Synopsis of study report: 173/2001K1
Location in Module 5:

Study Code:
BY217/FHP034

Report Date:
15-Aug-2001

Title of the study:
A study to investigate the absorption, metabolism, excretion and pharmacokinetics of [^{14}C]-B9302-107 after oral and intravenous administration to six healthy male volunteers

Study center(s):
Pharma Bio-Research Group BV (PBR), Stationsweg 163, 9471 GP Zuidlaren, The Netherlands

Publication (reference):
Not applicable

Studied period (years):
03/2000 – 05/2000

Clinical phase:
I

Objectives:
To investigate the absorption, metabolism, excretion and pharmacokinetics of [^{14}C]-labeled B9302-107 after single intravenous and oral administration to six healthy volunteers

Methodology:
Single-centre, single-dose, open-label, two-way crossover study in six healthy volunteers with a washout period of at least 14 days between drug administrations

Eligibility screening and follow-up consisting of medical history, age, height and weight, physical examination, ECG recording, blood pressure and pulse rate, clinical laboratory and body temperature
Observation period from Day –1 to Day 8, if necessary stay in clinic prolonged up to maximally Day 12
Blood sampling for pharmacokinetic parameters were taken at t = 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 144 and 168 hours post dose. Blood or plasma was used for analysis of B9302-107, B9502-044 and radioactivity
Urine sampling: pre-dose, 0–4, 4–8, 8–12, 12–24h after drug administration, thereafter in 24h intervals until 504 hours
Faeces sampling: pre-dose, thereafter in 24h intervals until 504h after dosing
Safety assessments: adverse events, vital signs, ECG-recordings and clinical laboratory parameters
Analysis of total [^{14}C]-radioactivity in plasma, whole blood, urine, faeces and medication was performed by PBR.
Analysis of B9302-107 and its metabolite B9502-044 was performed by the Department of Drug Metabolism and Pharmacokinetics (RMP) at Byk Gulden.

No. of subjects (total and for each treatment):

Six (6)

Diagnosis and criteria for inclusion:

Healthy male volunteers
Age: 18–45 yrs (mean 35±5.9 yrs, range: 27–42 yrs)
Weight: 50–100 kg (mean 69.7±8.9 kg, range: 56–82 kg)

Test product:

Roflumilast

Dose:

500 µg oral, methocel suspension containing 1.62 MBq radioactivity
300 µg intravenous, lipid emulsion, containing 0.97 MBq radioactivity
(The intravenous medication was found to contain approximately 150 µg B9302-107 instead of 300 µg, and approximately 0.46 MBq [^{14}C]-radioactivity instead of 0.97 MBq. Moreover, the oral radioactivity target dose may not have been reached.)

Mode of administration:

Oral, intravenous

Batch No.:

FH/3/73

Duration of treatment:

Single dose

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

Pharmacokinetic parameters: $AUC_{(0-\infty)}$ C_{max}, t_{max}, $T_{1/2}$, A^e urine, A^e faeces and A^e total (A^e for total radioactivity)
Safety parameters: vital sign, ECG-recordings, clinical laboratory parameters, physical examination and adverse events

Statistical methods:

Descriptive analysis

SUMMARY - CONCLUSIONS

Summary:

Dose-normalised pharmacokinetic parameters of [^{14}C]-radioactivity, B9302-107 and B9502-044 in plasma and balance excretion of radioactivity (geometric mean, 68%-range)

Parameter	[^{14}C]-radioactivity		B9302-107		B9502-044	
(unit)	po	iv	po	iv	po	iv
C_{max}	9.56	6.58	3.62	4.67	5.5	2.03
(ng eq or ng/ml)	(7.23, 12.64)	(5.74, 7.55)	(2.53, 5.18)	(4.17, 5.24)	(4.10, 7.32)	(1.63, 2.53)
$AUC_{(0-\infty)}$	495.84	192.62	30.53	15.54	256.75	87.42
(ng eq or ngxh/l)	(377.4, 651.5)	(148.0, 250.7)	(22.2, 42.0)	(12.0, 20.2)	(191, 343.5)	(62.8, 121.7)
t_{max}*	3.0	0.50	1.5	0.50	5.0	4.5
(h)	(1.0, 3.0)	(0.5, 0.5)	(1.0, 3.0)	(0.5, 0.5)	(3.0, 24.0)	(3.0, 14.0)
$t_{1/2}$	46.18	53.61	20.79	17.69	25.03	23.87
(h)	(43.55, 48.96)	(46.16, 62.27)	(15.90, 27.17)	(12.61, 24.80)	(17.72, 35.37)	(15.46, 36.86)
A^e urine**	54.62	64.62	–	–	–	–
(%)	(50.2, 59.1)	(56.5, 69.9)				
A^e urine**	30.42	19.45	–	–	–	–
(%)	(22.4, 36.6)	(15.8, 22.0)				
A^e total**	85.03	84.03	–	–	–	–
(%)	(79.3, 89.3)	(76.4, 90.1)				
$F_{absorption}$ [+]	0.77	reference	–	–	–	–
(%)	(0.70, 0.85)					
$F_{bioavailability}$ [+]	–	–	0.59	reference	–	–
(%)			(0.52, 0.67)			

*: Median (range) **: Mean (min, max) [+]: Point estimate (90% CI)

Conclusions:

- Around 80% of the radiolabeled material was absorbed following oral administration of 500 µg [^{14}C]-B9302-107.

- The absolute bioavailability was around 59% after oral administration of B9302-107 for parent compound referenced to the intravenous standard.
- The total recovery of [^{14}C]-radioactivity (urine plus faeces), around 85%, was similar for oral and intravenous administration. This figure for recovery may be too low as the administered dose may have deviated from the target dose.
- The sum of parent compound and the metabolite B9502-044 accounted for 54% of the total [^{14}C]-radioactivity AUC after intravenous administration and 58% after oral administration, indicating the formation of other metabolites than B9502-044.
- Vital signs, ECG, physical examination and clinical laboratory measurements revealed no clinically relevant abnormalities.
- Oral (500 µg) and intravenous (150 µg) administration of Roflumilast was safe and well tolerated.