) unless otherwise specified

bpm, beats per min; T2DM, type 2 diabetes mellitus

moderate in severity; however, one participant treated with multiple doses of MEDI4166 at 50 mg experienced a severe TEAE of headache. This event was considered by the investigator to be unrelated to the study drug. TEAEs leading to study discontinuations in Part B included mild hyperglycaemia with multiple doses of MEDI4166 200 mg ($n = 1$; considered unrelated to the study drug) and moderately severe dyspepsia with placebo ($n = 1$; considered related to the study drug). With the exception of injection-site reactions, (Table 4), there was no evidence for a dose-related increase in the incidence or severity of TEAEs in either part of the study.

A subgroup analysis of participants with LDL-cholesterol levels <0.65 mmol/l during the study showed no increased incidence or severity of TEAEs (Tables 3 and 4). Furthermore, there were no clinically relevant changes in heart rate or blood pressure with MEDI4166 in either part of the study (data not shown).

Efficacy In Part B, treatment with multiple doses of MEDI4166 resulted in significant, dose-dependent decreases from baseline to day 36 in LDL-cholesterol levels compared with placebo (co-primary endpoint; $p < 0.0001$ at all tested doses; Table 5). However, no significant effect in the change from baseline to day 36 in glucose $AUC_{0–4h}$ post-MMTT was observed with multiple doses of MEDI4166 vs placebo (co-primary endpoint; $p > 0.05$ at all tested doses; Table 5). Similarly, in Part A, single administration of MEDI4166 resulted in dose-dependent decreases from baseline in LDL-cholesterol levels (Fig. 3a) but not glucose $AUC_{0–4h}$ post-MMTT (Fig. 3b).

In Part B, a dose-dependent decrease in free PCSK9 levels was observed with MEDI4166 at 200 mg and 400 mg vs placebo (Fig. 4a). In parallel with the decreased PCSK9 levels, there was a dose-dependent decrease from baseline in percentage of LDL-cholesterol levels with MEDI4166 (Fig. 4b). An appreciable increase in GLP-1 activity was only observed with MEDI4166 at 400 mg vs placebo in Part B of the study (ESM Fig. 1). This increase in GLP-1 activity was, however, not reflected in the observed changes from baseline in percentage of glucose $AUC_{0–4}$ post-MMTT, even at the 400 mg dose level (Fig. 4c).

In Part B, significant decreases in total cholesterol and apolipoprotein B levels from baseline to day 36 were observed at all tested doses of MEDI4166 vs placebo (Table 6). At higher

Table 2 Participant demographics and baseline characteristics in Part B of the study

Variable	MEDI4166			Placebo
	50 mg ($n = 9$)	200 mg ($n = 18$)	400 mg ($n = 21$)	($n = 15$)
Age, years	58.0 (7.4)	55.7 (5.4)	55.9 (7.3)	56.4 (4.4)
Sex, *n* (%)				
Male	1 (11)	12 (67)	13 (62)	5 (33)
Female	8 (89)	6 (33)	8 (38)	10 (67)
Race, *n* (%)				
Black	1 (11)	2 (11)	4 (19)	7 (47)
White	7 (78)	16 (89)	17 (81)	8 (53)
Multiple categories	1 (11)	0	0	0
BMI, kg/m^2	32.2 (4.0)	32.2 (4.8)	30.9 (3.9)	32.7 (4.0)
Heart rate, bpm	72.8 (11.2)	68.3 (6.0)	72.2 (10.4)	69.5 (7.6)
BP, mmHg				
Systolic	127.4 (13.7)	119.5 (13.1)	122.2 (10.7)	122.7 (11.8)
Diastolic	70.0 (12.6)	75.3 (5.9)	77.5 (6.1)	74.3 (7.7)
Duration of T2DM, years	10.2 (4.9)	9.1 (4.5)	9.7 (6.3)	9.5 (5.3)
HbA_{1c}				
mmol/mol	69.9 (9.0)	65.6 (9.1)	65.8 (8.5)	67.4 (9.5)
%	8.6 (0.8)	8.2 (0.8)	8.2 (0.8)	8.3 (0.9)
Fasting glucose, mmol/l	13.7 (2.7)	11.2 (2.2)	11.5 (3.2)	11.2 (3.0)
Fasting insulin, pmol/l	151.8 (84.8)	190.8 (80.0)	375.7 (570.1)	184.5 (154.8)
LDL-cholesterol, mmol/l	2.94 (0.76)	2.95 (0.95)	2.81 (0.80)	2.89 (1.08)
Concomitant medications, *n* (%)				
Metformin	9 (100)	18 (100)	21 (100)	15 (100)
Statins	2 (22)	4 (22)	9 (43)	6 (40)

Data are shown as mean (SD), unless otherwise specified

bpm, beats per min; T2DM, type 2 diabetes mellitus

doses of MEDI4166, significant reductions in triacylglycerol and lipoprotein(a) and increases in HDL-cholesterol levels were observed compared with placebo (Table 6). No clinically relevant impact on apolipoprotein A_1 levels was observed with MEDI4166 at any dose level (Table 6). Similarly, MEDI4166 had no effect on insulin AUC, HbA_{1c}, body weight or fasting plasma glucose levels (ESM Table 1). Moreover, no significant change from baseline to day 36 in fructosamine levels was observed at any tested dose of MEDI4166 vs placebo in Part B of the study (ESM Table 1).

