Received: 16 August 2022 | Revised: 17 November 2022 | Accepted: 1 December 2022

DOI: 10.1111/dom.14932

ORIGINAL ARTICLE

WILEY

Safety, tolerability, pharmacodynamics and pharmacokinetics following once-daily doses of BI 187004, an inhibitor of 11 beta-hydroxysteroid dehydrogenase-1, over 28 days in patients with type 2 diabetes mellitus and overweight or obesity

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Funding information
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Abstract

Aims: To study the oral 11 beta-hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitor BI 187004 (NCT02150824), as monotherapy and in combination with metformin, versus placebo in patients with type 2 diabetes mellitus (T2DM) affected by overweight or obesity.

Materials and Methods: This Phase II, randomized controlled trial investigated multiple rising doses of BI 187004 as monotherapy (Arm 1: 20, 80 or 240 mg) and in combination with metformin (Arm 2: 240 mg), in adults with T2DM and a body mass index of 28–40 kg/m^2.

Results: In total, 103 patients (Arm 1: n = 62, Arm 2: n = 41) were included in this study. BI 187004 was rapidly absorbed and exposure increased approximately dose-dependently. Target engagement of 11β-HSD1 was observed with near-full inhibition of 11β-HSD1 in the liver [decreased (5α-tetrahydrocortisol + 5β-tetrahydrocortisol)/tetrahydrocortisone ratio]; hypothalamic–pituitary–adrenal axis activation was also seen (increased total urinary corticosteroids). No clinically relevant changes from baseline with BI 187004 treatment were observed for bodyweight or meal tolerance test parameters, or in most efficacy endpoints testing glucose and lipid metabolism; a significant increase was observed in weighted mean plasma glucose ($p < .05$ for 80 and 240 mg BI 187004) but not fasting plasma glucose. Drug-related adverse events were reported for 14 patients (22.6%) in Arm 1 and 10 patients (24.4%) in Arm 2, most frequently headache, diarrhoea, flushing and dizziness. A dose-dependent increase in heart rate was seen with BI 187004 treatment.

Conclusions: BI 187004 was generally well tolerated in patients with T2DM. Despite complete 11β-HSD1 inhibition, no clinically relevant effects were observed with BI 187004.

KEYWORDS
antidiabetic drug, antiobesity drug, clinical trial, metformin, phase I-II study

1 | INTRODUCTION

Clinical characteristics of metabolic syndrome, such as type 2 diabetes mellitus (T2DM) and obesity, are thought to be linked to increased production of cortisol and activation of the glucocorticoid receptor.[1] Circulating levels of cortisol are typically unchanged in people with obesity,[2] and therefore local tissue generation of cortisol, primarily via 11 beta-hydroxysteroid dehydrogenase-1 (11β-HSD1),[3,4] is of greater relevance in metabolic syndrome.

The enzyme 11β-HSD1 converts inactive cortisone to active cortisol and is highly expressed in liver and adipose tissue;[5] however, the expression and activity of 11β-HSD1 in obesity and T2DM are variable, and data describing these relationships are conflicting.[6] Compared with healthy controls, patients with obesity but without T2DM have increased 11β-HSD1 activity in adipose tissue but decreased activity in the liver,[7,8] and those patients with both obesity and T2DM have increased 11β-HSD1 liver activity and sustained adipose tissue activity.[9,10]

Current treatments for T2DM, such as metformin, are often unable to stop disease progression or maintain long-term glycaemic control, and combination therapies are often required.[11,12] Inhibition of 11β-HSD1 can reduce glucocorticoid-mediated hepatic glucose output to improve glucose metabolism; therefore, 11β-HSD1 is a potential therapeutic target for T2DM and obesity.[6] Promising results have been seen in both preclinical studies and early clinical trials.[13-16]

BI 187004 is an oral, selective 11β-HSD1 inhibitor being investigated for the treatment of T2DM. In a single-rising-dose study in healthy male volunteers with overweight (body mass index ≥25 to <30 kg/m^2) or obesity (body mass index ≥30 kg/m^2), doses of 2.5-360 mg of BI 187004 were well tolerated and associated with sustained inhibition of 11β-HSD1 activity in the liver and adipose tissue.[17] In a multiple-rising-dose study in patients with T2DM and overweight or obesity, doses of 10-360 mg of BI 187004 were well tolerated, with targeted 11β-HSD1 inhibition of ≥80% seen with doses ≥40 mg.[17,18] In both studies, BI 187004 treatment was rapidly absorbed, and exposure increased non-proportionally with increasing dose. BI 187004 has a long half-life in patients with T2DM and overweight or obesity, but the limited effect on accumulation and the safety profile indicated that BI 187004 is suitable for once-daily dosing.[17,18]

Here we report the results of the subsequent Phase II trial of BI 187004 in patients with T2DM and overweight or obesity.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This multicentre, randomized, double-blind, placebo-controlled, parallel-group study investigated three dosing schemes of BI 187004 monotherapy (Arm 1) and one dosing scheme of BI 187004 as an add-on to metformin background therapy (Arm 2) in patients with T2DM who are affected by overweight or obesity (Figure 1).

In total, 216 patients were screened across three centres in Germany and 103 patients entered the study: 62 in Arm 1 and 41 in Arm 2. The majority of screening failures were because of violations of the inclusion/exclusion criteria, primarily because of having glycated haemoglobin (HbA1c) measurements out of range or antidiabetic medication not as required, or having clinically relevant concomitant or chronic diseases. All eligible patients were men or postmenopausal/hysterectomized women, aged 18-80 years, with a diagnosis of T2DM and body mass index of 28-40 kg/m^2, who had a prescribed diet and exercise regimen. Arm 1 patients were either therapy naïve or previously treated with one oral antidiabetic therapy. Arm 2 patients were on a stable dose of metformin monotherapy (850-2500 mg).

Patients were excluded if they had received treatment with non-oral antidiabetic therapy or multiple oral antidiabetic medications within 12 weeks before screening; had fasting plasma glucose (FPG) levels of >240 mg/dL on two consecutive days after screening; or had a plasma cortisol level of >83 nmol/L after a dexamethasone suppression test, a peak plasma cortisol level of <377 nmol/L or an adrenocorticotrophin hormone (ACTH) peak level of <4.4 pmol/L after corticotropin-releasing hormone (CRH) injection before Visit 3. Full inclusion and exclusion criteria are provided in the Supporting information, Appendix S1.

