CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-169

Pharmacology Review(s)

Barry N. Rosloff, Ph.D.
9/25/00

Pharmacologist Review of NDA 21-169
Submission of 8/31/00

Sponsor: Janssen Research Foundation
1125 Trenton-Harbourtown Road
Titusville, NJ 08560-0200

Drug: galantamine (Reminyl^{R})

Category: Alzheimer's Disease

Previous Pharmacologist Review: Original Summary of 5/1/00

Contents of Submission: Responses to approvable Action Letter of 7/29/00.

Summary and Evaluation:

1. Histological exam of cervix in rat carcinogenicity study

Cervix was only examined histologically in rats with gross lesions. In view of an equivocal increase in cervical sarcomas, as well as a borderline increase in uterine adenocarcinomas, we requested that the sponsor perform histological exams of cervix in all animals, and that this could be done during phase IV. The sponsor commits to doing this.

2. Additional information for the Mouse Lymphoma Assay and CHO Chromosome Aberration Assay

The originally submitted report of the Mouse Lymphoma Assay was incomplete and confusing. The additional information submitted on 6/8/00 and in the present submission is adequate. (Galantamine was negative in this assay).

The originally submitted CHO study showed some sporadic/equivocal increases in aberrations which were not clearly drug related for reasons discussed in my original review. However one of these reasons was that the values were said to be within historical control limits, yet no historical data were submitted. Such data are included in the present submission; curiously, most of the mean values for % cells with aberrations, in both the drug groups and concurrent controls, were ***above*** the historical controls. This was not discussed by the sponsor. At any rate, considering the totality of the evidence, it can be concluded that galantamine was not positive in this assay.

It is concluded that the above assays may be included in the labeling.

3. Mention of an additional mechanism of action in the "Description" and "Mechanism of Action" sections of labeling.

In addition to inhibition of acetylcholinesterase (AChE), the sponsor wants to state that galantamine acts as a modulator of the nicotinic receptor. The data originally submitted in support of the latter action are discussed in my original review of 5/1/00 (page 44), as are reasons for not including it in the labeling (page 59). Such reasons included the fact that that the action was only demonstrated in vitro (and in single ion channels but not in whole cell responses), the drug concentrations at which it occurred were not clear (also complicated by the fact that a biphasic effect is seen, with desensitization or antagonism at higher concentrations), the fact that it is not clear that other drugs marketed for Alzheimer's Disease do not share this action, and the fact that galantamine has no clear efficacy or safety differences from other drugs marketed for Alzheimer's Disease which might be explained by this additional action. At least some of these points were discussed in a previous telecon with the sponsor.

The present submission contains further arguments for inclusion of this additional mechanism of action in the labeling. References not included in the original submission are cited; however these newer references are not included in the present submission; also some of these references are noted as being "in press" or "paper now in final stages of preparation" or "data on file". This may be a moot point, however, since it is the opinion of this reviewer that even if the findings discussed were verified by independent review of the data, they would not form a sufficient basis for inclusion of this additional action in the labeling. The sponsor's primary arguments are as follows:

a) It is stated that galantamine is "a prototype of a novel class of nicotinic enhancers," that members of this class are called "APL's", or "allosterically potentiating ligands," and that galantamine is the most potent member. The point seems to be that this is a well-recognized action of galantamine. (It was noted that the phenomenon of nicotinic receptor sensitization by APLs "has now been confirmed by several laboratories"; as indicated in my original review, most or all of the supporting data submitted had appeared to come from a single lab and/or from the same authors).

   The degree to which galantamine's action as an "APL" is well-recognized aside (it does not appear to have reached the level of reification in textbooks, although there are certainly drugs which are though to act by allosterically modifying receptor function, e.g. benzodiazepines/GABA receptors), it is instructive to note that the identification of a drug with a specific mechanism of action is not necessarily a clear-cut matter. Certainly, postulated mechanisms of action change over time with changes in prevailing scientific theory. The designation of a specific mechanism of action of a drug can also depend on what was and was not studied; for example, one might wonder if, had galantamine been studied as an APL from the outset, and had not been tested for AChE inhibition, would there be any objection to citing APL as the mechanism of action in the labeling?