Pharmacokinetics There was a dose-dependent increase in mean serum concentrations of MEDI4166 after a single dose (Fig. 5a) and at week 5 of multiple weekly dosing (Fig. 5b). MEDI4166 was absorbed with a T_{max} of 2.0–5.5 days and had a $T_{½}$ of 3.8–7.0 days (Tables 7 and 8). Exposure to a single dose or multiple doses of MEDI4166 (as measured by C_{max} and $AUC_{0–inf}$) appeared to be nonlinear. In Part B, however, MEDI4166 showed exposure that was greater than proportional to dose increases and demonstrated high interindividual variability (Tables 7 and 8).

Immunogenicity In Part A, 20% (6/30) of participants receiving MEDI4166 had treatment-emergent anti-drug antibody-positive responses. Of these participants, 17% (5/30) presented with treatment-induced responses and 3% (1/30) presented with treatment-boosted responses. In Part B, 23% (11/48) of participants treated with MEDI4166 had treatment-emergent anti-drug antibody-positive responses; all events were treatment-induced. Of participants who received placebo, 10% (1/10) in Part A and 7% (1/15) in Part B had treatment-emergent anti-drug antibody-positive responses; all events were treatment-induced. Visual analyses of pharmacokinetic profiles of individuals who were anti-drug antibody-positive vs those who were anti-drug antibody-negative did not suggest a major impact of immunogenicity on MEDI4166 pharmacokinetics or pharmacodynamics (data not shown).

Discussion

In this phase 1, randomised, placebo-controlled, double-blind study in overweight or obese participants with type 2 diabetes,

Table 3 Summary of safety in Part A of the study (primary endpoint)

Safety variable	MEDI4166					Placebo
	10 mg ($n = 6$)	30 mg ($n = 6$)	100 mg ($n = 6$)	200 mg ($n = 6$)	400 mg ($n = 6$)	($n = 10$)
TEAE	5 (83)	4 (67)	4 (67)	1 (17)	4 (67)	5 (50)
Treatment-related AE	2 (33)	2 (33)	1 (17)	0	3 (50)	3 (30)
Leading to discontinuation	0	0	0	0	0	0
Serious AE	0	0	0	0	0	0
≥Grade 3 severity	0	0	0	0	0	0
Deaths	0	0	0	0	0	0
TEAEs by PT if reported in ≥2 participants						
Nausea	2 (33)	0	1 (17)	1 (17)	1 (17)	5 (50)
Headache	0	3 (50)	1 (17)	0	0	2 (20)
Vomiting[a]	2 (33)	0	0	0	0	1 (10)
Hot flush	2 (33)	0	0	0	0	0
Subgroup analysis in those with LDL-cholesterol <0.65 mmol/l						
Participants (n)	0	0	1 (17)	1 (17)	2 (33)	0
TEAEs	0	0	0	0	1 (50)	0

Data are shown as n (%)

[a] Adverse event of special interest

AE, adverse event; PT, preferred term

Table 4 Summary of safety in Part B of the study

Safety variable	MEDI4166			Placebo
	50 mg ($n = 9$)	200 mg ($n = 18$)	400 mg ($n = 21$)	($n = 15$)
TEAE	7 (78)	13 (72)	18 (86)	13 (87)
Treatment-related AE	4 (44)	9 (50)	13 (62)	11 (73)
Leading to discontinuation	0	1 (6)	0	1 (7)
Serious AE	0	0	0	0
≥Grade 3 severity	1 (11)	0	0	0
Deaths	0	0	0	0
TEAEs by PT if reported in ≥2 participants				
Injection-site reaction	1 (11)	5 (28)	7 (33)	4 (27)
Injection-site erythema	0	4 (22)	3 (14)	0
Diarrhoea	4 (44)	2 (11)	4 (19)	3 (20)
Headache	3 (33)	1 (6)	3 (14)	4 (27)
Dyspepsia	0	3 (17)	1 (5)	1 (7)
Nausea	1 (11)	0	2 (10)	1 (7)
Constipation	1 (11)	0	0	3 (20)
Urinary-tract infection	0	2 (11)	0	0
Pruritus	0	0	2 (10)	0
Tachycardia	0	0	0	2 (13)
Cough	0	0	0	2 (13)
Subgroup analysis in those with LDL-cholesterol <0.65 mmol/l				
Participants (n)	2	8	15	1
TEAEs	2 (100)	5 (63)	13 (87)	0

Data are shown as n (%)

AE, adverse event; PT, preferred term

Table 5 Change from baseline to day 36 in LDL-cholesterol and glucose $AUC_{0\text{-}4h}$ post-MMTT in Part B of the study (co-primary endpoints)