All patients provided written informed consent before entering the study, which was conducted in accordance with Good Clinical Practice (Committee for Proprietary Medicinal Products/International Council on Harmonisation/135/95), the Declaration of Helsinki and applicable regulatory requirements.

2.2 | Randomization and blinding

Patients in Arm 1 were randomized 1:1:1:1 to receive oral tablets of one of three BI 187004 doses (20, 80 or 240 mg) or matching placebo once daily for 28 days. Patients in Arm 2 were randomized 1:1 to receive 240 mg oral tablets of BI 187004 or matching placebo once daily for 28 days. All study participants, investigators and site staff were blinded to the assigned treatment group, but dose-level allocation in Arm 1 was not blinded.

Patients in Arm 1 who were receiving oral antidiabetic monotherapy before screening underwent a 28-day washout period, and all patients completed a 14-day placebo run-in before the 28-day treatment period (from day −14).

2.3 | Procedures

Treatment was taken with a glass of water in a fasted state at approximately the same time every day.

The treatment period ran from day 1 to day 28, with the follow-up period on days 29-49. Assessments of FPG, bodyweight,

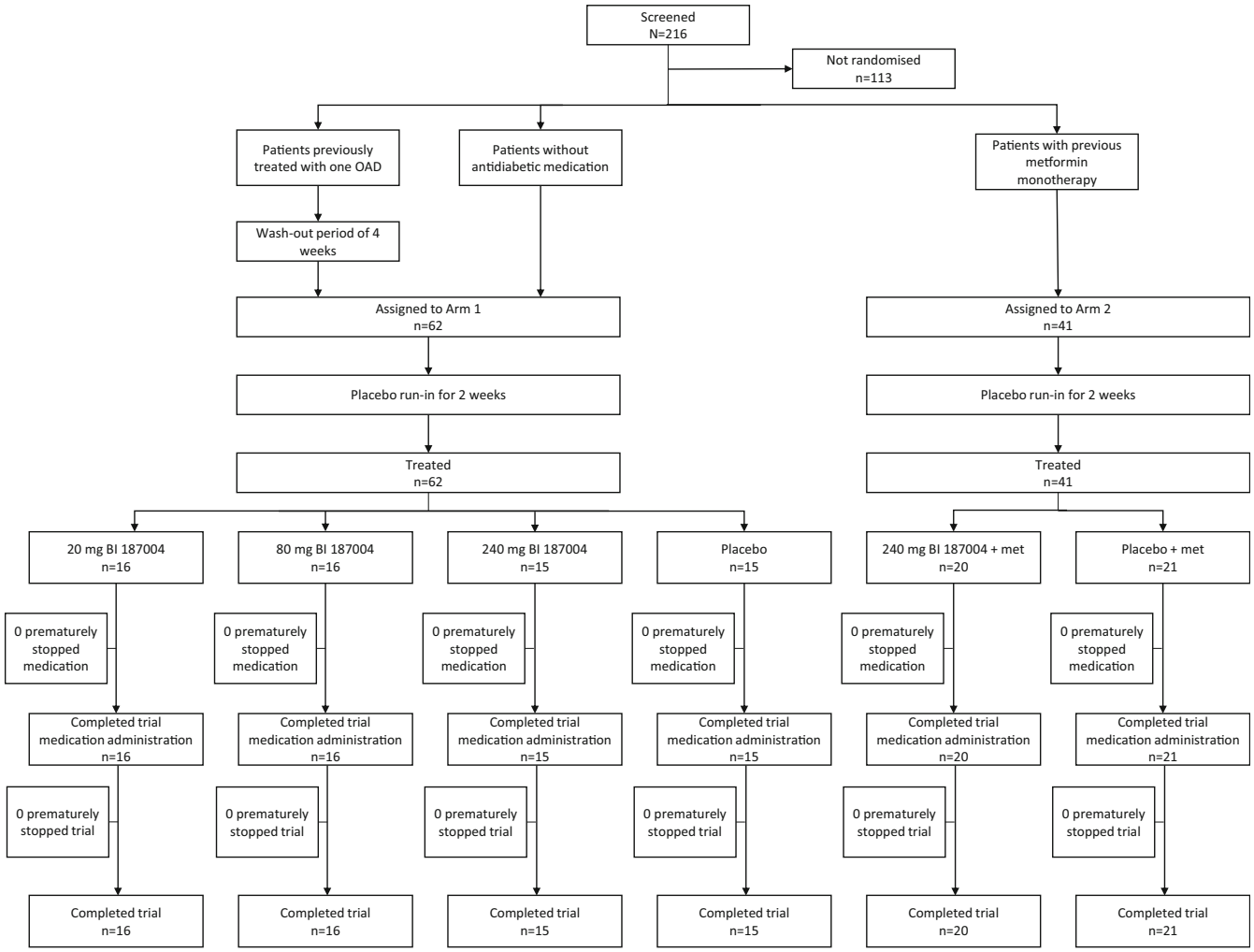


FIGURE 1 Experimental design showing the allocation of patients to each treatment arm and dosing group and patient disposition. met, metformin; OAD, oral antidiabetic drug

pharmacokinetics (PK), hormones of the hypothalamic-pituitary-adrenal (HPA) axis (including cortisol, ACTH and androstenedione) and safety laboratory tests were carried out weekly from treatment day 1 to the end of follow-up (day 49). Assessments of pharmacodynamics (PD) and 12-lead electrocardiogram (ECG) were carried out on days 1, 28 and 35, with PD also assessed on day 42. The waist-to-hip ratio was assessed on days 1, 28 and 49, and lipids were assessed on days 1, 14, 28, 35 and 49. HbA1c and 1,5-anhydrogluticol (1,5-AG) levels were measured at baseline (day −1/1) and on day 28. Weighted mean daily glucose (WMG) profiles were collected over a single 24-h period on day −1 and day 28 (details in the Supporting information, Appendix S1). Blood samples for the determination of homeostatic model assessment for insulin resistance (HOMA-IR), homeostatic model assessment-beta (HOMA-beta) and C-peptide were taken in a fasted state on day −1 and day 28 as part of the WMG profile. A meal tolerance test (MTT) was performed with the WMG (details provided in the Supporting information, Appendix S1); C-peptide, insulin and blood glucose were assessed 30, 60 and 120 min after the start of the MTT.

2.4 | Outcomes

The primary endpoint was the number of patients with drug-related adverse events (AEs). Further safety and tolerability endpoints were assessed as the changes from baseline in clinical laboratory values, vital signs and ECG measurements, and the occurrence of AEs.