It is thus somewhat arbitrary, and probably technically incorrect, to label the mechanism of action of galantamine and marketed AD drugs as (or only as) inhibition of AChE. These drugs are structurally diverse, each has a variety of pharmacological actions, and all are used for a disease whose cause and pathophysiology are far from being well-understood. However, correct or otherwise, all have been primarily studied as AChE inhibitors for the treatment of AD. (This certainly includes galantamine; until relatively recently the pharmacological workup has centered around this action). In view of the fact that there are no known clinical efficacy or safety differences between these drugs which might be explainable by additional actions, it seems that listing a variety of pharmacological actions for each (which could differ because of what was studied as well as because of true differences among the drugs) is potentially misleading and that the lesser of two evils would be to note only AChE inhibition as the postulated mechanism of action.

(As an aside, the question of including all *potentially* clinically relevant actions in drug labeling in general might be considered. This information might be useful to a clinician in choosing a specific drug based on the characteristics of a given patient, the potential for specific drug interactions, recent advances in knowledge about the disease, etc. On the other hand, there is the potential to mislead; in the past sponsors have used such information to imply differences from, if not advantages over, other drugs. The interested clinician could obtain additional information from the literature).

b) It is stated that the APL effect is seen at "submicromolar" concentrations ...."i.e. around and below the concentration range at which...AChE inhibition occurs." No specifics are mentioned except for "data on file" showing an effect at 0.1 uM. Among the references cited are some which were previously submitted in which 1 uM was the lowest concentration of galantamine tested.

c) It is stated that the APL effect has been demonstrated in *human* nicotinic receptors (in vitro).

d) It is stated that Exelon and metrifonate (which are considered to be effective in AD) do not act as APLs. (Physostigmine, also effective in AD, is an APL). It is also stated that "Of the cholinesterase inhibitors currently under development as AD drug therapeuticals, galantamine is the most potent, if not the only nicotinic APL."

e) It is stated that galantamine at 1-10 uM increased glutamate and GABA release in rat and human brain slices via the APL mechanism; presumably supporting the idea that this action can have functional consequences.

f) The sponsor downplays the role of AChE inhibition as a mechanism of clinical efficacy of galantamine. (In fact, it is seemingly implied that the

degree of inhibition produced by galantamine is inadequate to account for its efficacy, which is curious in view of the fact that the sponsor still wishes to include AChE inhibition as one of the mechanisms of action). The degree of inhibition in human brain is calculated to be low compared to that produced by other cholinesterase inhibitors used in AD, although this calculation is very indirect and based primarily on animal data. It is also stated that clinical observations have indicated that galantamine produces nicotinic effects not explainable by cholinesterase inhibition alone. (However, note that although galantamine was not directly compared with other drugs, there has been no indication in clinical trials conducted under the IND that galantamine has a significantly different clinical profile from that of marketed AD drugs).

4. **Inclusion of proposed mechanism of production of uterine adenocarcinomas in labeling**

The sponsor's proposed mechanism is that galantamine caused a decrease in prolactin levels leading to a switch from the normally occurring state of age-related progesterone dominance to one of estrogen dominance, resulting in prolonged endometrial stimulation and consequent endometrial tumorigenesis. Since prolactin is not luteotrophic in humans, it was concluded that any effects of galantamine on prolactin in humans will not result in effects on the female genital tract similar to those seen in rats. (This proposed mechanism, and evidence for and against it, is discussed in more detail in my review of 5/1/00, p. 57-58).

The relevance to humans notwithstanding, it does not seem that the proposed mechanism has been well established for galantamine. Consistent with this hypothesis were decreases in plasma prolactin, decreases in mammary gland activity and neoplasia, and increased ovarian cycling. However, the link between reduced prolactin and the hypothesized state of estrogen dominance is not clear. Estrogen levels were not measured. Aside from uterine tumors and the finding of increased granulocytic infiltration, there were no histological effects in uterus which might be indicative of increased stimulation (e.g. no drug effects on hyperplasia, metaplasia, or height of epithelium). Also, whereas the decrease in plasma prolactin (and the occurrence of most of the above-mentioned associated histological changes) were seen only at HD, uterine tumors were increased at both MD and HD; furthermore, even at HD, there was no correlation between prolactin level and the presence of uterine tumors in individual animals. For these reasons, it is recommended that the proposed mechanism not be included in the labeling.