Lipid variable	MEDI4166			Placebo
	50 mg ($n = 9$)	200 mg ($n = 18$)	400 mg ($n = 21$)	($n = 15$)
LDL-cholesterol				
LS mean (95% CI), mmol/l	−1.25 (−1.66, −0.84)	−1.97 (−2.26, −1.68)	−1.96 (−2.23, −1.70)	−0.03 (−0.35, 0.28)
p value[a]	<0.0001	<0.0001	<0.0001	–
Mean change, % (SD)	−37.8 (43.7)	−70.8 (13.2)	−66.1 (27.4)	1.4 (15.8)
Glucose $AUC_{0\text{–}4h}$ post-MMTT				
LS mean (95% CI), mmol/l × h	−10.86 (−17.69, −4.02)	−4.23 (−8.73, 0.28)	−2.59 (−7.14, 1.95)	−4.84 (−9.95, 0.28)
p value[a]	0.1617	0.8589	0.5145	–
Mean change, % (SD)	−20.25 (7.06)	−10.13 (14.77)	−3.65 (18.17)	−8.32 (16.05)

[a] *p* values are vs placebo

LS, least squares

the primary endpoint of Part A was met, but only one of the two co-primary endpoints in Part B was met. In Part A, the incidences of TEAEs were comparable between treatment arms and MEDI4166 was generally well tolerated at all tested doses. In Part B, a significant decrease from baseline to day 36 in LDL-cholesterol levels was observed at all tested doses of MEDI4166 vs placebo but no significant differences in glucose $AUC_{0\text{–}4h}$ post-MMTT were observed between treatment groups. Based on these results, further clinical development of MEDI4166 as a dual-targeted therapy for patients with type 2 diabetes who are at risk for cardiovascular disease was discontinued.

Most TEAEs observed with MEDI4166 were mild or moderate in severity. The incidence of gastrointestinal-related TEAEs with MEDI4166, such as vomiting and nausea, is consistent with the safety profile of other GLP-1 receptor agonists approved for type 2 diabetes [23]. Furthermore, the TEAE of injection-site reactions aligns with results from previous clinical trials with approved GLP-1 receptor agonists [24] and PCSK9-antibody inhibitors [25]. No potential safety concerns with MEDI4166 were identified in the subgroup analysis of participants exhibiting very low levels of LDL-cholesterol following treatment. These results should, however, be interpreted with caution due to the relatively small sample sizes (typical of early-phase clinical trials).

The observed exposures to MEDI4166 at all tested doses were much lower compared with predictions based on preclinical studies in rats and cynomolgus monkeys. For example, in the preclinical studies, the observed vs predicted exposure following a single dose of MEDI4166 at 400 mg by AUC was 824.1 μmol/l × day vs 2228.1 μmol/l × day and by C_{max} was 65.2 μmol/l vs 176.3 μmol/l (M. Chodorge, MedImmune, personal communication). The presence of anti-drug antibodies did not affect the safety, pharmacokinetics or pharmacodynamics of MEDI4166 compared with participants who did not have anti-drug antibody-positive responses. Overall, MEDI4166

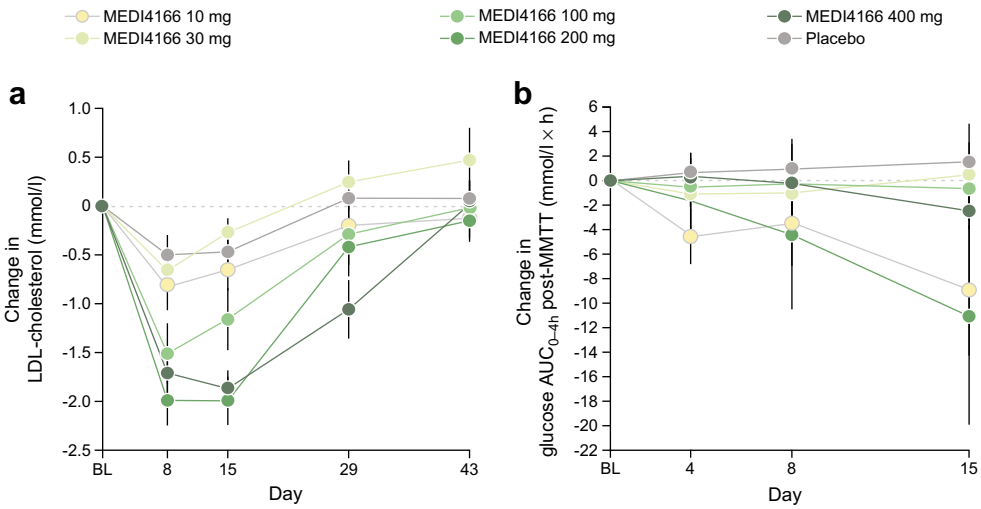

Fig. 3 Change from baseline in (**a**) LDL-cholesterol levels and (**b**) glucose $AUC_{0\text{–}4h}$ post-MMTT in Part A of the study with MEDI4166 at 10 mg, 30 mg, 100 mg, 200 mg or 400 mg ($n = 6$ for each dosing level) or placebo ($n = 10$). Data are means ± SEM. BL, baseline

