2 SYNOPSIS

Name of Sponsor/Company: OSI-prosidion Name of Finished Product: Name of Active Ingredient: PSN357AB	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

Title of Study:
A randomised, double-blind, placebo-controlled, multiple dose, time-lagged cohort dose escalation trial, investigating the pharmacodynamics, safety and tolerability, and the pharmacokinetics of PSN357AB in patients with type-2 diabetes

Principal Investigator:

PD [redacted]

Study Centre:

[redacted] Germany

Publication (reference): None at the time of this report	
Study Period (years): Jan 2006 – Sep 2006	**Clinical Phase:** IIa

Objective(s):

Primary:

1. To provide proof-of-concept for PSN357AB

Secondary:

1. To investigate the pharmacodynamics of PSN357AB in patients with type-2 diabetes mellitus in relation to doses
2. To assess the safety and tolerability
3. To investigate the dose linearity (dose proportionality), accumulation and PK of the ascending doses

Methodology:

This was a randomised, double-blind, placebo-controlled, multiple dose time lagged cohort, dose-escalating study to investigate the proof-of-concept and pharmacodynamics, safety, tolerability and pharmacokinetic characteristics of several dose steps of PSN357AB in patients with type-2 diabetes.

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Number of Patients (planned and analyzed):

Number of patients planned:	50
Number of patients screened:	78
Number of patients analyzed:	20
Number of patients withdrawn:	00
Number of patients completed:	20

Diagnosis and Main Criteria for Inclusion:

Male patients and female patients of non-childbearing potential diagnosed with type-2 diabetes mellitus according to WHO criteria; aged between 30 and 74 years, inclusive, with a BMI of 22–35 kg/m^2, inclusive and HbA_{1c} at screening between 7.5% and 10%, inclusive.

Test Product(s), Doses and Mode of Administration, Batch Number:

Test product/formulation:	PSN357AB
Strength:	5 mg/mL
Doses:	1.0, 5.0, 7.5 mg/mL
Mode of administration:	Oral solution as repeat dosing for 14 days
Batch No.:	[redacted]

*The final dose decided upon was to be based on the safety assessment of the previous dose. The study was prematurely terminated after a dose level of 5 mg/kg.

Reference (Placebo) Therapy, Dose and Mode of Administration, Batch Number:

Test product/formulation:	Placebo
Doses:	Matching test product regimen
Mode of administration:	Oral
Batch Nos.:	[redacted] and [redacted]

Duration of Treatment:

The approximate study duration for each patient was at least 35 days to a maximum of 63 days.

Criteria for evaluation:
Primary:

Efficacy parameter: Plasma glucose and insulin profiles, glucose after oral glucose tolerance test (OGTT), fructosamine, fasting blood glucose (FBG), mean blood glucose (MBG)

Secondary:

Safety and tolerability: safety laboratory including safety glucose, physical examination, vital signs, 12-lead ECG, adverse events, MRI scan

Pharmacokinetics: C_{max}, AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$, $AUC_{0-t,\ Day\ 1}$ / $AUC_{0-t,\ Day\ 13}$, ratio $AUC_{0-\infty,\ Day\ 13}$ / $AUC_{0-\infty,\ Day\ 1}$, t_{max}, MRT, $t_{1/2}$, ratio of $AUC_{0-24,\ Day\ 13}$ / $AUC_{0-24,\ Day\ 1}$

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Statistical Methods:

All demographic, efficacy, pharmacodynamic, pharmacokinetic, safety and tolerability variables were listed and summarised, as appropriate.

Continuous data were summarised by treatment group and for the complete study population, using means of descriptive statistics. Categorical data were summarised by frequency tables including counts and percentages.

Pharmacodynamics:

All PD data were analyzed based on the available data. PD endpoints included insulin and glucose (including OGTT results for glucose) and were listed, plotted and summarised including changes from baseline. For glucose and insulin, differences between pre-dose values and 10 and 24 hour post-dose values were computed between Day 1 and Day –1, Day 13 and Day –1, Day 13 and Day 1, Day 13 and Day 7, Day 7 and Day 1 and Day 7 and Day –1.

The following derived PD parameters were computed: area under the effect curve (AUE) until 10 and 24 hours. Maximum effect (E_{max}) and time to peak (t_{max}) were calculated for glucose and insulin. FBG and MBG were summarised and scatter plots are provided for HbA_{1c} measured at study enrolment (on the x axis) versus PD parameters OGTT on Day 15 and FBG and MBG on Day 13, followed by a listing presenting the individual data in these scatter plots. Additionally, PD parameters were summarised by presenting descriptive statistics of differences to pre-treatment (i.e., Day –1) as nominal differences (mmol/L) and as percent changes to Day –1 (%) and as baseline-adjusted data.

Safety:

For quantifiable safety data, changes from baseline were calculated and summarised by means of descriptive statistics, as appropriate.

Adverse events were summarised by treatment group, MedDRA 7.0, severity and relation to IMP. The descriptive statistics presented for each system-organ class and preferred term were the number of patients with event (N), the percent of patients exposed with event (%), and the number of events (E). All AEs were listed by patient, including demographic information, dose, MedDRA 7.0 system organ class and MedDRA 7.0 preferred term. Vital signs, ECG, MRI scans, laboratory data including safety glucose were listed including change to baseline and descriptively summarised. For the manually assessed QTc endpoints dose-response relationship was examined graphically using box-plots (including arithmetic mean).

