Final Report

Study Title	(^{14}C)-Lu 02-648 (CEP-1347): A study of biliary excretion following oral administration to the rat
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Covance Study Number	356/141
Covance Report Number	356/141-D1140
Sponsor Reference	Lundbeck GLP No. 99576 Lundbeck Activity No. 150-3827
Report Issued	February 2002
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On arrival they were examined for external signs of ill health, and were then inspected by a qualified veterinarian prior to allocation to the study.

All animals were acclimatised at Covance for three days prior to bile duct-cannulation surgery, and were weighed shortly after arrival at Covance, and immediately before surgery.

Environment

From arrival of the rats at Covance (27 February 2001) until the date of the final excretion collection (08 March 2001), they were kept in rooms thermostatically maintained at a temperature of 19 to 22°C, with a relative humidity of between 47 and 52%, and exposed to fluorescent light 12 h (0600 to 1800)/12 h dark.

All animal holding facilities were designed to give a minimum of 15 air changes/h. Temperature and relative humidity were recorded on a daily basis.

The rats were initially housed in wire-floor polypropylene cages suspended over trays containing soft white sawdust bedding, which was changed at least every three days. From the time of their bile duct-cannulation surgery until the final excretion collection, the animals were held in all-glass metabolism cages ("Metabowls") suitable for the separate collection of bile, urine and faeces.

Diet and drinking water

The rats were allowed free access to a commercial pellet diet (SQC Rat and Mouse Maintenance Diet No 1, Special Diet Services, Witham, Essex). A diet analysis sheet is maintained on file at Covance for each batch of diet used.

All animals were allowed free access to mains water *via* an automatic watering system (communal housing) or bottles (attached to the metabolism cages). Periodic analysis of the drinking water for heavy metals and chlorinated hydrocarbons was undertaken by ALcontrol UK for Yorkshire Environmental. The results of these analyses are maintained in a central file at Covance.

From the day prior to surgery, until the end of the in-life period, the rats were acclimatised to drink a glucose-enriched salt solution, containing glucose (2.5% w/v), potassium chloride (0.25% w/v) and sodium chloride (0.9% w/v).

Identification of the test systems

Each animal was individually identified on arrival at Covance by tail marking. A label was attached to each holding cage, with details including study number,

animal numbers and sex. A similar label was also attached to each Metabowl. An additional label was used for each room, with details including study number and Project Licence number.

Experimental procedures

Morbidity and mortality

All animals were observed at least once per day. Additional observations were made throughout the working day as necessary.

Bile duct-cannulation

Six animals were operated on 4 days prior to dose administration. Before surgery, an antibiotic (Penbritin) was administered by intramuscular injection (*ca.* 0.1 mL).

Rats were anaesthetised using Isoflurane. A central area of the abdomen and an area from the nape of the neck towards the tail were shaved and cleaned with disinfectant. Cannulation was performed through a mid line incision, through which the bile duct was dorsally exteriorised. The biliary cannula was inserted into a small cut towards the liver and ligatures used to secure the catheter. The distal end of the cannula was passed through a hole cut in the muscle wall at the side of the animal and pushed, using a trocar, under the skin to emerge from an incision made at the nape of the neck. The body wall and skin incision were closed using either sutures or clips. Sutures were used to attach a stainless steel swivel device designed to allow freedom of movement of the animal whilst retaining the patency of the bile cannula.

Post surgery, a mild analgesic (Rimadyl, subcutaneous) was administered (*ca.* 0.1 mL). The animals were then placed in individual Metabowls suitable for the collection of bile, urine and faeces and allowed to recover for approximately 4 days.

Following this acclimatisation period, three animals were deemed to be visually healthy, and therefore were dosed. The three remaining animals were terminated and discarded.

Dose administrations

Each animal received a single oral gavage administration at a nominal dose volume of 3 mL/kg body weight. A nominal dose of 30 mg/kg body weight, equivalent to a nominal radioactive dose of 4.6 MBq/kg, was administered.