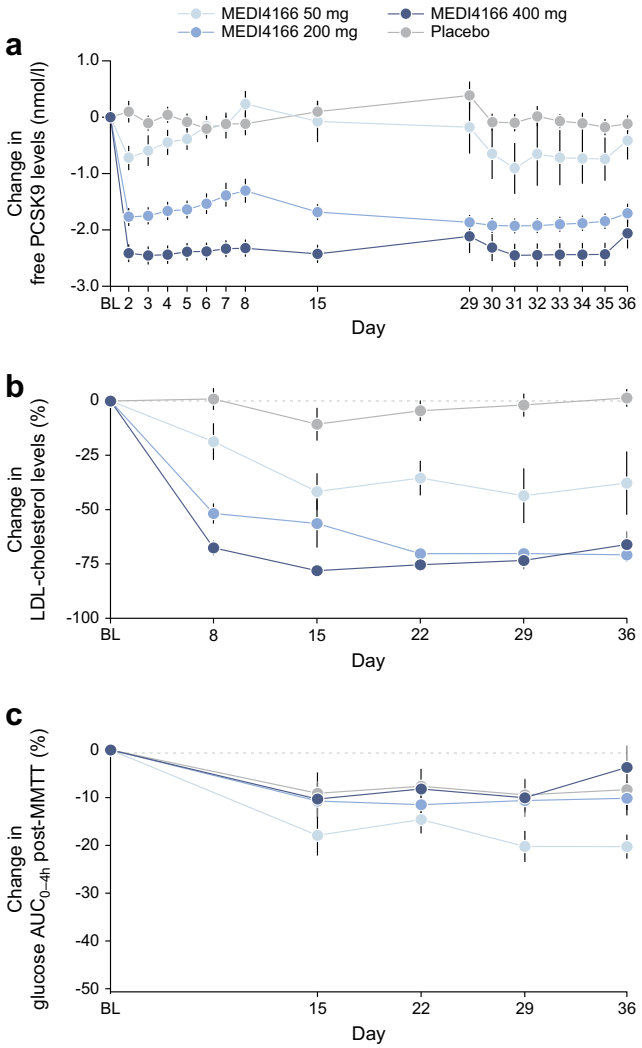

Fig. 4 Change from baseline in (**a**) free PCSK9 levels, (**b**) percentage LDL-cholesterol levels, (**c**) and percentage glucose $AUC_{0–4h}$ post-MMTT over time in Part B of the study with MEDI4166 at 50 mg ($n = 9$), 200 mg ($n = 18$) or 400 mg ($n = 21$) or placebo ($n = 15$). Data are means ± SEM. BL, baseline

was well tolerated and was associated with a pharmacokinetic profile potentially suitable for a once-weekly dosing regimen, despite being associated with a high degree of interindividual variability.

Robust and significant dose-dependent decreases in LDL-cholesterol levels were observed with single (33–63%) and multiple doses (44–68%) of MEDI4166. In addition to reduced LDL-cholesterol levels, at the higher dose levels of MEDI4166 there were significant decreases from baseline in total cholesterol, apolipoprotein B and lipoprotein(a) levels in Part B. The effect of MEDI4166 on LDL-cholesterol levels is comparable to effects seen in early-phase trials with other PCSK9 inhibitors. Specifically, dose-dependent decreases from baseline in LDL-cholesterol levels were observed with alirocumab (25–75%) in individuals with primary hypercholesterolaemia [26] and with evolocumab (66%) in individuals with heterozygous familial hypercholesterolaemia [27]. Moreover, both alirocumab and evolocumab significantly decreased other lipid variables, including total cholesterol, apolipoprotein B and lipoprotein(a) levels [26, 27]. The efficacy of GLP-1 receptor agonists in improving glycaemic control and decreasing body weight has been clearly demonstrated in type 2 diabetes [19, 28]. Treatment with MEDI4166, however, had no clinically relevant impact on postprandial glucose levels, fasting glucose levels, HbA_{1c} levels or body weight at any of the doses used in our study. The ability of MEDI4166 treatment to decrease LDL-cholesterol levels but not glucose levels may be explained by the decrease in free PCSK9 levels and lack of sufficient GLP-1 activity, respectively. Our results suggest that the effects of MEDI4166 on GLP-1 activity were inadequate for improving glycaemic control as measured by glucose $AUC_{0–4h}$ post-MMTT. Conversely, the clear impact of MEDI4166 treatment on decreasing free PCSK9 levels parallels its robust effect of reducing LDL-cholesterol levels. It is unclear why MEDI4166 differentially affects LDL-cholesterol and glucose levels but this may be related to insufficient potency at the GLP-1 receptor combined with lower-than-expected exposure, as described below.

