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BI 1356, a Novel and Selective Xanthine Based DPP-4 Inhibitor, Demonstrates Good Safety and Tolerability with a Wide Therapeutic Window

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o. 0586P

ADA 22-26 June 2007, C

ABSTRACT

thine analogue, which exhibits a high potency for DPP-4 inhibition, lf-life of circulating incretin hormones, and improves glucose preclinical studies.

, double-blind, placebo controlled single rising dose study in healthy male 21-65 years, BI 1356 was administered at doses ranging from 2.5 to ily to investigate the safety, tolerability, pharmacokinetics, and ics. BI 1356 was well tolerated. There were no serious adverse events aemic episodes were observed. The incidence of any adverse event (AE) 5, 38% for placebo) or of drug related AEs (19% vs. 31%) was not higher pared to placebo. The most common AEs reported were headache, ess and nausea with an incidence comparable between BI 1356 and ically relevant deviations in laboratory parameters (haematology, ical chemistry, and urinalysis) were reported. ECGs were centrally pecialised provider and did not show any clinically relevant deviations or a QT prolonging effect up to and including the 600 mg dose.

BI 1356 increased less than proportionally from 2.5 to 5 mg, while C_{max} sed more than proportionally from 25 to 100 mg and approximately r doses ranging from 100 to 600 mg. Renal excretion was low and does e main pathway for elimination of BI 1356. After single doses of 2.5 mg 6, DPP-4 activity was reduced by 73% and 86% within 3 h, respectively. after administration of 25-600 mg BI 1356, mean plasma DPP-4 inhibition 90%.

1356 was well tolerated and safe. The results of the pharmacokinetic and ic profile after single doses demonstrate the potency and full 24 hrs n of BI 1356. Based on an estimated therapeutic dose of 5 mg, the ow of BI 1356 is expected to be >100 fold.

INTRODUCTION

tes is characterised by insulin resistance and progressive lin secretion. Current oral antidiabetic agents cannot prevent ve failure of pancreatic ß-cells, leading to secondary drug

oach in the treatment of diabetes targets the incretins (e.g. ones secreted in the intestine in response to food intake. tes insulin and glucagon secretion. DPP-4 inhibitors increase s of intact GLP-1. BI 1356 is a potent, novel, orally available, bitor of DPP-4 (see also Poster Nos. 0588P and 0594P).

tudy was designed to evaluate the safety, tolerability, etics (PK), and pharmacodynamics (PD) of single rising doses healthy men.

OBJECTIVES

olerability of BI 1356 following administration of single rising f 2.5, 5, 25, 50, 100, 200, 400, and 600 mg BI 1356 in healthy

of the PK and PD parameters of BI 1356 after single doses

METHODS

le volunteers from ≥21 to ≤65 years of age and with a BMI 9.9 kg/m²

rmed consent

n

s administered as solution for doses 2.5 and 5 mg and as loses 25, 50, 100, 200, 400 and 600 mg

was administered in the morning after an overnight fast

inetic profiling was performed for up to 192 hours

ity was determined as a pharmacodynamic marker by diluted EDTA plasma with Ala-Pro-AFC as substrate and the increase in absorbance over time

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

- 64 Caucasian subjects were randomised to one of 8 treatment groups with a ratio of 3:1 active treatment to placebo
- One subject was randomised but not treated as theQRS interval >110 ms at baseline which was a violation of an exclusion criterion

Table 1: Subject characteristics at baseline

	Total subjects treated
N	63
Age (years±SD)	38.3 (9.4)
Weight (kg ±SD)	80.4 (10.2)
BMI (kg/m² ±SD)	24.8 (2.3)

RESULTS - PHARMACOKINETICS

Figure 1: Arithmetic mean (SD) plasma concentration of BI 1356 after single oral administration of 2.5 mg to 600 mg

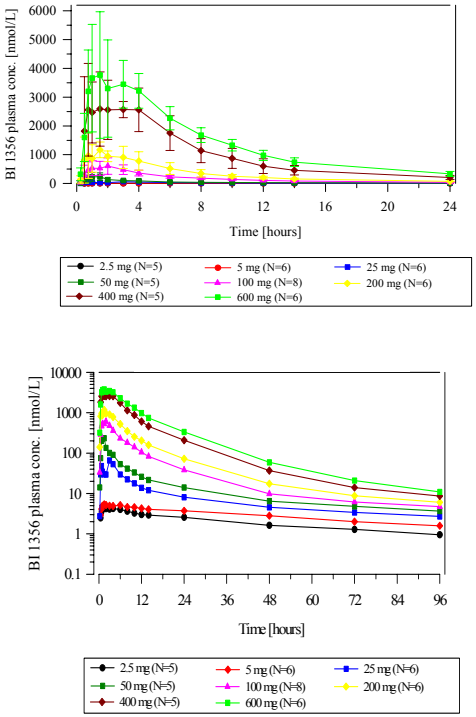


Table 2: Geometric mean (%gCV) of PK parameters after single oral administration of 2.5 to 600 mg BI 1356

