Selective Inhibition of 11beta-Hydroxysteroiddehydrogenase-1 with BI 187004 in Patients with Type 2 Diabetes and Overweight or Obesity: Safety, Pharmacokinetics, and Pharmacodynamics After Multiple Dosing Over 14 Days

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ABSTRACT

Objective To assess safety, tolerability, pharmacokinetics, and pharmacodynamics of treatment with the selective 11beta-hydroxysteroid dehydrogenase-1 (11beta-HSD1) inhibitor BI 187004 in male and female patients with type 2 diabetes and overweight or obesity.

Methods Randomized, double-blind, parallel-group, placebo-controlled multiple rising dose study, with 10–360 mg BI 187004 once daily over 14 days in 71 patients. Assessments included 11beta-HSD1 inhibition in the liver and subcutaneous adipose tissue ex vivo (clinical trial registry number NCT01874483).

Results BI 187004 was well tolerated and safe in all tested dose groups. The incidence of drug-related adverse events was 51.8 % (n = 29) for BI 187004 and 35.7 % (n = 5) for placebo. There were no clinically relevant deviations in laboratory or electrocardiogram parameters besides one patient on 360 mg discontinuing treatment due to moderate supraventricular tachycardia.

BI 187004 was rapidly absorbed within 2 h; exposure increased non-proportionally. The oral clearance was low, apparent volume of distribution was moderate to large, and terminal half-life with 106–124 h was rather long. Urinary tetrahydrocortisol/tetrahydrocortisone ratio decreased, indicating liver 11beta-HSD1 inhibition. Median inhibition of 11beta-HSD1 in subcutaneous adipose tissue biopsies was 87.9–99.4 % immediately after the second dose and 73.8–97.5 % 24 h after the last dose of BI 187004.

Conclusions BI 187004 was safe and well tolerated over 14 days and could be dosed once daily. Targeted 11beta-HSD1 enzyme inhibition of ≥ 80 % could be shown for BI 187004 doses ≥ 40 mg. This dose should be targeted in further studies to test blood glucose lowering in patients with type 2 diabetes and overweight or obesity.
Introduction

The clinical features of the metabolic syndrome with type 2 diabetes mellitus (T2DM), obesity, dyslipidemia, and arterial hypertension are thought to be related to the increased production of endogenous cortisol [1]. Besides, altered plasma cortisol levels also lead to tissue-specific changes in cortisol metabolism and might contribute to the development of metabolic syndrome [2]. The enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) is highly expressed in the liver and adipose tissues (AT) and catalyzes the conversion of the biologically inactive cortisone to active cortisol [3]. Data describing the interrelation of 11beta-HSD1 expression, obesity, and T2DM are conflicting. In obese subjects with and without T2DM, 11 beta-HSD1 was upregulated in subcutaneous AT compared to healthy lean controls [4–6]. In obese men with T2DM, 11 beta-HSD1 activity increased in the liver but sustained in AT [7, 8]. In contrast, euglycemic obese subjects showed decreased 11 beta-HSD1 activity in the liver but increased activity in subcutaneous AT [9]. The acute effect of 11 beta-HSD1 inhibition in subjects with obesity and T2DM is most likely the result of reduced glucocorticoid-mediated hepatic glucose output leading to improved glucose metabolism [10]. With this, a target population with obesity and T2DM could be treated with an 11beta-HSD1 inhibitor acting in AT and the liver.

The 11beta-HSD1 inhibitor INC13739 showed proof of concept for this mode of action in a 12 weeks trial in patients with T2DM failing metformin monotherapy [11]. However, despite the efficacious lowering of Hba1c, no further clinical studies were performed. To date, most 11beta-HSD1 inhibitor development programs have been discontinued, mainly due to insufficient lowering of glucose and Hba1c. Nevertheless, downregulation of tissue-specific cortisol metabolism continues to be of high interest in the development of new treatment options for patients with T2DM.