Secondary and exploratory efficacy endpoints included change from baseline in FPG level after 28 days of treatment and further metabolic, PD and PK parameters (Tables S1-S4). The effects of treatment on the HPA axis were assessed by the CRH test, the orthostatic test and the dexamethasone suppression test.

2.5 | Statistical analysis

The planned sample size for this study (N = 102) was not based on a power calculation but was chosen in line with other safety trials at this stage of development. The sample size per study arm (Arm 1: ∼n = 15 per dose group; Arm 2: ∼n = 21 per dose group) supported

an exploratory analysis of treatment effects on FPG from baseline following 28 days of treatment and allowed for the loss of single patients because of drop-out. Descriptive statistics were calculated for safety, PD and PK endpoints. The secondary and exploratory efficacy endpoints were analysed using an analysis of covariance (ANCOVA) model. For the secondary endpoint, the ANCOVA model had the treatment group as a fixed effect and baseline FPG as linear covariate fitted to the data for the change from baseline in FPG after 28 days of treatment. The ANCOVA was conducted on the treated set of patients, excluding values after the introduction of another antidiabetic medication.

2.6 | Trial registration

The trial was registered with ClinicalTrials.gov (NCT02150824) and EudraCT (2013-003646-16).

3 | RESULTS

3.1 | Trial subjects and compliance

Patient disposition is detailed in Figure 1. Patient characteristics and demographics were generally similar between dose groups within each treatment arm (Table 1) with some differences in time since T2DM diagnosis in both treatment arms and age in Arm 2.

Mean baseline efficacy variables were generally similar between dose groups within each treatment arm, although some differences were observed in FPG, WMG, systolic blood pressure, triglycerides and low-density lipoprotein (LDL) cholesterol in Arm 1, and in FPG, bodyweight, triglycerides and LDL cholesterol in Arm 2 (Table S1).

During the study, important protocol violations were reported for three patients in Arm 1 (20 mg, n = 2; 80 mg, n = 1): one for not meeting inclusion criteria (20 mg: HbA1c out of range or antidiabetic medication not as required) and two for violating exclusion criteria (20 mg: plasma cortisol or ACTH peak levels too low after CRH injection; 80 mg: prohibited medication use). Good compliance with trial medication (80%-120%) was reported for all patients.

3.2 | Safety and tolerability

Overall, investigator-defined drug-related AEs (primary outcome) were reported in 14 patients in Arm 1 and 10 patients in Arm 2 (Table 2). The proportion of patients with drug-related AEs was similar across almost all dose groups and both treatment arms; no patients in Arm 1 receiving 20 mg of BI 187004 were reported as having drug-related AEs. The most frequently reported drug-related AEs were headache in Arm 1 [n = 5, 8.1%: n = 3 80 mg (18.8%); n = 1 each for 240 mg and placebo (6.7% each)] and diarrhoea, dizziness and flushing in Arm 2 [n = 2 each, 4.9%; diarrhoea: n = 2 240 mg (10.0%); dizziness and flushing: n = 1 each for 240 mg (5.0%) and placebo (4.8%)].

Treatment-emergent AEs (TEAEs) were reported for most patients: 91.9% of patients in Arm 1 and 87.8% in Arm 2 (Table 2). The most frequent TEAE reported in both treatment arms was flushing [Arm 1 n = 50, 80.6%; n = 14 each for 20 mg (87.5%) and 240 mg (93.3%); n = 12 80 mg (75.0%); n = 10 placebo (66.7%); Arm 2 n = 31, 75.6%: n = 14 240 mg (70.0%), n = 17 placebo (81.0%)]. One severe TEAE of toothache was reported in Arm 1 for a patient receiving 80 mg BI 187004; this was not considered to be drug related. No serious AEs, AEs leading to treatment discontinuation, or deaths were reported in either treatment arm.

No major safety signals were observed in the clinical laboratory evaluation. However, a dose-dependent increase in mean ± SD pulse rate from baseline was seen in all BI 187004-treated patients: 20 mg, 1.8 ± 8.2 bpm; 80 mg, 2.3 ± 8.3 bpm; 240 mg, 8.5 ± 6.4 bpm; 240 mg + metformin, 3.4 ± 8.3 bpm; placebo, 0.3 ± 6.9 bpm; placebo + metformin, −0.8 ± 11.0 bpm.

3.3 | Pharmacokinetic outcomes

BI 187004 was rapidly absorbed in all treatment groups after the first and last doses; exposure increased in an approximately dose-dependent manner at first dose and in a less than dose-dependent manner at steady state (Table S2). Exposure to BI 187004 was slightly increased when administered with a metformin background, by approximately 7% at first dose and ∼9% at steady state. The apparent clearance of BI 187004 on day 1 was similar between the 20- and 80-mg dose groups and approximately 30% greater in the 240-mg dose group. At steady state (day 28), the apparent clearance increased with dose – again, most notably in the 240-mg dose group, with an increase of 79% relative to the 20-mg dose group (Table S2). The pre-dose plasma concentration of BI 187004 increased following the first dose and remained relatively uniform from day 7 onwards, consistent with the attainment of steady state (Table S3). Pre-dose concentrations for 240 mg + metformin appeared considerably higher than 240 mg BI 187004 alone, suggesting a potential influence of the background metformin therapy. However, the data for both 240 mg alone and in combination with metformin were highly variable (geometric coefficient of variation up to 315%). Overall, BI 187004 exhibits non-linear PK parameters at doses of >80 mg.

3.4 | Glucose and lipid metabolism

No clinically relevant change in FPG levels from baseline was seen in any BI 187004-treated groups in either arm (Figure 2A,B); however, non-significant numerical increases (1.6-7.2 mg/dL) were observed.

Treatment with BI 187004, but not placebo, increased WMG levels from baseline in Arm 1; in Arm 2, levels of WMG were increased in both BI 187004-treated patients and patients receiving placebo (Figure 2C). No clinically relevant changes were observed in any treatment group for MTT parameters (2 h post-prandial glucose; glucose, C-peptide and insulin $AUC_{0\text{-}2h}$) (Figures 2D, S1 and Table 3).