The tested doses of MEDI4166 in this study were based on a target-mediated drug disposition pharmacokinetic–pharmacodynamic model tailored for the study drug. Based on simulations using this model, MEDI4166 at the tested doses was expected to achieve ≥90% suppression of endogenous levels of PCSK9 levels, similar to that observed with alirocumab 150 mg (M. Chodorge, MedImmune, personal communication) [29]. Moreover, these doses were chosen to obtain GLP-1 activity similar to that observed with daily liraglutide 1.8 mg and weekly dulaglutide 1.5 mg (M. Chodorge, MedImmune, personal communication) [30]. Multiple doses of MEDI4166 at the highest dose tested (400 mg) suppressed PCSK9 almost completely and durably, and this translated to a sustained decrease in plasma LDL-cholesterol levels. However, the increase in GLP-1 activity observed with MEDI4166 did not lead to a clinically meaningful effect on glucose control. These results suggest an unbalanced dual pharmacology of MEDI4166 in humans that was not expected from early preclinical data. The pharmacokinetic–pharmacodynamic model was updated during the clinical study to determine feasibility for dose escalation. The lower-than-expected exposure, high interindividual variability, nonlinear pharmacokinetics and lack of glucose-lowering effects with MEDI4166 introduced a high level of uncertainty into simulated scenarios and did not support further dose escalation in the clinic (MedImmune, data not shown).

The original pharmacokinetic–pharmacodynamic model that was used to predict study doses was based, in part, on potency assessments conducted in the GLP-1 receptor cAMP accumulation CHO cell assay (for a brief description, please

Table 6 Change from baseline to day 36 in lipid variables in Part B of the study

Lipid variable	MEDI4166			Placebo
	50 mg ($n = 9$)	200 mg ($n = 18$)	400 mg ($n = 21$)	($n = 15$)
Total cholesterol				
LS mean (95% CI), mmol/l	−1.45 (−1.95, −0.96)	−2.49 (−2.84, −2.14)	−2.28 (−2.61, −1.96)	−0.21 (−0.60, 0.17)
p value[a]	0.0002	<0.0001	<0.0001	–
Mean change, % (SD)	−26.0 (29.8)	−52.3 (8.5)	−45.4 (20.3)	−2.6 (12.4)
Apolipoprotein B				
LS mean (95% CI), g/l	−0.38 (−0.50, −0.27)	−0.60 (−0.68, −0.51)	−0.59 (−0.67, −0.52)	−0.05 (−0.14, 0.04)
p value[a]	<0.0001	<0.0001	<0.0001	–
Mean change, % (SD)	−35.1 (31.0)	−60.7 (11.6)	−56.8 (21.5)	−2.5 (12.3)
Triacylglycerols				
LS mean (95% CI), mmol/l	−0.59 (−0.91, −0.27)	−0.89 (−1.11, −0.67)	−0.73 (−0.94, −0.52)	−0.43 (−0.67, −0.18)
p value[a]	0.4211	0.0078	0.0677	–
Mean change, % (SD)	−13.6 (26.5)	−36.2 (22.8)	−30.0 (19.9)	0 (41.0)
Lipoprotein(a)				
LS mean (95% CI), nmol/l	3.5 (−7.4, 14.4)	−10.8 (−18.4, −3.1)	−8.0 (−15.2, −0.7)	21.9 (13.2, 30.5)
p value[a]	0.0101	<0.0001	<0.0001	–
Mean change, % (SD)	18.9 (71.2)	−33.5 (29.3)	−17.4 (27.5)	33.8 (42.9)
HDL-cholesterol				
LS mean (95% CI), mmol/l	−0.02 (−0.10, 0.07)	0.05 (−0.01, 0.11)	0.12 (0.07, 0.18)	−0.02 (−0.08, 0.05)
p value[a]	0.9653	0.1286	0.0017	–
Mean change, % (SD)	−3.0 (17.3)	11.1 (11.7)	13.1 (17.9)	−1.8 (9.7)
Apolipoprotein A_1				
LS mean (95% CI), g/l	−0.05 (−0.13, 0.03)	−0.04 (−0.10, 0.01)	−0.04 (−0.09, 0.02)	−0.08 (−0.14, −0.02)
p value[a]	0.5783	0.4243	0.3162	–
Mean change, % (SD)	−3.3 (13.9)	−0.2 (8.7)	−4.0 (11.6)	−5.8 (8.0)