Once daily doses of 2.5–360 mg BI 187004 have already been tested in a single rising dose study [12]. The compound was safe and well tolerated in healthy male volunteers who were overweight or obese, and a significant and sustained 11 beta-HSD1 enzyme inhibition was observed in the liver and subcutaneous AT biopsies.

The study presented here evaluated the safety, tolerability, pharmacokinetics (PK), and tissue-specific pharmacodynamics (PD) of multiple rising doses of up to 360 mg once daily of the 11beta-HSD1 inhibitor BI 187004 in patients with T2DM who were overweight or obese.

Materials and Methods

Participants

Participants were male and postmenopausal or surgically sterilized female patients with T2DM, aged 20–70 years with body mass index (BMI) in the range of 28–40 kg/m². The main exclusion criteria were any evidence of a clinically relevant comitant disease and gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, or hormonal disorders besides T2DM, hyperlipidemia, or medically treated arterial hypertension. The study was undertaken according to the Declaration of Helsinki and Good Clinical Practice principles. The protocol was approved by the local independent ethics committee (Ärztekammer Nordrhein, Düsseldorf, Germany). All participants provided written informed consent before participation. The clinical trial registry number for this study is NCT01874483 (www.clinicaltrials.gov).

Study design and procedures

The study was a randomized, double-blind, placebo-controlled within dose groups, multiple rising dose trial conducted at a single center in Germany. In total, 71 patients entered the trial; among these, 70 patients were treated in seven sequential dose groups. Within each dose group, two subjects received a placebo, and eight subjects were treated with BI 187004 at doses of 10, 20, 40, 80, 160, 240, and 360 mg over 14 days, respectively.

Sixty-nine patients completed the study. One patient randomized to receive 40 mg BI 187004 discontinued the trial before the first administration of the investigational product because of the adverse event (AE) left bundle branch block, and one patient discontinued treatment on day 6 because of a drug-related AE (moderate supraventricular tachycardia).

The subjects were admitted to the study center on day -3, 60 h prior to the treatment initiation, and discharged on day 15. Follow-up on an ambulatory basis was performed for at least 10 days after discharge. The active drug was provided as a powder for oral solution (PfoS). At the time of use, the oral solution for dosing was prepared using the PfoS and a co-supplied aqueous solvent containing HP-beta-cyclodextrin 100 mg/mL. Subcutaneous AT sample was collected at two different time points for each subject on day -2 (baseline), day 2 (for technical reasons, 10–45 min after the second dose), and day 15 (24 h after the last dose) via incision biopsy in the umbilical region.

Plasma samples for PK analysis were obtained from day 1 to day 2 and from day 14 to day 15 (pre-dose, 0.3, 0.6, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24 h), and pre-dose on day 3 to day 13, day 16 to day 22. For the 10 and 360 mg groups, samples were obtained additionally on days 24, 26, and 28 (in the morning). For PK and PD analysis, 24-h urine collection was performed from day -1 to day 2 and day 11 to day 15 at 4-h to 12-h intervals (relative to drug administration).

Safety assessments

Safety and tolerability of BI 187004 were assessed descriptively using the following investigations: recording of adverse events, clinical laboratory parameters (hematology, coagulation, enzymes, substrates, electrolytes, hormones, and urinalysis), vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG) with special attention to corrected QT (QTc) prolongation, and physical examination (occurrence of findings). All clinical laboratory parameters were taken 0:15 h prior to drug administration and 1:00–1:15 h prior to breakfast.

