The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

SYNOPSIS

Name of Sponsor/Company: Takeda Europe Research & Development Centre Ltd.	Individual Study Table Referring to Part IV of the Dossier.	*(For National Authority Use Only)*
Name of finished product: Not applicable	Volume:	
Name of active ingredient: TAK-375	Page:	

Title of study:	(^{14}C)-TAK-375 - A Phase I, Open-label Study of the Absorption, Metabolism and Excretion following a Single Oral Dose to Healthy Male Subjects
Study site:	Covance Clinical Research Unit Ltd., Leeds, UK.
Reference:	None

Period of study: 7 March 2002 to 3 April 2002	**Phase of development:** Clinical Phase I

Primary Objectives:

- To evaluate the pharmacokinetics of total radioactivity, TAK-375 and metabolites M-I to M-IV following a single oral administration of (^{14}C)-TAK-375 to healthy male subjects
- To obtain a mass-balance by quantifying the urinary and faecal excretion of radioactivity
- To characterise the relative proportions of (^{14}C)-TAK-375 and its radiolabelled metabolites in serum, urine and faeces

Secondary Objective:

- To further determine the safety and tolerability of a single oral dose of TAK-375 in healthy male subjects

Methodology:

Study design: Single oral dose study
Type of blinding: Open-label
Type of control: None

Number of subjects (planned and analysed):

Six subjects, studied as a single group, entered and completed the study as planned. Data for all subjects were included in the safety and pharmacokinetic analyses.

Diagnosis and main criteria for inclusion:

Healthy male Caucasian subjects aged between 30 and 50 years.

Test product, dose levels and batch numbers:

TAK-375 at a nominal dose level of 16 mg, containing 3.16 MBq (87.2 µCi) (^{14}C)-TAK-375. The dose was administered orally as a 140 mL aqueous solution containing non-radiolabelled TAK-375 (lot M375-023) and (^{14}C)-TAK-375 (lot CFQ13068).

Duration and mode of administration of treatment:

Subjects participated in a single treatment period and received a single oral dose of (^{14}C)-TAK-375, in the fasted state, in the morning of Day 1.

Criteria for evaluation:

Pharmacokinetics:

Blood samples for the analysis of TAK-375 and metabolites M-I to M-IV in serum; total radioactivity in serum and whole blood; and metabolic profiling of serum. Urine samples for the analysis of TAK-375 and metabolites M-I to M-IV; total radioactivity; and metabolic profiling. Faecal samples for the analysis of total radioactivity and metabolic profiling.

Safety and tolerability:

Adverse events, vital signs, 12-lead ECG, clinical laboratory evaluations and physical examination.

Statistical methodology:

Descriptive statistics for demographic, adverse event, vital signs, clinical laboratory and pharmacokinetic data.

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Summary:

Subject disposition:

Six subjects entered and completed the study as planned.

Pharmacokinetic results:

The pharmacokinetic parameters of TAK-375, metabolites M-I, M-II, M-III and M-IV and total radioactivity in serum are presented in the following table:

Parameter	TAK-375 (N=6)	M-I (N=6)	M-II (N=6)	M-III (N=6)	M-IV (N=6)	Total Radioactivity (N=6)
AUC(0-t_z) (ng.h/mL)+	14.0 (208)	8.91 (76.8)	374 (40.7)	2.37 (391)	67.0 (22.7)	2565 (31.9)
AUC(0-∞) (ng.h/mL)+	14.2 (203)	9.63 (74.6)	377 (40.8)	11.9 (16.8)#	71.5 (22.4)	3618 (13.5)*
C_{max} (ng/mL)+	13.7 (219)	8.88 (41.6)	125 (30.8)	2.08 (163)	12.1 (16.5)	552 (23.6)
t_{max}† (h)	0.333 (0.217-0.333)	0.667 (0.333-0.667)	0.667 (0.333-0.667)	0.667 (0.333-0.667)	0.667 (0.333-1.50)	0.500 (0.333-0.667)
$t_{½}$~ (h)	1.24 (0.616)	0.730 (0.271)	2.26 (0.790)	1.26 (0.0706)#	3.49 (0.438)	112 (8.17)*

Geometric mean (CV%) data are presented N = Number of subjects studied + ng equiv for total radioactivity
† Median (min-max) ~ Arithmetic mean (SD) NC=Not calculated # N = 3 * N = 4

Concentrations of total radioactivity in serum and whole blood

The concentrations of total radioactivity in whole blood were lower than those observed in serum for all time points, the arithmetic mean ratio for the concentrations of total radioactivity in whole blood to serum remaining relatively constant up to 24 hours post-dose and ranging from 0.57 to 0.73.

