COVANCE
THE DEVELOPMENT SERVICES COMPANY

File Note

Study No:	665/452	File Note No:	2

Initiated By:	A Lambert	Date:	24 September 2001
Authorised By:	[signature]	Date:	24/9/01
Original:	Tox SD Admin	Date Issued:	25/9/01
Copies:	Quality Assurance Department Initiator, Authoriser (count as one if initiated and authorised by the same person) J GLAISTER, A BASFORD, C SMITH, NECROPSY, S BROGDEN, J IKPEME, MANAGER AH7 RESOURCE MANAGEMENT, RESOURCE ESTIMATION, D GOODWIN (1ST COPY), D GOODWIN (2ND COPY), STATISTICS, J STEWART		
Protocol amendment to be issued (enter either Yes or No):		Yes	

NB Include Action by and Date at the end of relevant paragraphs

DOCUMENTATION

After continued observations of vomiting in the high dose group, accompanied with poor food consumption and weight gain it has been decided by the Sponsor that further dosing at 200 mg/kg/bid will be suspended.

After a two-day wash-out period these animals will re-commence dosing, on 27 September 2001, at the reduced level of 25 mg/kg/bid.

A full Day 1 toxicokinetic bleed will be performed and the animals will continue to the scheduled necropsy after at least 14 days dosing. The final (Day 28) TK bleed will also be performed on these animals.

Study synopsis

SHORT SUMMARY

Covance study number 665/452; Novo Nordisk Reference Number NN 201254.
The study consisted of four groups of three male and three female beagle dogs. The control group was dosed with the placebo vehicle alone. Doses were administered twice daily with a three-hour split. Low dose animals were given NNC 0025-0000-2648 at 50 mg/kg/bid and the intermediate group was dosed at 100 mg/kg/bid. Dosing continued daily for 28 days. Dosing of the high dose group at 200 mg/kg/bid was suspended after dosing on Day 12 due to persistent clinical findings including, salivation, vomiting and loose/liquid faeces and weight losses. Facial swelling was also noted in one female after the second dose at 200 mg/kg/bid on Day 1. After a washout period of about 72 hours, dosing recommenced at 25 mg/kg/bid. This dose level was maintained until the end of the study (14 days), generally with no further observations. Salivation and vomiting were recorded frequently in most animals treated at 100 mg/kg/bid over the first 8/9 days of treatment and generally resolved thereafter. Loose or liquid faeces were also observed in most animals treated at 100 mg/kg/bid sporadically throughout the study. Body weights and food consumption were adversely affected by treatment at doses of 100 and 200 mg/kg/bid in females. Alkaline phosphatase levels were up to 1.9 times higher than pre-treatment values in some treated groups at the end of treatment. There were no macroscopic or microscopic findings due to effects of the test article. This study established the dose of NNC-0025-0000-2648 of 50 mg/kg/bid to be a No Observed Adverse Effect Level (NOAEL) in beagle dogs after repeat daily administration for 28 days.

TITLE OF STUDY

NNC 0025-0000-2648: 28 Day Fixed Dose Oral (Gavage) Administration Toxicity in the Dog.

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STUDY IN COMPLIANCE WITH GLP

☑ yes ☐ No ☐ not required

GUIDELINES FULFILLED NA

STUDY PERIOD

13 September 2001 to final report date

INTRODUCTION

The test article, NNC-0025-0000-2648 has potential in the treatment of Type II diabetes.

PRINCIPLE OF TEST

To determine the toxicity of the test article, NNC 0025-0000-2648 (Abr.:25-2648), following oral (gavage) administration to the dog twice daily for 28 days.

ANIMALS

Twelve male and twelve female purpose-bred beagle dogs, aged four to six months on arrival, were obtained from Harlan UK.
After about three weeks acclimatisation, at the start of treatment, males weighed 6.08 to 9.84 kg and females weighed 6.04 to 8.55 kg.

TEST MATERIAL