[a] *p* values are vs placebo

LS, least squares

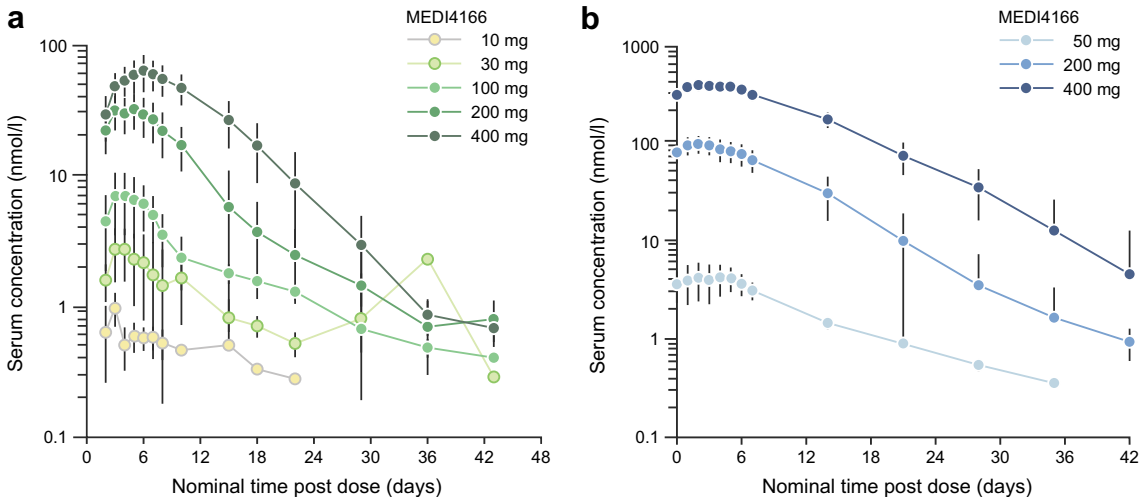

Fig. 5 (**a**) Serum concentrations of MEDI4166 over time following a single dose at 10 mg, 30 mg, 100 mg, 200 mg or 400 mg ($n = 6$ for each dosing group) in Part A of the study and (**b**) serum concentrations of MEDI4166 at week 5 following weekly administration at 50 mg ($n = 9$), 200 mg ($n = 18$) or 400 mg ($n = 21$) in Part B of the study. Data are geometric means ± SEM and are plotted on a logarithmic scale (base 10)

Table 7 Summary of pharmacokinetics in Part A of the study

Variable	MEDI4166				
	10 mg ($n = 6$)	30 mg ($n = 6$)	100 mg ($n = 6$)	200 mg ($n = 6$)	400 mg ($n = 6$)
C_{max}, nmol/l	0.83 (0.12, 4.35)	3.14 (1.34, 7.50)	8.01 (3.40, 18.78)	35.83 (17.69, 72.56)	65.19 (32.63, 130.06)
T_{max}, days[a]	3.0 (2.0–6.0)	3.5 (2.0–6.0)	2.5 (2.0–5.0)	4.0 (2.0–5.0)	5.5 (5.0–6.0)
$T_{½}$, days	NC	3.8 (0.1, 94.2)	5.0 (1.4, 18.5)	5.1 (4.4, 6.0)	4.5 (4.2, 4.8)
$AUC_{0–last}$, nmol/l × day	6.28 (0.83, 48.84)	30.90 (14.04, 68.27)	75.64 (35.96, 158.97)	334.49 (158.40, 706.15)	824.10 (388.20, 1749.42)
$AUC_{0–inf}$, nmol/l × day	NC	28.72 (18.97, 43.46)	91.86 (39.04, 216.15)	339.42 (161.47, 713.40)	828.33 (390.83, 1755.58)
CL/F, l/day	NC	6.7 (4.4, 10.1)	7.0 (3.0, 16.4)	3.8 (1.8, 7.9)	3.1 (1.5, 6.6)

Data are geometric means (95% CIs), unless otherwise specified

[a] Median (range)

$AUC_{0–inf}$, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-last}, area under the plasma concentration–time curve from time 0 to the time of the last measurable plasma concentration; CL/F; apparent clearance; C_{max}, maximum observed plasma concentration; NC, not calculated; $T_{½}$, terminal phase elimination half-life; T_{max}, time to observed plasma concentration

see ESM Methods) [31]. As MEDI4166 is an antibody–peptide fusion molecule, the measurements and dose–response relationship were compared with a GLP-1-Fc(γ4) fusion protein, synthesised in-house. In this GLP-1 receptor overexpressing CHO cell line, MEDI4166 demonstrated a half maximal effective concentration of 2560 pmol/l compared with 10.4 pmol/l for the reference compound GLP-1-Fc(γ4) (based on the half-maximal effective concentration; ESM Table 2). This corresponds to a 246-fold difference in potency between the two compounds (ESM Fig. 2a). However, in the EndoC-βH1 (human insulinoma) cell line, which express endogenous GLP-1 receptors, the potency of MEDI4166 at the human GLP-1 receptor was 472-fold lower than the GLP-1-Fc(γ4) (ESM Table 2 and ESM Fig. 2b). This suggests that the transfected GLP-1 receptor cAMP accumulation CHO cell assay, in which the original potency assessments were made and on which the pharmacokinetic–pharmacodynamic modelling was based, overestimated the potency of MEDI4166 due to a high level of GLP-1 receptor expression. The relatively more physiological cell line, EndoC-βH1, may have provided a more accurate estimate for the dose predictions in relation to GLP-1 activity. Taken together, these results suggest that, at the doses tested in this study, MEDI4166 demonstrated insufficient GLP-1 receptor stimulation and that substantially higher doses of MEDI4166 would be required to achieve clinical efficacy in terms of glycaemic control. Such high doses, however, would not be feasible in humans and, hence, further clinical development of MEDI4166 was terminated.