5. **Exclusion of mention of increase in cervical sarcomas in labeling**

Three (5 %) cervical sarcomas were seen at HD; none in other groups. (Cervix was only examined in rats with gross lesions). We recommended this be put in labeling in view of the fact that the increase was statistically significant, the incidence was above the historical control range (four groups with 0 %, one with 4 %), and the drug also caused an increase in uterine adenocarcinomas. The sponsor's reasons for not including the cervical sarcomas in the labeling are (1) the incidence of sarcomas in uterus and vagina

were not increased and (2) the combined incidence of sarcomas in female genital tract (cervix + vagina + uterus) was "similar" to that in historical controls. (The combined incidence in the galantamine study was 1.7 %, 0 %, 5%, and 6.7 % in controls, LD, MD, and HD, respectively. The incidences in four historical control groups were said to be 0, 2, 4, and 6%; however this appears to be incorrect based on the historical control data submitted in NDA volume 1.47, p. 396-7, which shows five groups with incidences of 0, 0, 2, 4, and 4 %. [It is presumed that these historical control data were obtained from organs which were only examined when gross lesions were present (as was done in the galantamine study), although this was not specifically stated]).

The validity of combining tumors across organs in this way aside, it is acceptable to defer a decision on putting cervical sarcomas in the labeling until the sponsor performs histological exams on the cervices of all rats in the study, as they are committing to do (see #1, above). In the meantime, the drug is already being labelled as a potential uterine carcinogen.

6. **Addition of AUC multiples to description of fertility study in labeling**

The sponsor wants to use the AUC multiples, rather than the mg/kg or mg/m^2 multiples, for the animal-to-human comparison for the fertility study described in the Carcinogenesis, Mutagenesis, and Impairment of Fertility section of labeling, in order to be more consistent with the wording used in the rest of this section (which uses only the AUC multiples). However, as explained in my review of 5/1/00, AUC multiples were not used for the fertility study since plasma levels were only measured through 8 hours post-dose, thus not giving an accurate estimation of the daily AUC; furthermore, the reproduction studies were done in Sprague-Dawley rats, whereas studies on drug metabolic profile were done in Wistar rats. In order to maintain consistency it is recommended that mg/kg and mg/m^2 multiples be used for all studies, and AUC multiples used where appropriate. The following is the recommended wording for this section, which also incorporates points 4 and 5 above, i.e. mention of a mechanism for production of uterine tumors is omitted, as is mention of the finding of increased cervical sarcomas:

Carcinogenesis:

Draft

Mutagenesis:

(No change).

Fertility:

7. Changes to Pregnancy section

Although not requested by the sponsor, it is recommended that mg/kg multiples be added for consistency. The recommended wording is:

RECOMMENDATIONS:

1. The sponsor's responses to our preclinical requests made in our letter of 7/29/00 (page 4) are adequate, i.e. the requested information for the genotoxicity studies was provided, and the sponsor has committed to performing histological exams on cervix in all animals in the 24 month rat carcinogenicity study.

2. Regarding the sponsor's proposed changes to labeling:

   a) Mention of a mechanism of action aside from inhibition of acetylcholinesterase in the "Description" and "Mechanism of Action" sections should not be made. (See #3, above).

   b) The proposed mechanism of action for production of uterine adenocarcinomas in the rat carcinogenicity study should not be included. (See #4, above).

   c) The mention of an increase in cervical sarcomas in the rat carcinogenicity study may be omitted. (See #5, above).

   d) Other recommended changes in wording (primarily regarding listing of various animal-to-human multiples) for the carcinogenesis, fertility, and pregnancy sections are given in #6 and 7, above.

/S/

Barry N. Rosloff, Ph.D.

cc: NDA 21,169, sub. of 8/31/00 and division file

M. Fanari, G. Fitzgerald, B. Rosloff

Barry N. Rosloff, Ph.D.
5/1/2000

Pharmacologist Review of NDA 21-169
Original Summary

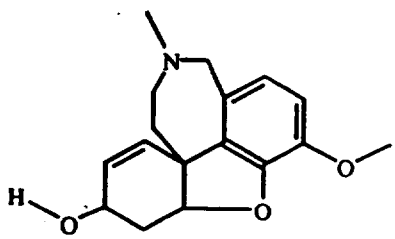
SPONSOR: Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, New Jersey 08560-0200

DRUG: galanthamine (Reminyl®)
(see attached page for structure)

CATEGORY: cholinesterase inhibitor for use in Alzheimer's Disease

NOTE: Doses in toxicity/ carcinogenicity/ reproduction studies expressed as free base.