TABLE 1 Baseline patient demographics in Arm 1 and Arm 2 by dose group

Characteristic	Arm 1					Arm 2		
	BI 187004 20 mg (n = 16)	BI 187004 80 mg (n = 16)	BI 187004 240 mg (n = 15)	Placebo (n = 15)	Total (n = 62)	BI 187004 240 mg + met (n = 20)	Placebo + met (n = 21)	Total (n = 41)
Sex, male, n (%)	13 (81.3)	11 (68.8)	12 (80.0)	11 (73.3)	47 (75.8)	18 (90.0)	16 (76.2)	34 (82.9)
Race, n (%)								
White	16 (100)	16 (100)	15 (100)	15 (100)	62 (100)	20 (100)	20 (95.2)	40 (97.6)
American Indian/Alaska native	0	0	0	0	0	0	1 (4.8)	1 (2.4)
Age, years, mean ± SD	58.6 ± 11.6	59.4 ± 8.6	55.7 ± 7.8	57.6 ± 7.3	57.9 ± 8.9	62.1 ± 7.8	57.2 ± 9.8	59.6 ± 9.1
BMI, kg/m^2, mean ± SD	32.8 ± 3.7	34.2 ± 3.7	32.6 ± 3.6	32.3 ± 3.9	33.0 ± 3.7	30.0 ± 2.4	31.5 ± 3.4	30.8 ± 3.0
eGFR, mL/min/1.73 m^2, mean ± SD	92.4 ± 12.1	87.7 ± 18.2	96.3 ± 21.2	102.5 ± 18.0	94.6 ± 18.0	95.6 ± 17.8	96.2 ± 21.8	95.9 ± 19.7
HbA1c, %, mean ± SD	7.5 ± 0.9	7.2 ± 0.6	7.3 ± 0.6	7.2 ± 0.8	7.3 ± 0.7	7.9 ± 0.6	7.9 ± 0.6	7.9 ± 0.6
FPG, mg/dL, mean ± SD	155.7 ± 25.7	157.1 ± 31.2	173.7 ± 24.9[a]	154.5 ± 31.9	159.9 ± 29.0[b]	167.5 ± 24.8	154.0 ± 25.6	160.6 ± 25.8
Time since T2DM diagnosis, years, mean ± SD	6.4 ± 5.6	6.4 ± 5.5	7.6 ± 4.4	5.5 ± 3.1	6.5 ± 4.7	7.7 ± 4.8	9.2 ± 4.8	8.5 ± 4.8
Metformin daily dose, mg, mean ± SD	–	–	–	–	–	1817.5 ± 481.6	1642.9 ± 404.4	1728.0 ± 446.9
>500 to ≤1000 mg, n (%)	–	–	–	–	–	4 (20.0)	5 (23.8)	9 (22.0)
>1000 to ≤1500 mg, n (%)	–	–	–	–	–	1 (5.0)	2 (9.5)	3 (7.3)
>1500 to ≤2000 mg, n (%)	–	–	–	–	–	13 (65.0)	14 (66.7)	27 (65.9)
>2000 mg, n (%)	–	–	–	–	–	2 (10.0)	0	2 (4.9)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, glycated haemoglobin; HOMA-beta, homeostatic model assessment-beta; HOMA-IR, homeostatic model assessment for insulin resistance; met, metformin; SD, standard deviation; T2DM, type 2 diabetes mellitus.

[a]n = 14.

[b]n = 61.

TABLE 2 Summary of treatment-emergent adverse events

Treatment-emergent adverse events	Arm 1					Arm 2		
	BI 187004 20 mg (n = 16)	BI 187004 80 mg (n = 16)	BI 187004 240 mg (n = 15)	Placebo (n = 15)	Total (n = 62)	BI 187004 240 mg + met (n = 20)	Placebo + met (n = 21)	Total (n = 41)
Any TEAE, n (%)	14 (87.5)	15 (93.8)	15 (100)	13 (86.7)	57 (91.9)	18 (90.0)	18 (85.7)	36 (87.8)
Investigator-defined drug-related AEs, n (%)	0	5 (31.3)	4 (26.7)	5 (33.3)	14 (22.6)	6 (30.0)	4 (19.0)	10 (24.4)
Headache	0	3 (18.8)	1 (6.7)	1 (6.7)	5 (8.1)	0	0	0
Disturbance in attention	0	0	1 (6.7)	0	1 (1.6)	0	0	0
Hypogeusia	0	0	1 (6.7)	0	1 (1.6)	0	0	0
Dizziness	0	0	0	0	0	1 (5.0)	1 (4.8)	2 (4.9)
Orthostatic intolerance	0	0	0	0	0	0	1 (4.8)	1 (2.4)
Diarrhoea	0	0	0	0	0	2 (10.0)	0	2 (4.9)
Abdominal discomfort	0	0	0	1 (6.7)	1 (1.6)	0	0	0
Upper abdominal pain	0	0	0	1 (6.7)	1 (1.6)	0	0	0
Nausea	0	0	1 (6.7)	0	1 (1.6)	1 (5.0)	0	1 (2.4)
Constipation	0	1 (6.3)	0	0	1 (1.6)	0	0	0
Hyperglycaemia	0	0	0	1 (6.7)	1 (1.6)	0	0	0
Polydipsia	0	0	0	1 (6.7)	1 (1.6)	0	0	0
Decreased appetite	0	0	0	0	0	1 (5.0)	0	1 (2.4)
Orthostatic hypotension	0	1 (6.3)	0	0	1 (1.6)	0	1 (4.8)	1 (2.4)
Flushing	0	0	0	0	0	1 (5.0)	1 (4.8)	2 (4.9)
Listless	0	0	1 (6.7)	0	1 (1.6)	0	0	0
Nocturia	0	0	1 (6.7)	0	1 (1.6)	0	0	0
Dry skin	0	0	1 (6.7)	0	1 (1.6)	0	0	0
Generalized rash	0	0	0	1 (6.7)	1 (1.6)	0	0	0
Fatigue	0	1 (6.3)	0	0	1 (1.6)	0	0	0
Severe AEs, n (%)	0	1 (6.3)[a]	0	0	1 (1.6)	0	0	0
Serious AEs, n (%)	0	0	0	0	0	0	0	0
AEs leading to discontinuation of trial medication, n (%)	0	0	0	0	0	0	0	0

