Definitive Protocol

Study Title	DU 127090: 16 Day Oral (Gavage Administration) Dose Range Finding Study in the Monkey
Study Director	R P Jones
Sponsor	Solvay Pharmaceuticals B.V. P.O.Box 900 1380 DA Weesp The Netherlands
Study Monitor	Dr H G Keizer
Performing Laboratory subcontractors listed in Appendix 3).	Covance Otley Road, Harrogate North Yorkshire HG3 1PY ENGLAND
Covance Study Number	65/55
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Achieved concentration

Analysis of the formulations for achieved concentration will be performed on the formulation provided for Day 7. The analysis will be performed by Covance. A sample (10ml) from each formulation will be stored frozen (-20°C) for possible future analysis.

TEST SYSTEM

Species, strain and supplier

Sufficient purpose-bred cynomolgus monkeys (*Macaca fascicularis*) will be obtained from Shamrock (GB) in order to provide 4 healthy animals of each sex. This document dated Jan 99

Specification

The animals will be in the weight range 1.5 to 3 kg on arrival.

Environment

The animals will be housed in an exclusive room, air-conditioned to provide a minimum of 10 air changes/hour. Routinely, the temperature and relative humidity ranges will be 18 to 25°C and 40 to 80% respectively. Fluorescent lighting will be controlled automatically to give a cycle of 12 hours light (0700 to 1900) and 12 hours dark.

The animals will be housed singly during the day in cages of 1.1 m high with a floor area of 0.8 m^2. Where possible, animals of the same group and sex will be group housed overnight.

Diet and water

Each animal will be offered 100 g of SQC Mazuri Primate Diet (Special Diets Services Ltd., Witham) a 25g Bonio biscuit (Spillers) and a piece of fresh fruit each day after dosing. Any residual food will be removed and estimated in the afternoon. Each batch of diet is analysed for specific constituents and contaminants and contaminants. Typical values are presented in Appendix 1.

Mains water will be provided *ad libitum* via an automatic watering system or bottles. The water is periodically analysed for specific contaminants. Typical values are presented in Appendix 2.

No contaminants are expected to be present in diet or water at levels, which might interfere with achieving the objective of the study.

ANIMAL HEALTH AND WELFARE

All procedures to be carried out on live animals as part of this study will be subject to the provisions of United Kingdom National Law, in particular the Animals (Scientific Procedures) Act, 1986.

In order to monitor the welfare of an individual or group of animals, additional observations to those already detailed may be instigated at the discretion of the Study Director. In certain instances this may include treatment as advised by a Covance animal welfare veterinary surgeon.

PRE-EXPERIMENTAL PROCEDURES

Acclimatisation and health procedures

All animals will be held at the suppliers' premises for a conditioning period. During this time they will be tested for tuberculosis and any prophylactic treatments received will be documented in the study records.

On arrival, all animals will be given a clinical inspection for ill health and tested for tuberculosis if necessary. They will be acclimatised for a period of at least 4 weeks.

A veterinary inspection will be performed before the start of dosing to ensure their suitability for study.

Allocation to treatment group

Not relevant.

of the test system

vill be individually identified by electronic implant/tattoo as follows:

Group codes	Identification numbers	
	Male	Female
Pink	1-2	3-4

be appropriately identified with study information including study number number/s.

EXPERIMENTAL OBSERVATIONS

signs

als will be observed throughout the working day for signs of ill health or overt In addition, each animal will be given a detailed physical examination at intervals. An individual record will be maintained of the clinical condition of imal. Post-dosing observations may be performed at the discretion of the Study or.

bidity and mortality

nimals will be examined at the beginning and the end of the working day. Any al which shows marked signs of ill health will be isolated and may be killed and opsied after consultation with the Study Sponsor.

dy weights

lividual body weights will be recorded on days 1, 4, 8, 12 and before necropsy

ood consumption

he amount of food consumed will be calculated as g/animal/week.

Toxicokinetics

Blood samples (1.5 ml) will be taken from all animals on Days 1, 7 and 10. Samples will be taken into lithium heparin pre-dose and at 1, 5, 7, 8, 12 and 24 hours post dose.

The plasma will be retained and stored deep frozen (-20°C) prior to despatch to the Sponsors subcontractor, Cephac Bioanalytical Research Center, France (Appendix 7).

TERMINAL PROCEDURES

Necropsy and tissue preservation (Appendix 3)
All animals including decedents will be subject to necropsy.

After an overnight period without food and following sedation with ketamine, an intravenous sodium pentobarbitone overdose will be given prior to exsanguination. A full macroscopic examination will be performed under the general supervision of a pathologist and all lesions will be recorded.

All tissues denoted by (•) from all animals will be preserved in the appropriate fixative/s.

Histopathology (Appendix 3)
No histopathological assessment of tissues will be undertaken in the first instance.

DATA EVALUATION

Data from treated animals will be compared with historical control data.