Measurement of urinary corticosteroids

The urinary samples for determination of urinary free cortisol (UFC), urinary free cortisone (UFE), urinary total cortisol (UFT), urinary total cortisone (UTE), and their metabolites 5alpha- or allo-tetrahydrocortisol (aTHF), 5beta-tetrahydrocortisol (THF), and tetrahydrocortisone (THE) were analyzed using a validated LC-MS/MS method. The ratio (aTHF + THF)/THE was used to indirectly assess 11beta-HSD1 inhibition in the liver.
Concentration measurements of BI 187004 in plasma and urine

BI 187004 concentrations in plasma and urine samples were measured using validated bioanalytical methods using a high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The assay method consisted of a solid-supported liquid-liquid extraction of human plasma, coupled with quantitative LC-MS/MS determination of the extracted samples and validated for the concentration range of BI 187004 of 3–3,000 nmol/L. The BI 187004 plasma concentration data were generated from 11 analytical runs. For each accepted run, the acceptance criteria for the calibration standards and quality controls were met.

The BI 187004 concentrations in urinary samples were measured using an LC-MS/MS method which was validated for the concentration range of BI 187004 of 5–5,000 nmol/L. The BI 187004 urine concentration data were generated from five analytical runs. For each accepted run, the acceptance criteria for the calibration standards and quality controls were met.

The acceptance criteria for the plasma and urine assay were: (i) a regression coefficient ($R^2$) of $\geq 0.98$; (ii) at least 75% of calibration standards with $\leq 15$% RSE (relative error/accuracy), and (iii) each accepted curve contained at least six concentration levels.

Concentration measurement of BI 187004 in adipose tissue

The BI 187004 concentrations in human AT samples were measured using a protein-precipitation extraction of homogenized human AT, coupled with quantitative LC-MS/MS determination of the extracted samples. The assay was qualified for the BI 187004 concentration range of 2.5 – 10,000 ng/g. The BI 187004 AT concentration data for study samples were generated from seven analytical runs. For each run, the acceptance criteria for the calibration standards and quality control samples were met. Acceptance criteria for all sample analysis runs were $\leq 25$% RSD (relative standard deviation/precision) and $\pm 25$% RE (relative error/accuracy) for calibration standards and quality control samples.

Ex vivo measurement of 11beta-HSD1 activity

Inhibition of 11beta-HSD1 in AT was measured by conversion of deuterized (d2)-cortisone to d2-cortisol ex vivo in subcutaneous AT biopsies. Immediately after open incisional biopsies, tissue samples were cut into fragments, placed into 48-well tissue culture plates, and incubated in the assay buffer. The tissue fragments were incubated in triplicate sets in media with d2-cortisone and a 1 μM test substance to establish the background level of d2-cortisol. After overnight incubation, about 80 μL of the supernatant were snap frozen and stored at $-60°C$. Then d2-cortisone and d2-cortisol were measured using a validated LC-MS method, with the formation of d2-cortisol being an indirect indicator for enzyme activity.

Statistical analysis

The inhibition of 11beta-HSD1 in AT was calculated as individual percent change from baseline to day 2 and day 15 of the absolute deuterized cortisol measurements and expressed in medians. Safety laboratory parameters, including hormone measurements, are given as mean ± SD, PK parameters except for $T_{\text{max}}$ (time of maximum observed drug concentration), and PD parameters as geometric mean (gMean) ± geometric coefficient of variation ( %gCV). $T_{\text{max}}$ is given as the median ± range. PK and PD parameters were determined as described previously [13]. Dose proportionality of BI 187004 was explored using a power model.

Percentage change from baseline of total urinary corticosteroid excretion (sum of UFF, UFE, aTHF, TH, TH/E) and metabolic parameters were analyzed using the analysis of covariance model including treatment effect and baseline as covariate (Supplementary Tables 4 and 5).

Results

Subject demographics

Sixty-nine of 70 treated subjects completed the trial according to the clinical trial protocol. All patients in this trial were white, except for one black/African American patient and one Asian patient, both in the 240 mg dose group. The proportion of male and female subjects differed between the dose groups. Baseline characteristics (age, sex, body weight, BMI, waist to hip ratio, fasting plasma glucose, and HbA1c) are summarized in Table 1.