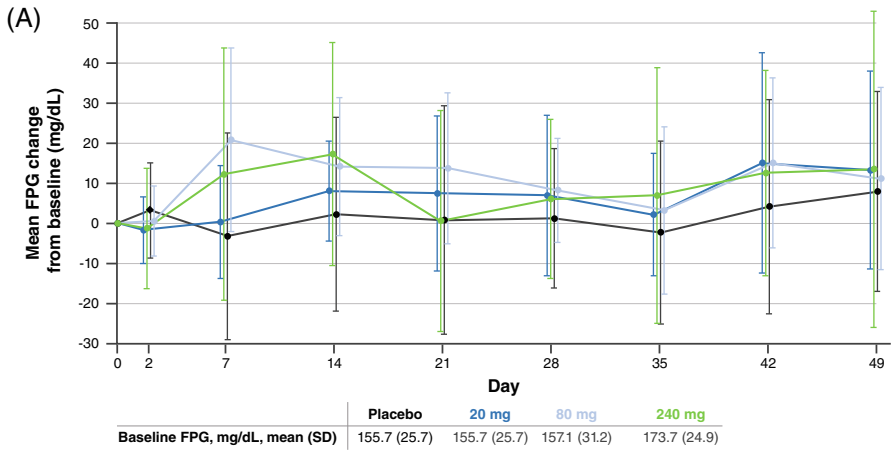
Abbreviations: AE, adverse event; GI, gastrointestinal; met, metformin; TEAE, treatment-emergent adverse event.
[a]One severe TEAE of toothache was reported, which was not considered to be drug related.

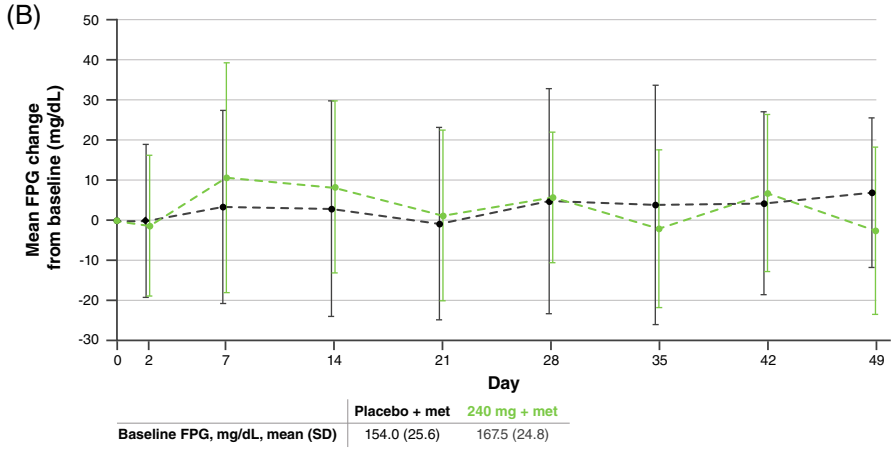
No clinically relevant changes from baseline were observed for levels of HbA1c, 1,5-AG, high-density lipoprotein cholesterol, blood pressure or waist-to-hip ratio in any treatment group after 28 days of treatment (Table 3). LDL cholesterol was significantly ($p < .05$) reduced from baseline in all Arm 1 BI 187004 treatment groups compared with placebo (adjusted mean ± SE; 20 mg: −13.1 ± 5.4 mg/dL; 80 mg: −16.0 ± 5.6 mg/dL; 240 mg: −14.2 ± 5.6 mg/dL), but this reduction was driven by increases in the placebo group (+11.0 ± 3.89 mg/dL). No differences in LDL cholesterol between BI 187004 and placebo were observed in Arm 2. Treatment with BI 187004 dose-dependently, but non-significantly, decreased triglyceride levels, with reductions seen with 80 mg and 240 mg of BI 187004 in Arm 1, and with 240 mg of BI 187004 in Arm 2, compared with placebo; however, in Arm 1, baseline values were higher in in BI 187004 treatment groups than the placebo group. Total cholesterol and very LDL cholesterol levels were dose-dependently decreased at day 28 following BI 187004 treatment in both arms. There was no clinically significant effect observed on HOMA-IR, HOMA-beta, fasting plasma insulin or fasting C-peptide (Table 3).

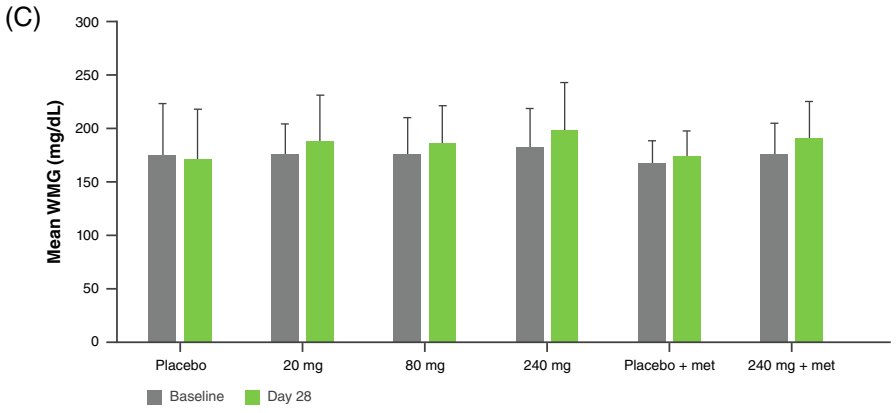
Significant ($p < .05$) changes from baseline in bodyweight were seen with 240 mg of BI 187004 (both arms) compared with placebo after 28 days (Table 3); however, the changes were driven by bodyweight increases in the placebo groups.

3.5 | Assessments of the hypothalamic-pituitary-adrenal axis

Abnormal CRH test results at day 29 were reported for two patients in the placebo group in each treatment arm: n = 1 each for maximum ACTH of <4.4 pmol/L and maximum cortisol of <377 nmol/L in each treatment arm. No abnormal dexamethasone suppression test results







