Clinical Study Synopsis for Public Disclosure

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Title of trial:	Evaluation of relative bioavailability of BI 44847 in different ethnic groups (subjects of white, Asian, and African origin), and evaluation of effect of diet and acarbose coadministration on bioavailability following oral administration of 200 mg BI 44847 in healthy male volunteers. An open-label, single-dose, parallel-group, phase I study (group 1 with additional crossover aspects)
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objectives were to investigate the relative bioavailability of BI 44847 in different racial groups (white, Asian, and African subjects) and to investigate the effect of different types of diet and acarbose coadministration on the bioavailability of BI 44847 in white subjects.
Methodology:	To assess bioavailability in different racial groups, the study was performed according to an open-label, parallel-group design with single-dose administration of BI 44847 in healthy white, Asian, and African subjects. In 2 additional treatment periods, the effect of different types of diet and acarbose coadministration was investigated in white subjects, according to an open-label, single-dose, 3-way crossover design.
No. of subjects:	
planned:	entered: 36
actual:	entered: 37 (13 white subjects, 12 Asian subjects, 12 African subjects) Treatment A: 200 mg BI 44847 in white subjects treated: 13 analysed (for primary endpoints): 12 Treatment B: 200 mg BI 44847 coadministered with acarbose in white subjects treated: 12 analysed (for primary endpoints): 12 Treatment C: 200 mg BI 44847 after intake of a Japanese diet in white subjects treated: 12 analysed (for primary endpoints): 12

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	Treatment D: 200 mg BI 44847 in Asian subjects treated: 12 analysed (for primary endpoints): 12 Treatment E: 200 mg BI 44847 in African subjects treated: 12 analysed (for primary endpoints): 12
Diagnosis and main criteria for inclusion:	Healthy male subjects at the age of 18 to 40 years with a body mass index (BMI) of 18 to 25 kg/m² and a body weight of at least 45 kg were to be included in the study. The subjects were white, Asian, and African.
Test product:	BI 44847 administered as tablet within treatments A, B, C, D, and E
dose:	200 mg
mode of admin.:	Oral
batch no.:	B071003095
Comedication:	Acarbose (Glucobay®) as tablet in treatment B
dose:	100 mg 3 times daily
mode of admin.:	Oral
batch no.:	B081002898
Duration of treatments:	Within treatments A, D, and E, a single dose of BI 44847 was administered. Within treatment B, acarbose was administered for 2 days, on the second day a single dose of BI 44847 was coadministered with the morning dose of acarbose. Within treatment C, a single dose of BI 44847 was administered after the subjects had eaten a Japanese diet for 6 days. BI 44847 administrations in treatments A, B, and C were separated by wash-out periods of at least 14 days.
Criteria for evaluation:	
Clinical pharmacology:	*Pharmacokinetic parameters of BI 44847* The following primary pharmacokinetic endpoints were assessed by non-compartmental analysis: $AUC_{0-\infty}$, AUC_{0-48}, AUC_{0-12}, C_{max} The following secondary pharmacokinetic endpoints were assessed by non-compartmental analysis: t_{max}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, AUC_{t1-t2} (for time intervals 0-2, 2-4, 4-12, 12-24, 0-4, and 0-24 h), Ae_{t1-t2} (for time intervals 0-4,

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	4-8, 0-8, 8-12, 12-24, 0-12, and 0-24 h), fe_{t1-t2} (for time intervals 0-4, 4-8, 0-8, 8-12, 12-24, 0-12, and 0-24 h), $CL_{R,t1-t2}$ (for time intervals 0-4, 4-8, 0-8, 8-12, 12-24, 0-12, and 0-24 h) *Pharmacodynamic parameter* Urinary glucose excretion (for time intervals 0-4, 0-8, 0-12, and 0-24 h)
Safety:	The safety evaluation was based on physical examinations, measurements of vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECG), clinical laboratory tests (haematology, clinical chemistry, and urinalysis), the incidence of adverse events (AEs), and an assessment of global tolerability.
Statistical methods:	Point estimators (geometric means [gMean]) of the median intrasubject ratios of the primary endpoints and of urinary glucose excretion for the time interval 0-24 h and their 2-sided 90% confidence intervals were calculated. For the investigation of relative bioavailability in different racial groups, the statistical model was an analysis of variance (ANOVA) on log-transformed parameters including a 'treatment effect'. For the evaluation of an effect of diet and acarbose coadministration on relative bioavailability, the model was an ANOVA on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'. Confidence intervals (CI) are based on the residual error from the ANOVA. Additional analyses were performed on a data-driven basis to investigate the effect of the predicted lactase phenotype on bioavailability and urinary glucose excretion between the different racial groups. For all other parameters, descriptive statistics were calculated.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	Thirty-seven subjects were entered in this trial: 13 white subjects, 12 Asian subjects, and 12 African subjects. One white subject discontinued the trial on the first day of treatment A and was replaced by another subject. Thus, 12 white subjects were analysed with respect to the influence of a Japanese diet and of acarbose coadministration and 36 subjects were analysed with respect to racial differences in the bioavailability of BI 44847.