Metabolic parameters

To analyze any changes in metabolic parameters after the BI 187004 treatment, fasting plasma glucose, fasting insulin, and 1.5-anhydroglucitol were measured, and the homeostasis model assessment-insulin resistance index was calculated. Placebo-corrected change from baseline on day 15 for all parameters did not show any dose-dependent effect (Supplementary Table 5). Furthermore, body weight and waist-to-hip ratio remained unchanged after 14 days of BI 187004 treatment.

Safety

During this trial, 39 of 70 patients (55.7 %) were reported with ≥ 1 AE, and 34 patients (48.6 %) were reported with drug-related AEs. Both the frequency of patients reported with any AE (placebo: 6/42.9 %; BI 187004: 33/58.9 %) and drug-related AEs (placebo: 5/35.7 %; BI 187004: 29/51.8 %) were higher in the total BI 187004 group than in the placebo group. No dose-dependent trend was observed in the overall occurrence of AEs. All AEs were of mild or moderate intensity, and severe AEs were reported. One patient in the 360 mg dose group discontinued the treatment because of supraventricular tachycardia; this AE was assessed as drug-related with moderate intensity. No serious AE or death occurred during the trial.

The overall most common AEs on the system organ class level were general disorders and administration site conditions (placebo: 42.8 %; BI 187004: 814.3 %, driven by influenza-like illness), nervous system disorders (placebo: 0; BI 187004: 11/19.6 %, only disorder: headache), and gastrointestinal disorders (placebo: 0; BI 187004: 9/16.1 %, such as diarrhea, flatulence, and vomiting).

A potential dose-dependent trend was observed for the occurrence of pollakiuria; this AE was not reported in the lower BI 187004 dose groups (10–40 mg) but for six patients in the higher BI 187004 dose groups (80–360 mg). The occurrence of pollakiuria was, however, comparable between the placebo group and the total BI 187004.
group (Placebo: 2/14.3 %, BI 187004: 6/10.7 %). All pollakiuria occurrences were considered to be drug-related by the investigator.

There were no notable findings with respect to clinical laboratory evaluations and vital signs. Concerning ECG recordings, one clinically relevant abnormal ECG finding was observed in this trial. This ECG finding was reported for a patient on 360 mg BI 187004. On day 6, about 1 h after administration of study medication in the morning, supraventricular tachycardia, followed by supraventricular tachyarrhythmia absoluta, were recorded in the ECG. The ECG finding was assessed by the investigator to be drug-related with moderate intensity. Treatment with study medication was discontinued immediately. Pharmacologic cardioversion with 600 mg propafenone orally led to a normalization of the sinus rhythm in the late evening. The patient was monitored with ECG telemetry until the next morning. For the following 8 days, the patient remained at the trial site, and all following ECGs showed no clinically relevant findings. No hypoglycemic episodes were reported. Fast-}

ing plasma glucose was not affected over the treatment period of 14 days. Body weight was assessed at baseline, on day 15, and at the end-of-trial (day 22–28). Changes in body weight could not be observed.

Hormones of the hypothalamus-pituitary-adrenal (HPA) axis were measured. As previously published [12, 14], 11beta-HSD1 inhibition leads to decreased serum cortisol levels leading to increased activity of the HPA axis with the increase in adrenocorticotropic hormone (ACTH) followed by an increased adrenal activity. In all BI 187004 dose groups, the mean ACTH levels increased but within the normal range during treatment and returned to baseline after discontinuation of BI 187004 (▶ Fig. 1a). Mean cortisol levels decreased on day 7 and increased again on day 15. The end-of-trial examination compared to day 15 revealed a slight increase in mean cortisol levels in the dose groups 10 mg and 20 mg, whereas, in the higher dose groups, the cortisol levels decreased slightly. However, compared to baseline, all follow-up cortisol levels were lower at the end-of-trial examination (day 22–28) (▶ Fig. 1b). All mean cortisol and ACTH levels were within the normal range (▶ Fig. 1). Among all dose groups, only four patients had ACTH levels above the normal range on day 15 (one patient each from dose groups 10, 40, 80, and 240 mg) (Supplementary Table 5). Besides slightly elevated mean androstenedione levels in the 160 mg dose group on day 15 in male subjects, all mean levels of sex-hormone binding globulin (SHBG), androstenedione, dehydroepiandrosterone-sulfate (DHEA-s), and total testosterone were within the normal range in both genders (Suppl. Table 2, 3). In detail, mean androstenedione and DHEA-s levels increased slightly in both genders without any dose dependency and decreased after discontinuation of treatment. Mean total testosterone levels of male subjects showed a tendency to increase in the 240 mg and 360 mg dose group and a slight increase in female patients returning to baseline after discontinuation of the treatment. SHBG levels showed no clinically significant changes.