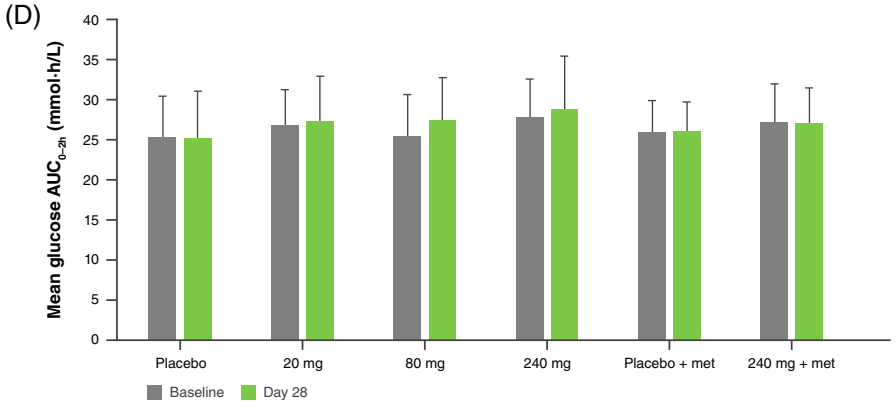


FIGURE 2 Changes from baseline in glucose metabolism parameters. Mean change from baseline in FPG measured throughout treatment (up to day 28) and for 11 days post-treatment in A, Arm 1 and B, Arm 2 with BI 187004 treatment or placebo. C, Mean change from baseline in WMG at day 28 with BI 187004 treatment or placebo. D, Changes in mean plasma glucose following a meal (meal tolerance test) at baseline and at day 28 with BI 187004 treatment or placebo. Data are presented as mean ± standard deviation. FPG, fasting plasma glucose; met, metformin; WMG, weighted mean daily glucose

TABLE 3 Changes from baseline in exploratory endpoint parameters at day 28, following treatment with BI 187004 or placebo

	Arm 1				Arm 2	
Change from baseline at day 28, adjusted mean (SE)	**BI 187004 20 mg (n = 16)**	**BI 187004 80 mg (n = 16)**	**BI 187004 240 mg (n = 15)**	**Placebo (n = 15)**	**BI 187004 240 mg + met (n = 20)**	**Placebo + met (n = 21)**
HbA1c, %	−0.05 (0.10)	0.03 (0.10)	0.11 (0.10)	0.08 (0.10)	0.00 (0.09)	−0.28 (0.09)
FPG, mg/dL	6.6 (5.0)	8.0 (5.0)	6.8 (5.4)[a]	0.9 (5.2)	6.1 (4.5)	4.5 (4.4)
Bodyweight, kg	0.60 (0.35)	0.29 (0.35)	−0.40 (0.36)	0.84 (0.36)	−0.11 (0.32)	0.91 (0.30)
Waist-to-hip ratio						
Male	−0.011 (0.013) (n = 13)	0.019 (0.014) (n = 11)	0.002 (0.014) (n = 12)	−0.008 (0.014) (n = 11)	0.008 (0.011) (n = 18)	−0.010 (0.012) (n = 16)
Female	−0.022 (0.026) (n = 3)	0.019 (0.020) (n = 5)	0.022 (0.026) (n = 3)	0.025 (0.023) (n = 4)	0.006 (0.031) (n = 2)	−0.006 (0.020) (n = 5)
SBP, mmHg	1.4 (2.5)	−2.8 (2.6)[b]	−2.3 (2.6)	−2.7 (2.6)[a]	−2.7 (2.2)	1.4 (2.2)[c]
DBP, mmHg	1.8 (1.4)	−1.9 (1.4)[b]	0.8 (1.5)	−0.4 (1.5)[a]	−0.8 (1.2)	1.5 (1.2)[c]
Triglycerides, mg/dL	−6.2 (15.5)	−34.9 (16.5)[a]	−57.1 (16.5)[a]	−17.8 (16.1)	−37.5 (13.8)	−5.0 (13.6)
LDL, mg/dL	−2.04 (3.75)	−4.99 (3.91)[b]	−3.18 (4.01)[a]	11.01 (3.89)	−8.38 (3.37)	−5.27 (3.27)
HDL, mg/dL	−0.82 (2.48)	−1.63 (2.55)[b]	2.40 (2.65)[a]	3.54 (2.55)	−0.85 (2.21)	−0.77 (2.17)
1,5-AG, mg/L	−0.83 (0.37)	−0.51 (0.37)	−0.58 (0.38)	−0.93 (0.40)	−0.10 (0.35)[d]	0.83 (0.33)
WMG, mg/dL	15.7 (4.7)[e]	12.3 (4.5)[a]	12.6 (4.7)[e]	−2.8 (4.5)[a]	8.2 (4.1)[f]	6.3 (3.7)
Glucose $AUC_{0\text{-}2h}$, mmol/h/L	1.06 (0.90)[b]	1.42 (0.72)[b]	1.07 (0.86)[a]	−0.33 (0.96)	−0.47 (0.77)[g]	0.11 (0.72)[c]
2 h PPG, mg/dL	17.9 (8.8)	25.5 (9.1)	17.7 (10.9)	1.7 (12.1)	−2.5 (9.2)	−3.8 (10.2)
C-peptide $AUC_{0\text{-}2h}$, pmol/h/L	0.20 (0.21)[b]	0.14 (0.15)	−0.09 (0.16)[e]	0.03 (0.14)	−0.08 (0.12)[d]	−0.01 (0.13)[c]
Insulin $AUC_{0\text{-}2h}$, pmol/h/L	56.0 (86.5)[a]	149.7 (86.8)	−79.1 (63.4)[e]	38.5 (91.8)	−86.2 (45.3)[d]	−47.7 (70.7)[c]
HOMA-IR, (mU/L) × (mmol/L)	1.2 (0.8)[b]	1.0 (0.5)	1.2 (0.7)[e]	−2.3 (1.8)	1.0 (0.4)[d]	−0.6 (0.6)
HOMA-beta, %	9.5 (4.5)[b]	−0.5 (4.4)	0.7 (2.0)[e]	−0.8 (5.8)	−1.4 (6.8)[d]	−8.7 (9.1)
Fasting C-peptide, pmol/L	0.05 (0.03)[b]	0.01 (0.04)	0.03 (0.04)[e]	−0.04 (0.03)	0.05 (0.05)[d]	0.01 (0.05)
FPI, pmol/L	20.1 (9.9)[b]	12.6 (7.0)	11.3 (7.0)[e]	−24.0 (17.5)[e]	10.5 (6.9)[d]	−11.3 (10.2)
Comparison vs. placebo, adjusted mean (SE)						
HbA1c, %	0.13 (0.14)	−0.04 (0.14)	0.04 (0.14)	-	0.28 (0.12)	-
FPG, mg/dL	5.7 (7.2)	7.2 (7.2)	5.9 (7.6)[a]	-	1.6 (6.3)	-
Bodyweight, kg	−0.24 (0.50)	−0.55 (0.50)	−1.25 (0.51)	-	−1.02 (0.44)	-
Waist-to-hip ratio						
Male	−0.003 (0.019) (n = 13)	0.027 (0.020) (n = 11)	0.009 (0.020) (n = 12)	-	0.018 (0.016) (n = 18)	-
Female	−0.047 (0.034) (n = 3)	−0.006 (0.031) (n = 5)	−0.003 (0.035) (n = 3)	-	0.012 (0.037) (n = 2)	
SBP, mmHg	4.0 (3.6)	−0.2 (3.7)[b]	0.4 (3.7)	-	−4.1 (3.1)	-
DBP, mmHg	2.2 (2.0)	−1.5 (2.1)[b]	1.2 (2.1)	-	−2.3 (1.8)	-
Triglycerides, mg/dL	11.5 (22.3)	−17.2 (23.1)[a]	−39.3 (23.1)[a]	-	−32.5 (19.4)	-