Galantamine was originally extracted from the bulb of the daffodil, *Narcissus pseudonarcissus*. It is known chemically as (4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide. It has an empirical formula of $C_{17}H_{21}NO_3$. HBr and a molecular weight of 368.27. The structural formula for galantamine is:



(4a*S*,6*R*,8a*S*) HBr (1:1)

Galantamine is a weak base with one ionization constant due to the azepine moiety (pKa = 8.2). The molecular weight of galantamine hydrobromide is 368.27. Galantamine is slightly lipophilic as demonstrated by a partition coefficient between *n*-octanol/buffer solution (pH 12.0) of 1.09. The solubility of galantamine in water (pH 6.0) is 31 milligrams/milliliter (mg/mL).

TABLE OF CONTENTS:

ONE YEAR P.O. TOXICITY IN RATS

A) Dosage

40-50/ sex at 1.6, 8, 16, and 32 mg/kg/day, by gavage. (See attached tables for specific numbers of animals scheduled to be sacrificed at 6 months, 12 months, and after a 4 week recovery period).

Strain: Sprague- Dawley
Study Performed By:
Drug lot #: "CDFs 2612 and 2643"

B) Results

1) Observed signs

Signs were seen at all doses except LD, and included in the following:

a) MD (8 mg/kg) and above: "behavioral change," twitching, tremors (minimal at MD), and perineal staining.

b) M-HD (16 mg/kg) and above: lacrimation, salivation, polyuria, and (F only) exophthalmos.

c) HD only: Chromodacryorrhea, chromorhinorrhea

Most of the above abated during the recovery period; exceptions were, all in HD F, salivation, chromodacryorrhea, and perineal staining. Signs were considered to reflect acetylcholinesterase inhibition.

2) Mortality

Increased in HD F (11/50 deaths, vs 1/50 controls). (See attached table for specific results). Most deaths in HD F occurred during the second half of the study. It was stated that there were "no compound-related morphologic lesions to explain these deaths;" 1 HD F (and 1 control M) were said to have died of malignant lymphoma.

3) Bodyweight

Decreased gain in all groups but LD F. (See attached figures). Final weight at HD was 75% and 78% of control in M and F, resp.

4) Food consumption

Decreased at MD and above and equivocally in LD M.

5) Physical/ auditory (handclap)/ophthalmoscopic exams

(Done pre-study and weeks 12/13, 25, 38/39, and 51/52; physical/auditory exam also done after recovery).

No drug effects. (No specifics were given regarding the physical/ auditory findings).

6) Hematology

(Done in approximately 10/sex/group months 3, 6, 9, and 12, and in all remaining control and HD rats after recovery period)

a) WBC

Decreased total WBC in HD M (with a trend in M-HD M), and in F at MD and above (not strongly D-R), at most times. At maximum effect mean values were ~60% of control. These decreases were primarily due to decreases in lymphocytes, although other cell types (but not clearly neutrophils) were also affected. Slight decreases, of smaller magnitude, seen after recovery in HD M.

b) PT

Slightly increased in M-HD and HD M and in F at MD and above (but not strongly D-R) at 1year. (Not measured at 3 and 9 months). Mean values at HD ~ 10% above control. After recovery, slightly increased in M only.

c) Other parameters measured: RBC, Hb, Hct, RBC morphology, reticulocytes (C and HD only), Heinz body determination (C and HD only), platelets.

7) Blood chemistry

(Done in same animals as above).

a) Glucose

Increased at all doses but LD at most times. Magnitude of effect was both dose- and time-related. At 1 year, mean values at HD were ~ 1.7x control. No effect after recovery period.

b) Ca, P, K, Cl

Decreases seen in Ca, P, and K, primarily at the higher doses but occasionally extending down to LD, D-R at most time points (but no effect on Ca and P in M at 1 year). Mean values at HD generally 80-90% of control. No effects after recovery period. Cl was slightly increased in HD M from 6 months on; lower doses sporadically affected. Cl still slightly elevated in HD M after recovery period.

c) AP and ALT

AP decreased at M-HD and HD F at all time points; mean ~ 3/4 control. ALT decreased at M-HD and HD F at 9 and 12 months; mean 1/2-3/4 control. ALT and AP were also decreased in HD F, to a somewhat lesser degree, after the recovery period. Trends toward decreases in AP seen in M but were generally not statistically significant.

d) Total protein and albumin

Total protein slightly increased in M-HD and HD M at 9 and 12 months. Albumin increased at all times in M-HD and HD M. No effect after recovery period.

e) Other parameters measured: AST, GGT, LDH, cholesterol, triglycerides, total bilirubin, globulin, BUN, creatinine, Na.