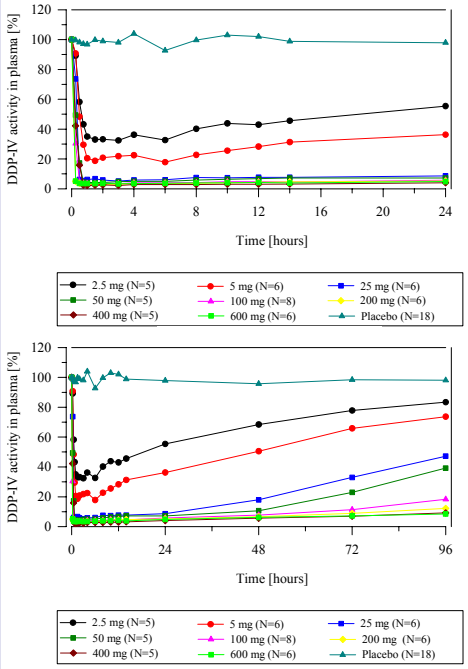
Parameter	2.5 mg solution	5 mg solution	25 mg tablet	50 mg tablet	100 mg tablet	200 mg tablet	400 mg tablet	600 mg tablet
AUC_{0-24} [nmol·h/L]	75.3 (19.1)	100 (23.0)	468 (33.6)	1041 (39.8)	3999 (21.8)	7829 (25.5)	22853 (36.3)	33010 (21.2
AUC_{∞} [nmol·h/L]	290 (33.8)	427 (33.0)	1111 (15.8)	1932 (25.7)	5692 (21.0)	10707 (16.8)	27720 (35.7)	39569 (19.6
C_{max} [nmol/L]	4.40 (19.1)	5.71 (19.4)	72.4 (40.2)	250 (47.0)	758 (38.8)	1443 (25.9)	3280 (36.7)	4338 (32.1)
t_{max}[1] [h]	2.05 (1.48 – 3.05)	1.47 (1.02 – 5.95)	2.97 (0.70 – 4.02)	0.73 (0.45 – 1.48)	1.73 (0.52 – 3.03)	1.13 (0.47 – 2.03)	3.00 (0.68 – 4.00)	2.21 (0.70 – 3.02
$t_{½}$ [h]	79.9 (34.7)	69.7 (17.2)	79.9 (24.6)	75.9 (5.60)	143 (19.8)	172 (43.2)	184 (50.9)	128 (41.3)

[1]median t_{max} and min-max range

- Exposure of BI 1356 increased less than proportionally from 2.5 to 5 mg. C_{max} and AUC increased more than proportionally from 25 to 100 mg and approximately proportionally for doses ranging from 100 to 600 mg.
- The terminal half-life ranged from 70-80 hrs for samples collected up to 120 hrs post-dose, and to 184 hrs for samples collected up to 192 hrs. The long terminal half-life can be explained by tight binding of BI 1356 to plasma DPP-4 protein. The effective half-life is in the range of 10-30 hrs (see also Poster No. 0588P)
- Renal excretion of BI 1356 was below 1% for doses up to 5 mg and increased dose-dependently

RESULTS - PHARMACODYNAMICS

Figure 2: Arithmetic mean DPP-4 activity measured in plasma after administration of 2.5 to 600 mg BI 1356



- 2.5 mg and 5 mg BI 1356 reduced DPP-4 activity by 73% and 86% within 3 hrs, respectively.
- Mean plasma DPP-4 activity was below 10% 24 hrs after administration of 25-600 mg BI 1356

RESULTS – SAFETY AND TOLERA

Adverse events

- There were no serious adverse events (SAEs) and no hypoglyc episodes
- The incidence of AEs with BI 1356 (27.7%) was not higher com placebo (37.5%), and no dose dependency was discerned
- Headache was reported most commonly with an incidence of 6 (37.5%) treated with placebo and 9 subjects (19.1%) treated wi
- The number of subjects with AEs considered possibly drug rela not higher with BI 1356 (19.1%) compared with placebo (31.3%

Clinical laboratory tests

- No clinically relevant changes were observed in routine blood t (haematology, coagulation parameters, clinical chemistry, and

12-lead ECG and vital signs

- No clinically relevant changes in blood pressure or heart rate
- No evidence for clinically relevant effects of BI 1356 on any EC

CONCLUSIONS

- The administration of single rising oral doses of 2.5 mg BI 1356 was well tolerated and safe
- The overall incidence of adverse events was not differ between BI 1356 and placebo
- The pharmacokinetic and pharmacodynamic profile is with a once-daily dosing regimen
- DPP-4 activity was reduced by >40% and >60%, 24 h administration of 2.5 and 5 mg BI 1356, respectively
- BI 1356 is a potent DPP-4 inhibitor with a wide therape dow of >100-fold based on an expected therapeutic do

ACKNOWLEDGEMENTS

We would like to thank all those who participated in this study and were involved in the preparation, conduct, and analysis of the study.

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