(Continues)

TABLE 3 (Continued)

Comparison vs. placebo, adjusted mean (SE)						
LDL, mg/dL	−13.05 (5.41)	−16.00 (5.56)[b]	−14.19 (5.60)[a]	-	−3.12 (4.70)	-
HDL, mg/dL	−4.36 (3.57)	−5.16 (3.61)[b]	−1.13 (3.69)[a]	-	−0.08 (3.09)	-
1,5-AG, mg/L	0.11 (0.54)	0.43 (0.54)	0.35 (0.55)	-	0.93 (0.48)[d]	
WMG, mg/dL	18.5 (6.5)[e]	15.1 (6.3)[a]	15.4 (6.5)[e]	-	2.0 (5.5)[f]	-

Abbreviations: 1,5-AG, 1,5-anhydroglucitol; $AUC_{0\text{-}2h}$, area under the concentration-time curve from 0 to 2 h; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-beta, homeostatic model assessment-beta; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; met, metformin; PPG, post-prandial glucose; SBP, systolic blood pressure; SE, standard error; WMG, weighted mean daily glucose.

[a] n = 14.
[b] n = 15.
[c] n = 20.
[d] n = 19.
[e] n = 13.
[f] n = 17.
[g] n = 18.

were reported during the course of the study. Orthostatic tests showed orthostatic hypotension in five subjects (n = 2 each for Arm 2 placebo and 240 mg; n = 1 for Arm 1 80 mg) and orthostatic intolerance in two patients (n = 1 each for Arm 2 placebo and 240 mg).

Mean cortisol was decreased from baseline following treatment with the higher two dose groups in Arm 1 and was increased in the placebo group, whereas cortisol levels were similar between BI 187004- and placebo-treated groups in Arm 2 (Table S4). In contrast, increases from baseline were seen for ACTH (within the normal range) and androstenedione with BI 187004 treatment, suggesting HPA axis activation, whereas no change was observed in those receiving placebo (Table S4).

3.6 | Pharmacodynamic outcomes

For all groups receiving BI 187004, the [5α-tetrahydrocortisol (THF) + 5β-THF]/tetrahydrocortisone (THE) ratio, an indicator of 11β-HSD1 inhibition in the liver, was decreased at day 1 and day 28 and for 13 days after the end of treatment, relative to placebo (Table S5). The total urinary corticosteroid (5α-THF + 5β-THF + THE + free urinary cortisone + free urinary cortisol) levels increased for all BI 187004 treatment groups at day 1 and day 28 and for 13 days after the end of treatment, relative to placebo, signifying activation of the HPA axis.

4 | DISCUSSION

Treatment with BI 187004 was well tolerated by all dose groups and inhibited 11β-HSD1 in the liver but did not lead to clinically meaningful improvements in glucose or lipid control.

As seen in the Phase I studies,[17,18] BI 187004 inhibited 11β-HSD1 in adipose tissue. The decrease in the (5α-THF + 5β-THF)/THE ratio indicates 11β-HSD1 inhibition in the liver, showing target engagement of BI 187004. Expression of 11β-HSD1 has been observed in the zona fasciculata,[19] the primary region of cortisol production within the adrenal gland. Although our study did not directly measure 11β-HSD1 in the adrenal gland, preclinical data in both rodents and non-human primates showed that treatment with BI 187004 induced hypertrophy of the zona fasciculata, showing that supratherapeutic doses of BI 187004 induce changes in the adrenal gland consistent with 11β-HSD1 inhibition (unpublished data on file; Boehringer Ingelheim International GmbH, Ingelheim, Germany). Total urinary corticosteroid levels were increased for all BI 187004 dose levels, suggesting that BI 187004 affects the HPA axis. Hormones of the HPA axis showed expected trends with BI 187004 treatment (decreased cortisol, increased ACTH and androstenedione), but these remained within the normal range. No hypercortisolism (abnormal dexamethasone suppression test results) was reported, but orthostatic tests gave pathological results in multiple subjects, suggesting hypocortisolism. However, these subjects had normal CRH tests, suggesting unimpaired HPA axis feedback. The PK results observed in this

trial were consistent with the results observed in previous single-rising-dose and multiple-rising-dose trials.[17,18]

Despite optimal target engagement observed in this study, with near-complete 11β-HSD1 inhibition in the liver, and data from the previous multiple-rising-dose study showing inhibition in both liver and adipose tissue,[18] treatment with BI 187004 did not show efficacy for the tested endpoints. No clinically meaningful changes from baseline were seen for FPG, HbA1c, 1,5-AG, blood pressure, waist-to-hip ratio or other biomarkers. The significant relative reductions versus placebo in bodyweight and LDL cholesterol were influenced by increases in the placebo group rather than treatment effects and were therefore not clinically relevant; there was no change in lipid-lowering background therapy over the course of the trial, and there is no clear rationale to explain the observed LDL cholesterol increase in the placebo group.

Although doses higher than the maximum tested dose used in this study (240 mg) have been investigated previously, these are unlikely to produce any further clinical effects. Doses of up to 360 mg were shown to be well tolerated in previous single- and multiple-rising dose studies[17,18]; however, the doses used in this trial were selected based on the target enzyme inhibition. In the 14-day multiple-rising dose study, BI 187004 doses of ≥40 mg resulted in the targeted ≥80% inhibition of 11β-HSD1 in ≥75% of patients.[18] The doses used in this study were therefore selected to represent a slightly sub-active dose (20 mg), a fully active dose (80 mg) and a high dose with a sufficient safety margin at steady state (240 mg).