There was no inhibition of "cholinesterase" in serum, RBC, or brain. (Blood taken 30-90 minutes post-dose).

8) Urinalysis

(Done in 10/sex/group months 3, 6, and 9, and in all surviving animals at month 12 and after recovery period).

Individual data were presented in a manner difficult to evaluate. Spot checking shows no clear or pronounced effects. A trend toward slightly higher SG seen in M at the higher doses. Parameters measured: volume (not at all time points), SG, color, clarity, pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, cells, casts, crystals.

9) Organ weights

Absolute and relative salivary gland weights were increased at 6 months in HD M and M-HD and HD F; at 12 months increases were seen at MD and above (except for absolute weight in MD M). Increases were D-R; at 12 months mean relative weight at HD was 1.6 x control. After recovery period, the effect was reduced in F and absent in M.

Decreases in absolute weights and increases in relative weights of several organs were seen, which likely are reflective of decreased bodyweights.

10) Gross pathology

No summary table given. According to the text, there were no drug effects at the 6 month sacrifice; at 12 months there was "a compound-related gross change described as tan lesions in the lungs of males and females at 40mg/kg." It was stated that these lesions were associated with microscopic findings as noted below.

11) Histopathology

(Routine exam done in C and HD at 6 month and terminal sacrifices, and on all rats which died prematurely. Gross lesions and salivary glands examined in all groups, including recovery groups. Lungs also examined in all groups at terminal sacrifice, and in recovery groups).

a) Lung

Increased incidence of foamy macrophage accumulation at 1 year sacrifice in M-HD and HD. Overall incidence relatively low:

	M	F
C	0/26	1/26
LD	0/25	0/25
MD	2/25	2/25
M-HD	4/25	4/25
HD	5/26	7/27

It was stated that "the macrophages tended to form tightly packed or loosely arranged clusters in alveoli, were generally not associated with inflammatory changes, and were characterized by a greatly expanded amount of cytoplasm which was generally pale and foamy". Severity was said to be minimal to mild. After the recovery period the lesion was seen in 2/8 HD M and 2/8 HD F (lower doses not examined), leading the sponsor to conclude that this was "persistent" change, although note that it was also seen in 1/9 recovery control F (but in 0/9 recovery control M).

b) Mandibular salivary gland

Acinar hypertrophy seen at 6 month sacrifice in M-HD and HD M and in F at MD and above; at 1 year it was seen at MD and above in both sexes with the following incidence:

	M	F
C	0/26	0/26
LD	0/25	0/25
MD	3/25	7/25
M-HD	19/25	23/25
HD	23/27	26/27

This lesion was not seen in recovery animals. It was considered to be an extension of the pharmacological action of the drug (i.e. increased cholinergic activity).

c) Spleen

Although not considered drug-related by the sponsor, there was a trend of increased hemosiderosis at HD (lower doses not routinely examined), particularly in F:

26 Weeks

	M	F
C	0/15	5/15
HD	2/15	10/15

52 weeks

	M	F
C	0/26	2/26
HD	2/27	7/27

d) Pituitary

Trend toward decreased incidence of adenoma at HD (lower doses not routinely examined) at 1 year sacrifice:

	M	F
C	7/26	6/26
HD	4/27	0/27

e) Kidney

Trend toward decreased incidence of "senile nephropathy" at HD (lower doses not routinely examined). Combined (6+12 months) incidence:

	M	F
C	26/41	12/41
HD	14/42	2/42

12) Plasma levels of parent drug

Samples taken just prior to dosing and at 2, 6, and 24 hr. post-dosing during weeks 4 and 50 in 5/sex/group satellite animals. AUC results summarized in attached tables. AUC increased roughly in proportion to dose, displayed no clear sex differences, and tended to be higher at 50 compared to 4 weeks. (Note that the values shown are probably not very accurate. Most pre-dose and 24-hour samples contained no drug; thus most AUCs were based on 2 time points. Many 2 and/or 6 hour samples at the 2 lowest doses also contained no detectable drug).

