Synopsis of study report: 50E/99
Location in Module 5:

Study Code:
BY217/FHP011

Report Date:
28-Jun-1999

Title of the study:

A PET study to investigate the pharmacokinetics and distribution of [^{18}F]B9302-107 into the lung, nose, stomach and brain after single oral administration of 0.5 mg to healthy volunteers

Study center(s):

Quintiles AB and Uppsala University PET Centre, Uppsala, Sweden

Publication (reference):

Not available

Studied period (years):

20 November 1998 – 18 December 1998

Clinical phase:

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Objectives:

- To investigate the *in vivo* distribution in the lung, nose, stomach and brain of [^{18}F]B9302-107 by positron emission tomography (PET) analysis and to investigate the pharmacokinetics of B9302-107 and its metabolites B9202-045 and B9502-044 after oral administration.

Methodology:

Single dose, open-label study design.

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

6

Diagnosis and criteria for inclusion:

- assessed as healthy, based on a pre-study examination including medical history, physical examination, ECG and clinical laboratory
- age between 18 - 45 years
- BMI (Body Mass Index) between 19 - 27 with a minimum weight of 60 kg
- written informed consent

Duration of treatment:

One single dose on study day

Test product:

[^{18}F]B9302-107

Dose:

0.5 mg

Mode of administration:

suspension for oral administration

Batch No.:

396549

Reference product:

Not applicable

Dose:

Not applicable

Mode of administration:

Not applicable

Batch No.:

Not applicable

Criteria for evaluation:

PET variables:

Descriptive evaluation of radioactivity in nose and stomach/intestines together with quantitative evaluation of B9302-107 concentration in nasal mucosa, brain, lung, and heart.

Pharmacokinetic variables:
Plasma concentrations of parent compound roflumilast (B9302-107) and metabolites (B9502-044 and B9202-045).
AUC, C_{max}, $t_{½}$, t_{max} of parent compound, and C_{max} and t_{max} only of metabolites.

Safety:
ECG, blood pressure, heart rate, AE, safety measurements at pre and final check

Statistical methods:
Parameters were presented descriptively.

SUMMARY – CONCLUSIONS

Summary:

The following table presents an overview of the pharmacokinetic characteristics for **parent compound B9302-107, metabolite B9502-044 and metabolite B9202-045**:

Characteristics	Parent compound B9302-107	Metabolite B9502-044	Metabolite B9202-045
$AUC_{(0-\infty)}$ [µg*h/l]	39.94 (29.38 - 54.30) [1)]	not ascertained	**Concentrations in** all plasma samples below the LLOQ (0.04 µg/l)
C_{max} [µg/l]	5.361 (3.896 - 7.375)	10.626 (6.854 - 16.475)	
$t_{½}$ [h]	12.56 (9.20 - 17.13)	not ascertained	
t_{max} [h]	0.92 ± 0.08	5.83 ± 1.42	

Geometric means (68%-range); t_{max}: mean±SEM; N=6; [1)] N=5

The following table presents drug equivalent concentrations in plasma for **parent compound B9302-107 and metabolite B9502-044** in the six subjects in this study. The data is provided as geometric means:

Mean time of PET scan (minutes)	Mean plasma concentration (drug equivalent concentration in µg/l) (68%-range)
31	33.71 (25.39 - 44.77)
60	23.76 (17.99 - 31.39)
113	15.28 (11.46 - 20.36)
180	12.01 (8.97 - 16.07)
240	10.77 (9.21 - 12.59)
302	9.99 (8.29 - 12.04)
360	9.71 (7.62 - 12.37)
460	9.64 (7.75 - 12.00)

PET results:
There was a rapid uptake of tracer from the intestines with significant extravascular localization in lung tissue, musculature (arms) and brain, although at different magnitudes with highest in lung tissue. No selective accumulation was found in the nasal mucosa.

Safety results:
The study medication was well tolerated. 3 subjects reported a total of 3 AEs, all headaches, none of which were judged to be related to the study drug. No serious AEs occurred during the study.

Conclusions:

From the PET studies it was shown that there was a rapid uptake of the study drug from the intestines. The study drug also localized in the extravascular space in lung, musculature and brain. No accumulation was found in the nasal mucosa.

Following single oral administration of 0.5 mg [^{18}F]B9302-107 as a suspension formulation to man, values of pharmacokinetic characteristics are comparable to the tablet formulation. The main conclusion of the work is that no specific accumulation could be observed in the nasal mucosa. The tissue-to-blood ratio is close to 1.0 (tissue-to-plasma ratio of 0.6), with no signs of increase from 2 hours after administration of drug.

There is a definite fraction of the drug that can be observed in brain, muscle and lung, and which is not related to the intravascular compartment. In the brain, the non-vascular concentration is about 8% of that of plasma, in muscle 15% and in lung 45%. The values for lung are here corrected for the density of the lung, with the assumption that the drug is not distributed in the air in the alveolus.