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Pharmacokinetic results

The main pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} of BI 44847 are given by treatment in the following table. AUC_{0-12} and AUC_{0-48} values were similar to $AUC_{0-\infty}$ values and thus are not shown.

Treatment	A: white	B: white/ acarbose	C: white/ Japanese diet	D: Asian	E: African
(N=12)	gMean	gMean	gMean	gMean	gMean
$AUC_{0-\infty}$ [nmol·h/L]	2290	2330	2400	4700	3730
C_{max} [nmol/L]	1930	2440	2000	4280	3090

The exposure to a single oral dose of 200 mg BI 44847 was highest in Asian subjects (treatment D) followed by African subjects (treatment E) and then white subjects (treatment A). When Asian and white subjects were compared, the adjusted gMean ratios for $AUC_{0-\infty}$ and C_{max} were 204.9% (90% CI 155.97, 269.04) and 222.1% (90% CI 172.35, 286.18), respectively. When African and white subjects were compared, the adjusted gMean ratios for $AUC_{0-\infty}$ and C_{max} were 162.5% (90% CI 117.70, 224.41) and 160.4% (90% CI 118.45, 217.32), respectively. Similar results were obtained when AUC_{0-12} values were evaluated. Asian subjects excreted almost 2-fold higher amounts of BI 44847 in the urine over 24 h compared with the other racial groups. Body weight differences did not account for the pharmacokinetic differences between races.

All African and Asian subjects in this trial were classified as lactose intolerant based on genotyping results. Three white subjects were classified as lactose intolerant while the others were lactose tolerant or had high lactase activity. By introducing the predicted lactase phenotype in the statistical model, the differences in $AUC_{0-\infty}$ and C_{max} between races could be dramatically reduced. When Asian and white subjects were compared, the adjusted gMean ratios for $AUC_{0-\infty}$ and C_{max} were 110.0% (90% CI 79.48, 152.14) and 136.8% (90% CI 97.82, 191.20), respectively. When African and white subjects were compared, the adjusted gMean ratios for $AUC_{0-\infty}$ and C_{max} were 87.2% (90% CI 56.54, 134.61) and 98.8% (90% CI 63.93, 152.67), respectively. However, 3 African subjects had genetic polymorphisms that could possibly reverse their lactose

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intolerance. By classifying these subjects as lactose tolerant, the differences in $AUC_{0-\infty}$ and C_{max} between African and white subjects were also reduced compared with the original analysis.

Intake of a Japanese diet (treatment C) did not influence the C_{max} and $AUC_{0-\infty}$ of BI 44847 in white subjects. Coadministration of BI 44847 and acarbose (treatment B) resulted in a 1.3-fold increase in C_{max} but did not influence $AUC_{0-\infty}$.

Pharmacodynamic results

Asian subjects excreted the highest amount of glucose in the urine over 24 h (arithmetic mean Ae_{0-24}) following BI 44847 administration, followed by white and African subjects as shown in the following table.

Treatment	A: white	B: white/ acarbose	C: white/ Japanese diet	D: Asian	E: African
(N=12)	Mean	Mean	Mean	Mean	Mean
Ae_{0-24} [mg]	19200	15300	18300	27700	19000

Differences in glucose excretion between racial groups could be dramatically reduced by including the predicted lactase phenotype in the statistical model.

Coadministration of acarbose resulted in a reduced amount of glucose eliminated in the urine over 24 h, which might be due to a reduced glucose absorption caused by acarbose.

Safety results:

No serious AEs, no AEs of severe intensity, and no AEs leading to discontinuation occurred during the trial. Of the 37 subjects entered and treated in the trial, 9 subjects reported at least 1 AE. The majority of the AEs were of mild intensity, only 1 AE was of moderate intensity (headache under acarbose treatment).

The investigator considered the following AEs to be related to the trial drugs: headache in 2 subjects (1 white, 1 Asian) under BI 44847 treatment, headache in 1 white subject under acarbose treatment, abdominal pain and nausea in 1 white subject under BI 44847 treatment, as well as flatulence in 3 white subjects under acarbose treatment. In those subjects who had experienced flatulence, global tolerability was assessed as 'satisfactory', while for all other subjects the global tolerability assessment was 'good'.

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Furthermore, there were no notable findings with respect to the clinical laboratory evaluation, vital signs, and ECG recordings.

Conclusions:

Results from this trial suggest that race does not play a role in the pharmacokinetics and pharmacodynamics of BI 44847. However, lactase enzyme activity may play an important role in the presystemic degradation of BI 44847 and may thus be responsible for the differences in the relative bioavailability of BI 44847 and the differences in urinary glucose excretion among healthy subjects.