APPEARS THIS WAY
ON ORIGINAL

GALANTHAMINE HYDROBROMIDE
26/52-WEEK ORAL TOXICITY STUDY IN RATS (MIN 921003)

DOSING SCHEDULE: (cont.)

Group	Number of Rats (Animal ID) Male	Number of Rats (Animal ID) Female	Daily Dose (mg/kg)	Drug Concentration (mg/ml)	Least Number of Dose Weeks
1	15 25 10 (001-050)	15 25 10 (221-270)	0	0	26 52 52 + 4 (recovery)
2	15 25 (051-090)	15 25 (271-310)	~~2~~ 1.4	0.4	26 52
3	15 25 (091-130)	15 25 (311-350)	~~10~~ 8	2.0	26 52
4	15 25 (131-170)	15 25 (351-390)	~~20~~ 16	4.0	26 52
5	15 25 10 (171-220)	15 25 10 (391-440)	~~40~~ 32	8.0	26 52 52 + 4 (recovery)

GALANTHAMINE HYDROBROMIDE: 26/52-WEEK ORAL TOXICITY STUDY IN RATS (MIN 921003)

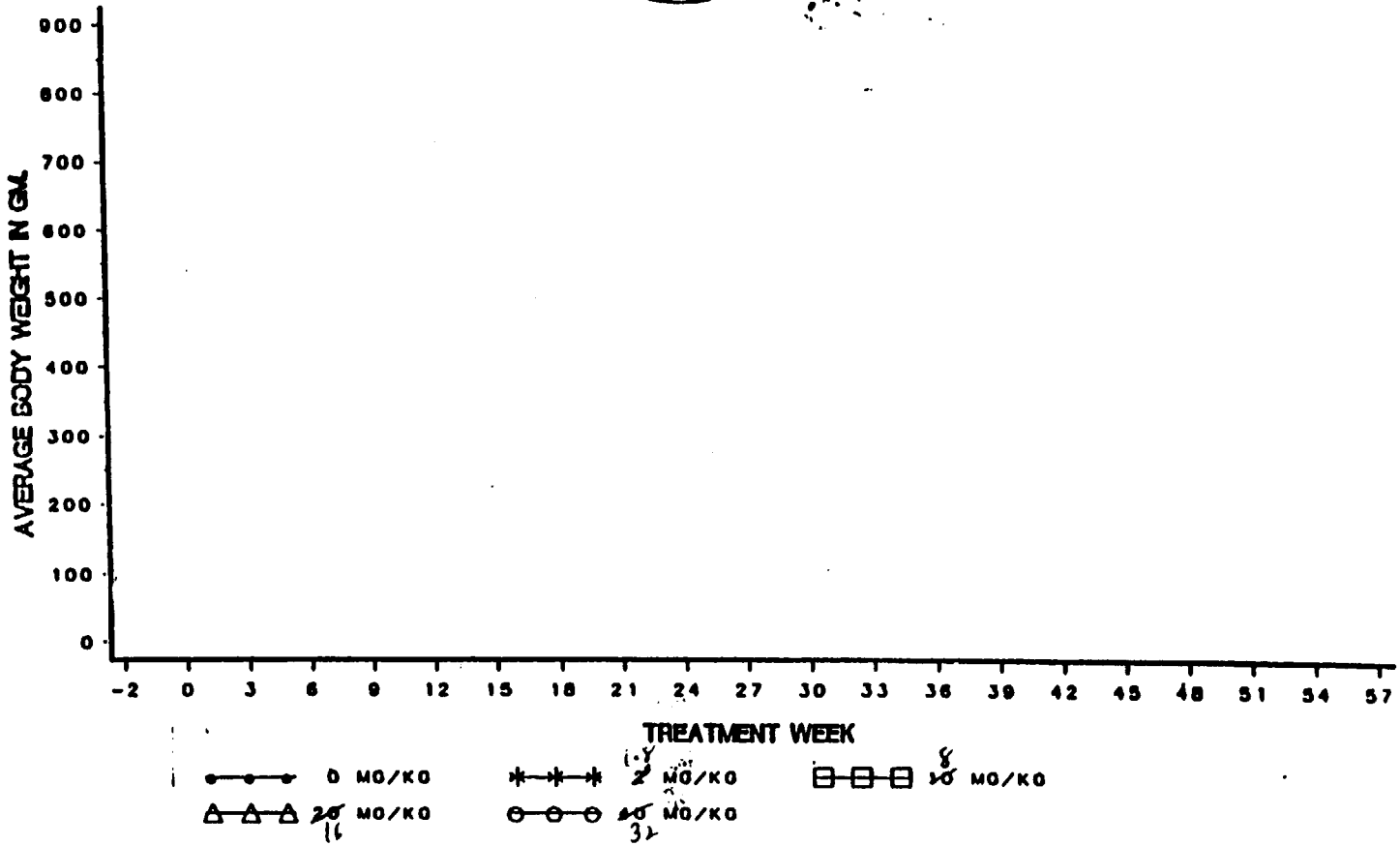
10.1. Summary of mortality

Sex:	Males					Females				
Group:	1	2	3	4	5	1	2	3	4	5
Dose (mg/kg):	0	~~2~~ 1.6	~~10~~ 8	~~20~~ 16	~~40~~ 32	0	~~2~~ 1.8	~~10~~ 8	~~20~~ 16	~~40~~ 32
Number of Rats:	50	40	40	40	50	50	40	40	40	50
Type of Death										
Found dead	1	0	1	0	2	1	0	0	1	11
Sacrificed moribund	0	0	0	1	1	0	1	0	0	0
Interim sacrifice (27 weeks)	15	15	15	15	15	15	15	15	15	13
Recovery sacrifice (57 weeks)	9	-	-	-	8	9	-	-	-	8
Terminal sacrifice (53 weeks)	25	25	24	24	24	25	24	25	24	18
Percent survival at termination[a]	100	100	96	96	96	100	96	100	96	72

[a]Based on the total number of animals minus the animals that were scheduled for interim and recovery sacrifice.