Total urinary corticosteroid excretion as an additional marker showing HPA axis activation (calculated by adding UFE and UFF as well as their metabolites αTHF, THF, and THE) increased after 14 days of treatment by a factor of about 2 (% of baseline ranging between 176.2–253.5 %) (Supplementary Table 4).
Pharmacokinetics

Absorption of BI 187004 was rapid; the median tmax was between 0.667 and 2.00 h after both single dose and multiple doses. Both maximum observed drug concentration (Cmax) and area under the concentration-time curve over dosing interval in steady state (AUCτ,ss) increased non-proportionally from dose groups 10 to 360 mg. Dose-normalized Cmax and AUC0–24 values were similar in the dose groups 10–160 mg but decreased in the 240 mg and 360 mg dose groups on day 1. After 14 days of BI 187004 administration, dose-normalized Cmax,ss and AUCτ,ss values decreased from the 10 mg to the 360 mg dose groups. The inter-subject variability was low for Cmax,ss and AUCτ,ss with a gCV between 12.3 and 38.6 %.

Accumulation of BI 187004 in plasma between days 1 and 14 was limited. The time to achieve a steady state after multiple BI 187004 doses differed between dose groups; it ranged non-proportionally between 4 and 8 days. The gMean oral clearance of BI 187004 (CL/F,ss) was low (2.01–6.47 L/h), and the gMean apparent volume of distribution (Vz/F,ss) was moderate to large (195–1160 L). The analysis of terminal half-life (t1/2,ss) was based on the BI 187004 dose groups (10 mg and 360 mg) with extended PK sampling ≥ 14 days after the last dose. gMean t1/2,ss was long, ranging from 106 h (10 mg) to 124 h (360 mg). The gMean cumulative BI 187004 fraction of dose excreted in the urine was 3.82–6.14 % on day 1 (fe0–24) and 5.83–10.3 % on day 14 (fe0–24,ss) (▶ Table 2, ▶ Fig. 2).

At 24 h after the last dosing (day 15), the AT/plasma concentration ratio was in a range of 9.79–16.3 % (▶ Table 3). The AT/plasma concentration ratio, immediately after the second dosing on day 2, ranged from 13.9–36.2 %.

11β-HSD1 inhibition in the liver

Ascending doses of BI 187004 led to the inhibition of 11β-HSD1 in the liver as assessed indirectly by the ratio of (aTHF + THF)/THE ratio (▶ Fig. 3). On day 1 (0–24 h), the placebo-corrected percent change from baseline gMean (aTHF + THF)/THE ratio decreased...
<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>BI 187004</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>10 mg gMean</td>
</tr>
<tr>
<td>Day 1</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-24}[nmol*h/L]</td>
<td>7,500 (48.1)</td>
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<tr>
<td>C_{max}[nmol/L]</td>
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<tr>
<td>t_{1/2a,h}</td>
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<td>CL_{R.2-24}[L/h]</td>
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<td>Day 14</td>
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<td>14,500 (28.2)</td>
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<tr>
<td>C_{max,SS}[nmol/L]</td>
<td>1,240 (25.3)</td>
</tr>
<tr>
<td>t_{1/2, SS}</td>
<td>106 (61.2)</td>
</tr>
<tr>
<td>V_{f}F/S[cm^3]</td>
<td>308 (62.4)</td>
</tr>
<tr>
<td>CL/F[cm^3]/h</td>
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</tr>
<tr>
<td>FE_{R.2-24a,SS, %}</td>
<td>10.3 (26.6)</td>
</tr>
</tbody>
</table>

**Table 2** Summary of pharmacokinetic parameters at steady state after multiple BI 187004 administrations on day 1 and 14.