Overall, the safety and pharmacokinetic profiles of MEDI4166 supported once-weekly dosing. Although treatment with MEDI4166 robustly and significantly decreased LDL-cholesterol levels, there were no significant or clinically relevant reductions in postprandial glucose levels or sufficient increases in GLP-1 activity. A particular strength of this study was the inclusion of individuals with type 2 diabetes in both parts of the study, allowing efficient conclusions on the potential clinical utility of MEDI4166 in the target population

Table 8 Summary of pharmacokinetics in Part B of the study

Variable	MEDI4166		
	50 mg ($n = 8$)	200 mg ($n = 17$)	400 mg ($n = 19$)
C_{max}, nmol/l	4.94 (2.37, 10.26)	112.18 (71.09, 177.18)	351.54 (237.05, 521.35)
T_{max}, day[a]	2.0 (0.0–4.0)	3.0 (0.0–6.0)	3.0 (1.0–7.0)
$T_{½}$, day	7.0 (4.4, 11.2)	4.9 (4.1, 5.8)	4.6 (3.7, 5.8)
$AUC_{0–tau}$, nmol/l × day	34.94 (21.15, 57.69)	633.21 (388.46, 1032.24)	2126.73 (1471.73, 3073.33)
$AUC_{0–inf}$, nmol/l × day	86.28 (42.37, 175.77)	1263.85 (720.51, 2216.79)	4509.55 (2736.92, 7430.32)
CLss/F, l/day	7.3 (2.6, 20.3)	2.0 (1.2, 3.3)	1.3 (0.9, 1.9)

Data are geometric means (95% CIs), unless otherwise specified

[a] Median (range)

$AUC_{0–inf}$, area under the plasma concentration–time curve extrapolated to infinity; AUC_{0-tau} area under the plasma concentration–time curve from time 0 to the end of the dosing interval; CLss/F; apparent clearance at steady state; C_{max}, maximum observed plasma concentration; NC, not calculated; $T_{½}$, terminal phase elimination half-life; T_{max}, time to observed plasma concentration

to be made. Based on the results from this phase 1 combined single and multiple ascending dose study, further clinical development of MEDI4166 as a dual-targeted therapy for patients with type 2 diabetes who are at risk for cardiovascular disease was discontinued.

Acknowledgements The authors thank W. Pu (formerly Clinical Biostatistics & Data Management at MedImmune LLC, Gaithersburg, MD, USA) for supporting the study design and statistical analyses for Part A of the study. The authors thank S. DiCostanza (Clinical Operations at MedImmune LLC, Gaithersburg, MD, USA) for study management and T. Yang (Clinical Biostatistics & Data Management at MedImmune LLC, Gaithersburg, MD, USA) for programming support. The authors acknowledge D. Hornigold (Cardiovascular, Renal, and Metabolism Research, MedImmune Ltd., Cambridge, UK) who contributed to the in vitro experiments described in the ESM. Some data from Part A of this study was presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes, Lisbon, Portugal (11–15 September 2017). Some data from Part B of this study were presented at the 54th Annual Meeting of the European Association for the Study of Diabetes, Berlin, Germany (1–5 October 2018). Editorial assistance was provided by V. R. Jayasinghe, of Oxford PharmaGenesis Inc., Newtown, PA, USA, and was funded by MedImmune LLC, Gaithersburg, MD, USA.

Data availability The data used in this article are not available for public use.

Funding This study was sponsored by MedImmune LLC, Gaithersburg, MD, USA (ClinicalTrials.gov registration no. NCT02524782). The sponsor provided overall scientific and operational oversight according to Good Clinical Practice Guidelines.

Duality of interest MJ, WC, MP, NW, TW, JN, CL and BH are employees of MedImmune and shareholders of AstraZeneca. GC is an employee and shareholder of AstraZeneca. LM is an employee and shareholder of ProSciento, Inc. PA was an employee of MedImmune and is an employee and shareholder of AstraZeneca.