Pharmacokinetics:

The 24-hour individual median pharmacokinetic concentration-time curves were plotted on linear and on logarithmic scale. Derived PK parameters were listed and summarised. Median concentration-time curves (with minimum-maximum error bars) were also presented for all doses, based on scheduled sampling times. All curves were displayed using a unique concentration axis per dose-level, if appropriate.

Calculation of AUC0-t and AUC0-∞ was conducted using the linear trapezoidal method.

The maximum plasma concentration (C_{max}), the corresponding time (t_{max}) as well as the trough concentrations (C_{min}) were read directly from the plasma concentration-time data.

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SUMMARY OF RESULTS

Pharmacodynamics:

Glucose concentration profiles over time and the results for the area under the effect curve within the night-time phase ($AUE_{0\text{-}10\ h}$) after first and repeated dosing of PSN357AB were not distinguishable from placebo, considering the huge inter-subject variability.

PSN357AB had no concise dose-related influence on night-time glucose concentration, except that lowest concentrations at night-time were observed somewhat earlier after PSN357AB (t_{max} 3.6 and 5.1 hours post-dose) compared with placebo (t_{max} 5.5 and 6.5 hours post-dose) after first and multiple dosing.

Insulin secretion at night-time or after intake of food during the day was not influenced remarkably by PSN357AB

Fructosamine concentrations after multiple dosing and after OGTT did not show a relevant change after PSN357AB compared with baseline values of Day –1.

There was no apparent correlation between the patients' DM status at screening (HbA_{1C} value) and FBG, MBG or glucose concentration after OGTT when PSN357AB was administered.

Safety:

Multiple doses of 1 and 5 mg/kg b.w. of PSN357AB, administered orally over 14 days, were safe and well tolerated in male and one female type-2 DM patient. During the whole study, 8 mild or moderate treatment-emergent AEs were reported by 5 (25%) patients. The 5 AE judged to be possibly related to the IMP comprised headache, exanthema and pruritus. Trombophlebitis, pharyngolaryngeal pain and moderate diarrhoea were judged as being not or unlikely related. Distribution of AEs across treatment groups was comparable. There were no deaths, no SAEs or other significant AEs in this study.

There was no significant trend over time in any laboratory variable that was attributable to the IMP, apart from a slight increase in eosinophils after 5 mg/kg. Additionally, hs-CRP values tended to be higher at the end of the study after placebo compared with 1 and 5 mg/kg b.w. of PSN357AB. The safety laboratory did not indicate any changes in liver or kidney function.

MRI gave indication for a slight increase in liver volume after multiple doses of 5 mg/kg b.w. of PSN357AB compared with placebo and the 1-mg/kg dose, which is a known adaptation of the liver to the pharmacological effects of PSN357AB on the glycogen metabolism.

Vital signs were similar for all treatment groups. No clinically relevant abnormalities were observed in 12-lead ECG parameters during the study.

Monitoring for safety glucose revealed no differences across treatment groups and no individual value was below 3.3 mmol/L. No patient presented signs of hypoglycaemia.

Pharmacokinetics:

After administration of single and multiple doses of 1 and 5 mg/kg b.w. of PSN357AB as an oral solution, PSN357AB occurred in plasma shortly after dosing, indicating a rapid absorption from the intestine. C_{max} values were achieved around 1 hour after dosing.

A 5-fold increase in dose led to a supra-proportional increase of 8- to 9-fold in peak (C_{max}) and to a 10- to 11-fold increase in total (AUC) exposure.

PSN357AB was eliminated with a terminal elimination half-life ($t_{1/2}$) ranging from 12.77 to 14.81 hours (geometric mean) after single and multiple dosing, without showing time invariance.

Mean residence time (MRT) increased from single to multiple dosing independent from dose level by approximately 10%.

PSN357AB accumulated in plasma from Day 1 to Day 13 by approximately factor 2.6 for 1 mg/kg and by approximately factor 1.8 for 5 mg/kg.

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Conclusions:

- PSN357AB had no remarkable effect on night-time or day-time glucose and insulin concentrations when administered as oral solution of 1 and 5 mg/kg b.w. Other parameters such as fasting blood glucose, mean blood glucose and fructosamine were also not affected. Glucose challenging with an oral glucose tolerance test also revealed no consistent effects.
- In the overall conclusion, this proof-of-concept study with PSN357AB failed to show any significant effects on pharmacodynamic surrogate parameters in patients with type-2 diabetes.
- PSN357AB had a good safety and tolerability profile after multiple dosing of 1 and 5 mg/kg b.w. with 8 AEs reported from 5 patients.
- Plasma exposure to PSN357AB increased supra-proportional with dose. PSN357AB showed accumulation after multiple dosing versus single dosing by factor 2.6 and by factor 1.8 for 1 mg/kg and 5 mg/kg, respectively. The terminal elimination half-time ($t_{1/2}$) ranged between 12.77 and 14.81 hours (geometric means) after single and multiple dosing, indicating no time invariance of PSN357AB pharmacokinetics in patients with diabetes.

Date of the Report: 15 October 2007