BODY WEIGHT CURVES

GALANTHAMINE HBR: 26/52 WK ORAL TOX IN RATS - (MIN021003)
CONTROLS VS TREATED
SEX=MALE

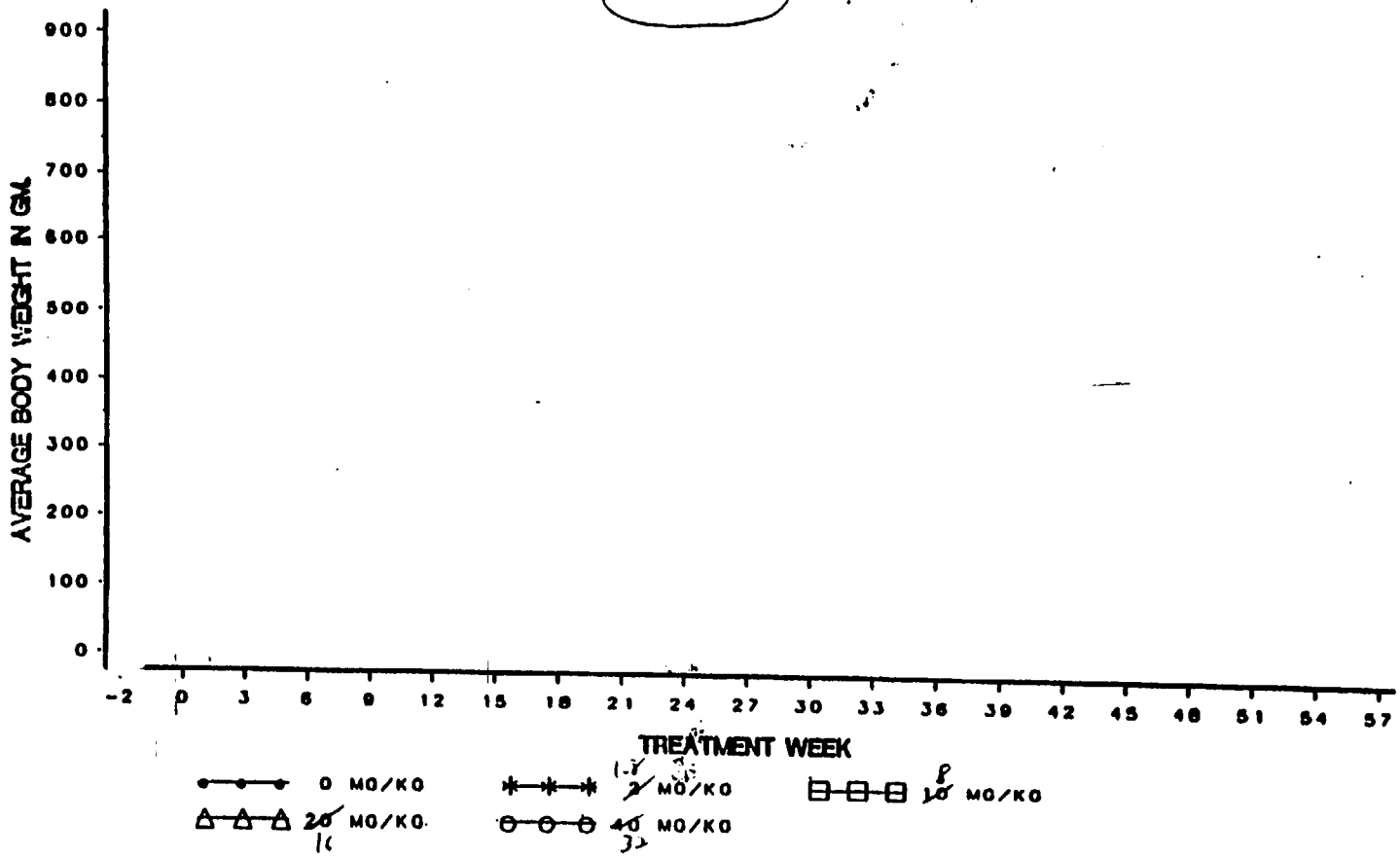


PRE-DOSE TIME(WEEKS < 0) IS NOT PLOTTED IN SAME SCALE AS POST-DOSE TIME

BODY WEIGHT CURVES

GALANTHAMINE HBR: 26/52 WK ORAL TOX IN RATS (MIN921003)
CONTROLS VS TREATED
SEX-FEMALE

28APR93
CLXXW



PRE-DOSE TIME(WEEKS < 0) IS NOT PLOTTED IN SAME SCALE AS POST-DOSE TIME

Table 5

Areas under the concentration versus time curves (AUC's) for galanthamine in plasma from rats in week 4 of a Toxicology 26/52-week oral toxicity study of galanthamine HBr (MIN 921003)[a]

Animal Number	Week	Sex	AUC for Galanthamine (hr(ng/ml)) Individual	Mean ± Std. Dev.
10 mg/kg/day				
451	4	M	665	
452			606	
453			2221	1189 ± 872
454			2051	
455			404	
476	4	F	3839	
477			630	
478			567	1518 ± 1435
479			1997	
480			555	
20 mg/kg/day				
456	4	M	4348	
457			4775	
458			4884	4467 ± 790
459			3157	
460			5170	
481	4	F	5344	
482			4424	
483			6703	5333 ± 1380
484			6647	
485			3548	
40 mg/kg/day				
461	4	M	11777	
462			10430	
463			8253	11193 ± 3288