Weight loss has been reported with other 11β-HSD1 inhibitors.[20,21] However, as a class, 11β-HSD1 inhibitors are expected to improve glucose tolerance but not produce clinically relevant weight loss. Furthermore, 11β-HSD1 inhibitors have shown inconsistent glucose-lowering effects, and most development programmes in T2DM have been discontinued.[22] Development of 11β-HSD1 inhibitors has continued in various Phase I and II studies,[23] including in therapy areas such as wound healing[24] and in the treatment of non-alcoholic fatty liver disease,[25] Cushing's syndrome[26] and Alzheimer's disease.[27] Carbenoxolone is a naturally derived, non-selective 11β-HSD1 inhibitor that was shown to increase insulin sensitivity in healthy men[15] and patients with T2DM without obesity[14] but not in patients with obesity with or without T2DM.[28,29] Studies in patients with T2DM have shown that the selective 11β-HSD1 inhibitor INCB13739 lowers HbA1c and FPG.[20,30,31]

BI 187004 was selected for clinical investigation based on its safety profile, PK parameters and strong enzyme inhibition. Two other 11β-HSD1 inhibitors were tested for potential clinical development in T2DM and obesity: BI 135585 and BI 163538. Phase I-II studies of BI 135585 showed that the compound strongly inhibited 11β-HSD1 at 24 h after dosing; however, this was not maintained after 14 days of continuous treatment.[32] Treatment with BI 163538 showed a lower potency, small safety margins and weaker target enzyme inhibition than BI 187004, and therefore clinical development was not pursued (unpublished data on file; Boehringer Ingelheim International GmbH). As previously described, Phase I studies of BI 187004 showed that treatment was well tolerated and produced strong target enzyme inhibtion.[17,18] The present paper reports data indicating that strong inhibition of 11β-HSD1 by BI 187004 does not translate to clinical efficacy, and therefore this compound and treatment class were not further investigated.

The reason that INCB13739 showed decreased mean FPG after 28 days of treatment in patients with T2DM and overweight/obesity[30] but BI 187004 did not show any impact on blood glucose in an equivalent population over the same time frame is not yet clear. One explanation could be that treatment with BI 187004 requires more than 28 days to substantially affect blood glucose. This rationale is supported by data from a diet-induced obese and insulin-resistant cynomolgus macaque model: BI 187004-treated animals were weight stable and maintained whole-body insulin sensitivity over the 8-week treatment phase, in contrast to the vehicle control group, which gained weight and underwent significant metabolic deterioration (unpublished data on file; Boehringer Ingelheim International GmbH). Hence, the available data are consistent with a modest effect of BI 187004 on whole-body insulin sensitivity and bodyweight at a dose of 10 mg/kg once daily. These data are in line with euglycaemic hyperinsulinaemic clamp study data from INCB13739 that showed markedly improved hepatic and peripheral insulin sensitivity after 28 days of treatment.[30] In the current study no clamp experiments were performed, and the lack of any clinically significant change to HOMA-IR and HOMA-beta might be because of the insufficient sensitivity of HOMA-indices (which are only based on fasting values of glucose and insulin) to detect small changes in insulin sensitivity and secretion.

Furthermore, the population of the 12-week trial of INCB13739 in combination with metformin was slightly different, with a higher baseline HbA1c of 8.2%-8.3% and a large proportion of patients of Hispanic origin (49%-67%) across the treatment groups[20,31]; the patients in the current study were 99% White with a baseline HbA1c of 7.2%-7.9%. Given that the INCB13739 12-week data showed an HbA1c reduction of approximately 0.4% after 4 weeks in the highest dose group,[20,31] whereas BI 187004 did not show any effect on blood glucose, one might speculate whether ethnicity and baseline HbA1c could have also factored into the apparent lack of efficacy of BI 187004. In addition, treatment with another 11β-HSD1 inhibitor MK-0916 in patients with T2DM over 12 weeks showed modest HbA1c and bodyweight reductions, but, as with BI 187004, no significant effects were seen for FPG or 2 h post-prandial glucose.[33] The population of this study also had lower baseline HbA1c than the INCB13739 study (7.2%-7.4%), and the minimal efficacy results were attributed to both this factor and a decrease in intracellular cortisol.[33] Despite the apparent reductions in HbA1c and FPG seen with INCB13739,[20,31] and the modest HbA1c and bodyweight reductions seen with MK-0916,[21,33] no further studies were performed for either therapy.

In conclusion, treatment with BI 187004 as monotherapy and in combination with metformin was well tolerated in patients with T2DM. The frequency of drug-related AEs was low and balanced across treatment groups. Despite target engagement and complete 11β-HSD1 inhibition in the liver, no clinical effects were observed with BI 187004 treatment. After 28 days of treatment, BI 187004

produced a significant increase in WMG levels but had no clinically relevant effect on FPG. Based on the results of this and previous studies,[17,18] indicating that 11β-HSD1 inhibition is not a relevant mechanism for the treatment of T2DM or obesity, further clinical development of this compound has been halted.

ACKNOWLEDGMENTS

Medical writing support in the preparation of this manuscript was provided by Susie Eaton, MBio, and Tom Priddle, DPhil, of OPEN Health Communications (London, UK), funded by Boehringer Ingelheim. We thank all the participants and study investigators who took part in the clinical study described here.

CONFLICT OF INTEREST

SB, MN and BP are employees of Boehringer Ingelheim. LPM has received travel grants and speaker fees from Novo Nordisk A/S, Eli Lilly and Gan & Lee Pharmaceuticals. TH is shareholder of Profil, which received research funds from Adocia, AstraZeneca, Biocon, Boehringer Ingelheim, Crinetics, Eli Lilly, Gan & Lee Pharmaceuticals, Genova, Nestlé, Neuraly, Novo Nordisk, Sanofi and Zealand Pharma, has received speaker honoraria from Eli Lilly, Gan & Lee Pharmaceuticals and Novo Nordisk, and is a member of advisory panels for Novo Nordisk.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14932.

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript and secondary analyses in peer-reviewed journals and regulatory and reimbursement activities are completed, normally within 1 year after the marketing application has been granted by major Regulatory Authorities. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Bianzano S, Nordaby M, Plum-Mörschel L, Peil B, Heise T. Safety, tolerability, pharmacodynamics and pharmacokinetics following once-daily doses of BI 187004, an inhibitor of 11 beta-hydroxysteroid dehydrogenase-1, over 28 days in patients with type 2 diabetes mellitus and overweight or obesity. *Diabetes Obes Metab*. 2023;25(3):832-843. doi:10.1111/dom.14932