**Discussion**

Here, we present the first clinical data for the 11beta-HSD1 inhibitor BI 187004 in healthy subjects. The compound was tested in a randomized, double-blind, placebo-controlled, multiple rising-dose study using BI 187004 2.5–360 mg in healthy volunteers. The incidence of AEs in healthy subjects as well as in patients with type 2 diabetes is expected for this type of trial.

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affinity binding to a protein and/or protein site, which would prolong the time of BI 187004 remaining in plasma. (ii) Differential binding of BI 187004 to specific blood cell components leading to slower than anticipated clearance; in vitro studies showed no difference in blood cell partitioning at low concentrations (10 and 100 nmol/L). These data do not support the hypothesis of a tighter binding of BI 187004 to certain blood constituents leading to the slow release in plasma with prolonged clearance (internal communication, data not shown). (iii) BI 187004 binds with a high affinity to certain tissues and is then only slowly released from one or even several tissue compartments leading to the described long terminal half-life; additional studies are needed to identify potential tissues with tight binding of BI 187004. (iv) BI 187004 binds very strongly to the target enzyme 11beta-HSD1, which then causes a prolonged release of the compound into the circulation resulting in a long terminal half-life. Further studies are necessary to specifically analyze the target binding of BI 187004 in different tissues depending on the overall tissue affinity of the compound. Strong binding to the target enzyme might be one mechanism supporting the hypothesis of high tissue affinity of BI 187004. Overall, more analyses will support a detailed understanding of the molecular mechanisms leading to the long terminal half-life of BI 187004. However, this long half-life appeared to have a limited effect on the accumulation of BI 187004 within the body according to day 14 exposure results (Table 2) which are very much comparable to the day 1 exposure in patients with T2DM (Table 2). Therefore, a once-daily dosing regimen is still recommended.

Compared with the BI 187004 concentration in plasma, the concentration in AT was relatively low (see Table 3). It has to be taken into account that on day 15, trough tissue concentrations were
measured, whereas, on day 2, non-trough tissue concentrations were measured as the AT biopsies were taken 10–45 min after the second dose for logistical reasons (▶Table 3). In healthy male volunteers, the AT/plasma ratio of BI 187004 was in the range of 8.58–11.4% 24 h after a single dose of BI 187004 [12].

As described previously [15], in response to 11beta-HSD1 inhibition in peripheral tissues, mainly liver and AT, serum cortisol levels tend to decrease, and due to negative feedback of the HPA axis, a compensatory increase of ACTH and adrenal cortisol secretion is seen. Adrenal androgen precursor hormones such as DHEA-s and androstenedione are expected to increase while overall serum cortisol should remain stable due to increased clearance leveling out increased adrenal secretion. Furthermore, sufficient (>90%) 11beta-HSD1 enzyme inhibition is expected to enhance the cortisol clearance from the body. In a single rising dose trial [12] with ascending doses of 2.5–360 mg BI 187004, all HPA axis hormones were stable and within the normal range. However, total urinary corticosteroid excretion increased by up to 2-fold. In line with these data, multiple doses of BI 187004 led to increased ACTH levels over a treatment duration of 14 days with a 2.48-fold increase in total urinary corticosteroid excretion. Although ACTH remained within the normal range, its levels increased during the 14 days of treatment. At this point, it is not clear whether, during long-term treatment, ACTH levels and urinary corticosteroid excretion would continuously increase or reach a plateau at some point. In clinical trials, when BI 187004 is used for longer than 14 days of treatment, safety measures such as pituitary and adrenal challenge tests should be included to closely monitor the effect of BI 187004 on the HPA axis.