Elimination of TAK-375 and metabolites M-I to M-IV

Renal elimination of TAK-375 was negligible, amounting to less than 0.001% of the dose administered. The fraction of the dose excreted in the urine as metabolites M-I to M-IV was also low (4.6% in total), with M-IV accounting for the majority of this overall recovery.

Urinary and faecal excretion of total radioactivity

The principal route of excretion of total radioactivity was in the urine, the mean recovery being 84%. The renal elimination of total radioactivity was rapid, being essentially complete by 96 hours post-dose. Faecal elimination of total radioactivity was minimal (4% of the dose).

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Metabolic Profiling of Radiolabelled Material in Serum, Urine and Faeces

Metabolic profiling revealed that the main circulating metabolites in serum at 20 minutes post-dose were M-II and S2, a glucuronide conjugate of mono-hydroxylated parent compound, which accounted for 30 and 21% of serum radioactivity, respectively. By four hours post-dose, MII and a glucuronide conjugate of dihydroxylated TAK-375 (S1) were the major metabolites, again accounting for approximately 57% of serum radioactivity in total. Other circulating metabolites, which were present at similar levels to the parent compound, were a second glucuronide conjugate of mono-hydroxylated parent (S3), parent oxidised in one position (S6) and de-hydrogenated TAK-375 (S8). Metabolic profiling of urine, revealed oxidised parent compound (U8) to be the major radiolabelled component, accounting for up to 30% of the administered dose. Glucuronidated di-hydroxylated TAK-375 (U5) and a glucuronide conjugate of mono-hydroxylated parent (U10) were also renally eliminated, accounting for up to 33% of the administered dose. Although up to 21 radiolabelled components were detected in faeces, quantification and identification proved difficult due to the low levels of radioactivity. No metabolite accounted for >1% of the administered dose and no major metabolites were apparent.

Safety and tolerability results:

(^{14}C)-TAK-375 was safe and well tolerated following single oral dose administration at the 16 mg dose level. All drug-related adverse events reported were mild in intensity, with the exception of a headache which was moderate in intensity. Seven of the 11 drug-related adverse events were reported by a single individual and three of the six subjects studied did not report any drug-related adverse events during the study. There were no serious events, deaths or other significant events during the study. No clinically relevant changes were seen in any of the safety parameters.

Conclusions:

- Following a single oral dose of 16 mg (^{14}C)-TAK-375, the pharmacokinetics of TAK-375 were as previously observed.
- As observed in a previous multiple oral dose study, the rank order of metabolites by prevalence in serum was M-II>M-IV>M-I>M-III, the overall systemic exposure for M-II, being 7 to 80-fold higher than for the parent drug. The metabolites were rapidly formed and, as for TAK-375, exhibited a monophasic disposition and a rapid elimination.
- A comparison of blood and serum radioactivity concentrations indicated little or no association of TAK-375 and related metabolites with blood cells.
- Systemic exposure of total radioactivity was 7-fold greater than the overall exposure of TAK-375 and metabolites M-I to M-IV combined. The remaining radioactivity in serum, which was not associated with the foregoing components, was slowly eliminated from the systemic circulation, resulting in a prolonged terminal elimination half-life of total radioactivity of 112 hours.
- Of the total radioactivity administered, a mean of 84% was renally eliminated with a further 4% voided in the faeces, resulting in a mean mass balance of 88%. Metabolites of TAK-375 accounted for the majority of the administered dose eliminated.
- Metabolic profiling of serum, urine and faeces has confirmed that TAK-375 undergoes extensive metabolism primarily consisting of oxidation to hydroxyl and carbonyl groups, with secondary metabolism to produce glucuronide conjugates.
- A single oral dose of 16 mg (^{14}C)-TAK-375 was safe and well tolerated in a group of healthy Caucasian male subjects.

Report version date: 3 February 2003