Contribution statement MJ, GC, MP, and BH were involved in the design and conduct of the study, data analysis and data interpretation. WC and TW were involved in the conduct of the study, data analysis and data interpretation. LM was involved in the design and conduct of the study, enrolling participants, data collection and data interpretation. NW was involved with data collection, analysis and interpretation. JN contributed to data collection, interpretation and analyses of preclinical studies. PA was involved with the study concept and design. CL was involved with the study concept and design, as well as the data interpretation. All authors contributed to writing this manuscript, approved the final draft for submission and are accountable for all aspects of the work. MJ is the guarantor of this publication, had full access to the data and had final responsibility for the decision to submit this manuscript for publication.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. International Diabetes Federation (2017) IDF Diabetes atlas - 8th edition. Available from https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html, accessed 24 Apr 2018
2. Fowler MJ (2011) Microvascular and macrovascular complications of diabetes. Diabetes Care 29:116–122
3. Grundy SM, Benjamin IJ, Burke GL et al (1999) Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 100(10):1134–1146. https://doi.org/10.1161/01.CIR.100.10.1134
4. Buse JB, Ginsberg HN, Bakris GL et al (2007) Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 115(1):114–126. https://doi.org/10.1161/CIRCULATIONAHA.106.179294
5. American Diabetes Association (2018) Standards of medical care in diabetes - 2018. Diabetes Care 41(Suppl 1):S1–S159
6. Garber AJ, Abrahamson MJ, Barzilay JI et al (2017) Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm - 2017 executive summary. Endocr Pract 23(2):207–238. https://doi.org/10.4158/EP161682.CS
7. Baigent C, Keech A, Kearney PM et al (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366:1267–1278
8. Leiter LA, Lundman P, da Silva PM et al (2011) Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabet Med 28(11):1343–1351. https://doi.org/10.1111/j.1464-5491.2011.03360.x
9. Schmieder RE, Tschöpe D, Koch C, Ouarrak T, Gitt AK, DIALOGUE study group (2018) Individualised treatment targets in patients with type-2 diabetes and hypertension. Cardiovasc Diabetol 17(1):18. https://doi.org/10.1186/s12933-018-0661-8
10. Kotseva K, De Bacquer D, De Backer G et al (2016) Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. Eur J Prev Cardiol 23(18):2007–2018. https://doi.org/10.1177/2047487316667784
11. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP (2017) PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev, issue 4, Art. No.: CD011748. https://doi.org/10.1002/14651858.CD011748.pub2
12. Aventis U.S. LLC (2018) Praluent (alirocumab) injection [package insert]. Sanofi-Aventis U.S. LLC, Bridgewater
13. Amgen Inc. (2017) Repatha (evolocumab) injection [package insert]. Amgen Inc., Thousand Oaks
14. Sabatine MS, Leiter LA, Wiviott SD et al (2017) Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol 5(12):941–950. https://doi.org/10.1016/S2213-8587(17)30313-3
15. Tran KL, Park YI, Pandya S et al (2017) Overview of glucagon-like peptide-1 receptor agonists for the treatment of patients with type 2 diabetes. Am Health Drug Benefits 10(4):178–188
16. Aroda VR (2018) A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials.

Diabetes Obes Metab 20(Suppl 1):22–33. https://doi.org/10.1111/dom.13162

17. Marso SP, Bain SC, Consoli A et al (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 375(19):1834–1844. https://doi.org/10.1056/NEJMoa1607141
18. Marso SP, Daniels GH, Brown-Frandsen K et al (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375(4):311–322. https://doi.org/10.1056/NEJMoa1603827
19. Potts JE, Gray LJ, Brady EM, Khunti K, Davies MJ, Bodicoat DH (2015) The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. PLoS One 10(6):e0126769. https://doi.org/10.1371/journal.pone.0126769
20. Miller KJ, Bowsher RR, Celniker A et al (2001) Workshop on bioanalytical methods validation for macromolecules: summary report. Pharm Res 18(9):1373–1383. https://doi.org/10.1023/A:1013062600566
21. Viswanathan CT, Bansal S, Booth B et al (2007) Quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. Pharm Res 24(10):1962–1973. https://doi.org/10.1007/s11095-007-9291-7
22. Shankar G, Devanarayan V, Amaravadi L et al (2008) Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. J Pharm Biomed Anal 48(5):1267–1281. https://doi.org/10.1016/j.jpba.2008.09.020
23. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL (2012) Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 344:d7771. https://doi.org/10.1136/bmj.d7771
24. Trujillo JM, Nuffer W, Ellis SL (2015) GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab 6(1):19–28. https://doi.org/10.1177/2042018814559725
25. McDonagh M, Peterson K, Holzhammer B, Fazio S (2016) A systematic review of PCSK9 inhibitors alirocumab and evolocumab. J Manag Care Spec Pharm 22(6):641–653q. https://doi.org/10.18553/jmcp.2016.22.6.641
26. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA (2012) Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 367(20):1891–1900. https://doi.org/10.1056/NEJMoa1201832
27. Dias CS, Shaywitz AJ, Wasserman SM et al (2012) Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. J Am Coll Cardiol 60(19):1888–1898. https://doi.org/10.1016/j.jacc.2012.08.986
28. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ (2017) Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. Diabetes Obes Metab 19(4):524–536. https://doi.org/10.1111/dom.12849
29. Stein EA, Mellis S, Yancopoulos GD et al (2012) Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 366(12):1108–1118. https://doi.org/10.1056/NEJMoa1105803
30. Dungan KM, Povedano ST, Forst T et al (2014) Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet 384(9951):1349–1357. https://doi.org/10.1016/S0140-6736(14)60976-4
31. Henderson SJ, Konkar A, Hornigold DC et al (2016) Robust anti-obesity and metabolic effects of a dual GLP-1/glucagon receptor peptide agonist in rodents and non-human primates. Diabetes Obes Metab 18(12):1176–1190. https://doi.org/10.1111/dom.12735