In wild-type mice, urinary corticosteroids are mostly excreted as metabolites of corticosterone and less than 10% as 11-Dehydrocorticosterone (11-DHC) metabolites, whereas in whole body 11beta-HSD1 knockout mice, 20–25% are excreted as 11-DHC metabolites [16]. In contrast, liver-specific 11beta-HSD1 knockout mice show similar glucocorticoid excretion patterns as wild-type mice [17]. Thus, at least in animal models, urinary steroid metabolite excretion might be substantially influenced by extrahepatic inhibition of 11beta-HSD1. In clinical studies, reduction in urinary

<table>
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<th>Dose (mg)</th>
<th>BI 187004 Plasma Cday2 gMean [% (gCV)]</th>
<th>BI 187004 AT Cday2 gMean [% (gCV)]</th>
<th>BI 187004 AT:plasma inhibition in AT median (min-max) day 2 [%]</th>
<th>BI 187004 Plasma Cday15 gMean (mean (gCV)) [nmol/L]</th>
<th>BI 187004 AT Cday15 gMean (gCV) day 15 [%]</th>
<th>BI 187004 AT:plasma ratio (mean (gCV)) day 15 [%]</th>
<th>11beta-HSD1 inhibition in AT median (min-max) day 15 [%]</th>
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<td>10</td>
<td>156 (56.1)</td>
<td>34.5 (38.3)</td>
<td>22.1 (49.5)</td>
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<td>511 (23.9)</td>
<td>142 (72.1)</td>
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<td>1,020 (30.0)</td>
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<td>99.3 (99.1–99.6)</td>
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<td>872 (54.6)</td>
<td>36.0 (94.7)</td>
<td>99.5 (98.2–99.6)</td>
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<td>245 (62.8)</td>
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<td>360</td>
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<td>925 (41.7)</td>
<td>34.8 (63.3)</td>
<td>99.4 (99.1–99.7)</td>
<td>2,780 (19.6)</td>
<td>454 (29.3)</td>
<td>16.3 (32.8)</td>
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</table>

*Table 3* Pharmacokinetic/pharmacodynamic relationship between BI 187004 concentration in adipose tissue and plasma and ex vivo 11beta-HSD1 inhibition in adipose tissue after multiple doses of BI 187004.

![Fig. 3](image-url) (aTHF+THF)/THE ratio over time after multiple oral dose administrations in subjects with type 2 diabetes mellitus. Data are mean ± standard deviation, n = 14 (Placebo), n = 7 (BI 187004: 360 mg after day 6), n = 8 (other BI 187004); Source: Boehringer Ingelheim International GmbH.

![Fig. 4](image-url) Median 11beta-HSD1 enzyme inhibition in adipose tissue after multiple BI 187004 administrations over 14 days in patients with type 2 diabetes on day 2 and day 15.; Data are median ± standard deviation, n = 14 (Placebo), n = 7 (BI 187004: 360 mg after day 6), n = 8 (other BI 187004); Source: Boehringer Ingelheim International GmbH.
(aTHF + THF)/THE ratio is still a relevant non-invasive indirect measure of 11 beta-HSD1 enzyme inhibition in the liver [18]. As described here, in patients with T2DM, inhibition of 11beta-HSD1 enzyme in the liver, as reflected by urinary (aTHF + THF)/THE ratio, decreased after a single dose and remained sustained in all dose groups. Thus, a dose-response relationship could not be established. In addition, only minimal changes were observed over time, suggesting that the maximum possible hepatic 11beta-HSD1 inhibition of BI 187004 was already reached in the lowest dose after single dosing. The urinary (aTHF + THF)/THE ratio data indicate that a low dose of BI 187004 might lead to significant and sustained 11beta-HSD1 inhibition in the liver. A reduction of the (aTHF + THF)/THE ratio by 70% after single dose treatment is in the range of what was previously reported for other 11beta-HSD1 inhibitor compounds: maximum decrease of the ratio went as high as 92% for ROS093151 after 4 weeks [19] and for AZD4017 after 9 days [20] and as low as 26% for PF-915275 after 14 days of treatment [21]. In patients with T2DM, treatment with BI 135585 decreased urinary (aTHF + THF)/THE ratio by 65–75% after a single dose and 75% after 14 days compared to placebo, occurring already in the lowest dose remaining sustained in all dose groups [14]. Currently, the reduction of which ratio has to be achieved to sufficiently inhibit 11beta-HSD1 in the liver still needs to be examined. With the caveats discussed above, the THF/THE ratio data indicate that a low dose of BI 187004 might lead to a significant and sustained 11beta-HSD1 inhibition in the liver.

