Synopsis of study report: 223/2001
Location in Module 5:

Study Code:
BY217/FHP036

Report Version:
Final

Title of the study:

A study to investigate the distribution, metabolism, excretion (mass balance) and pharmacokinetics of [^{14}C]-B9302-107 after oral and intravenous administration to six healthy volunteers

Study center(s):

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

Publication (reference):

Not applicable

Studied period (years):

03/2001 – 06/2001

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 21 days between drug administrations.

Eligibility screening and follow-up consisting of clinical laboratory, full physical examination, ECG recording, drug screen, HBs Ag, anti-HCV and anti- HIV ½.

Observation period from –17h to 176h; stay in the clinical could be prolonged depending on excretion of radioactivity in urine and faeces.

Blood sampling for pharmacokinetic parameters at t = 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 30, 36, 48, 72, 96, 120, 144, 168, 192, 216 hours post-dose. Plasma was used for analysis of B9302-107, B9502-044 and radioactivity. Whole-blood was used for analysis of total radioactivity at t = 0, 0.5, 1, 1.5, 3, 6, 10, 24, 48, 72, 96, 120, 144, 168, 192 and 216 hours post-dose. Plasma for genotyping (CYP2D6, CYP2C19, NAT-2) prior to the first dose.

Urine sampling: pre-dose, and 0-4, 4-8, 8-12, and 12- 24 hours after drug administration and in 24 hours intervals until 216 hours post-dose.

Faeces sampling: pre-dose, thereafter in 24 hour intervals until 216 h post-dose.

Safety assessments: adverse events, vital signs; ECQ recordings telemetric monitoring.

Analysis of total 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 (RPD/MP) at ALTANA Pharma (former Byk Gulden).

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

6

Diagnosis and criteria for inclusion:

Healthy male volunteers
Age: 18 – 45 years
Weight: 50 – 100 kg; normal weight according to Broca index

Test product:

Roflumilast

Dose:

0.5 mg oral solution in PEG containing 1.89 MBg radioactivity
0.3 mg intravenous solution containing 1.113 MBg radioactivity

Mode of administration:

Oral, intravenous (short term infusion)

Batch No.:

FH/3/181

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-∞), 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, adverse events

Statistical methods:

Descriptive analysis

SUMMARY - CONCLUSIONS

Summary:

Pharmacokinetic characteristics of [^{14}C]-radioactivity, B9302-107 and B9502-044 in plasma and balance excretion of radioactivity (geometric mean, 68 %-range) following a single oral dose of 0.5 mg and intravenous dose of 0.3 mg [^{14}C]-B9302-107 to healthy subjects (N=6).

PK Charac-teristics (unit)	[^{14}C]-radioactivity		B9302-107		B9502-044	
	po	iv	po	iv	po	iv
C_{max}	18.153	12.320	8.834	8.860	8.496	5.089
(µgeg, or µg/l)	(14.203,23.202)	(10.540,14.401)	(6.424,12.149)	(7.031,11.164)	(7.129,10.125)	(4.181,6.196)
AUC/0-∞	592.83	425.21	28.19	26.43	314.95	215.49
(µgeg, or µg x h/l)	(458.17,767.07)	(322.76,560.17)	(18.14,43.79)	(21.11,33.09)	(222.91,445.01)	(156.14,297.40)
t_{max}(h)*	0.50 (0.50,1.00)	0.50 (0.50,1.00)	0.50 (0.50,0.50)	0.50 (0.50,0.50)	4.00 (3.00,4.00)	4.00 (4.00,10.00)
$t_{1/2}$(h)	46.79 (30.36,72.11)	44.81 (31.11,64.54)	13.41 (8.30,21.66)	10.96 (6.84,17.56)	17.77 (14.72,21.44)	17.55 (15.19,20.29)
A^e urine+ (% of dose)	70.1 (62.9,74.0)	70.7 (62.9,77.8)	-	-	-	-
A^e faeces+ (% of dose)	20.2 (10.8,26.1)	20.6 (15.7,25.1)	-	-	-	-
A^e total+ (% of dose)	90.3 (82.9,94.5)	91.2 (86.2,94.8)	-	-	-	-
$F_{absorption}$++	0.84 (0.76,0.92)	reference	-	-	-	-
$F_{bioavailability}$++	-	-	0.64 (0.52,0.79)	reference	-	-

* Median (min, max)

\+ mean (min, max)

++ point estimate (90 % CI)

Conclusions:

Absorption following oral administration of 0.5 mg [^{14}C]-B9302-107 was about 84 % based on dose normalized plasma AUC values and 99 % based on urinary excretion of total radioactivity.

The absolute bioavailability based on dose normalized plasma AUC values for unchanged B9302-107 was 64 %. Total recovery of radioactivity amounted to 90 % of the dose, 70 % being excreted in urine and about 20 % in faeces after both routes of administration. Based on plasma AUC, the sum of parent compound and metabolite B9502-044 accounted for 57 % and 58 % of total radioactivity AUC after iv and po administration, respectively, thus indicating the formation of other metabolites than B9502-044.

Oral and intravenous administration of [^{14}C]-B9302-107 was safe and well tolerated.