In the trial presented here, for technical reasons, the first AT biopsies of the treatment were obtained 10–45 min after the second dose of 10–360 mg BI 187004; 11beta-HSD1 inhibition increased from 87.9% (10 mg) to 99.4% (360 mg). These data are in line with the AT biopsy data from the single rising dose trial [12], showing >90% inhibition 10 h after a single dose BI 187004. Twenty-four hours after the last dose on day 15, trough median 11beta-HSD1 inhibition was in the range of 73.8% (10 mg) to 97.5% (360 mg). Similar results were obtained with other 11beta-HSD1 inhibitors. INCBl3739 showed >90% inhibition in AT after a single dose for at least 24 h based on a decrease in the (aTHF + THF)/THE ratio [22]. Similarly, a single dose of AMG 221 sustained >90% 11beta-HSD1 inhibition in AT 24 h after dosing [23]. Likewise, a single dose of BI 135585 led to 90% inhibition of 11beta-HSD1 in AT 24 h after dosing [14]. Based on preclinical modeling [24], an inhibition of >90% of 11beta-HSD1 in AT is regarded as a prerequisite to obtaining sustained glucose-lowering efficacy. Therefore, a dose of at least 40–80 mg BI 187004 is thought to be needed to achieve long-term blood glucose lowering effect.

In summary, ascending doses of BI 187004 over 14 days led to a significant and strong reduction in urinary (aTHF + THF)/THE ratio indicating 11beta-HSD1 inhibition in the liver as well as >90% inhibition of 11beta-HSD1 in AT for doses >40 mg. As expected, BI 187004 did transiently activate the HPA axis. In contrast to the clinical development of other 11beta-HSD1 inhibitors, the trial was performed in the target population of T2DM patients who were overweight or obese. The absence of metabolic changes might be explained by the fact that the trial duration was only 14 days, and the trial was not powered to detect clinically relevant changes. Although there was no metabolic improvement, there were also no adverse metabolic changes showing that the compound was well tolerated in the target population.

It can be concluded that (i) the 11beta-HSD1 inhibitor BI 187004 is a safe and well-tolerated compound for up to 14 days in patients with T2DM and overweight or obesity, (ii) BI 187004 exhibits a significant and sustained 11beta-HSD1 enzyme inhibition in the liver and AT, (iii) after short-term treatment over 14 days BI 187004 did not affect plasma glucose levels, and (iv) longer-term studies are needed to assess the glucose-lowering efficacy of BI 187004.

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Conflict of Interest

The institution of TH (Profil) received research grants from the following pharmaceutical companies: Adocia, Astra Zeneca, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, G ü n th e r, Elf Lilly, Medtronic, Novo Nordisk, Novartis, Sanofi, and Senseonics in the past 12 months. In addition, TH received travel grants, consulting fees, and speaker honoraria from Elf Lilly, Mylan, and Novo Nordisk; LPM is an employee of Profil and received travel grants, congress fees, and speaker honoraria from Elf Lilly, Gan & Lee, and Novo Nordisk; SB, CS, MW are employees of Boehringer Ingelheim.

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