464			16549	
465			8956	
486	4	F	12056	
487			11483	
488			9532	11208 ± 2027
489			14002	
490			8965	

[a] Group 2 (2 mg/kg/day) was omitted because the concentrations in all samples were below the limit of quantification (ng/ml).

[Notebook Reference: NB-1531, 2/4/93, pp. 6, 7]

Table 6

Areas under the concentration versus time curves (AUC's) for galanthamine in plasma from rats in week 50 of a Toxicology 26/52-week oral toxicity study of galanthamine HBr (MIN 921003)[a]

Animal Number	Week	Sex	AUC for Galanthamine (hr(ng/ml)) Individual	Mean ± Std. Dev.
1.6 ~~2~~ mg/kg/day				
446	50	M	538	
447			NF[a]	
448			NF	190 ± 264
449			NF	
450			410	
471	50	F	726	
472			742	
473			416	608 ± 175
474			741	
475			416	
8 ~~10~~ mg/kg/day				
451	50	M	5671	
452			883	
453			3829	3296 ± 2000
454			2799	
455			NC[b]	
476	50	F	5986	
477			NC	
478			1207	2856 ± 2712
479			1374	
480			NC	
16 ~~20~~ mg/kg/day				
456	50	M	5827	
457			9470	
458			6860	7880 ± 1824
459			NC	
460			9364	
481	50	F	8001	
482			5656	
483			7523	6851 ± 931
484			6725	
485			6351	

(continued on next page)

Table 6 (cont.)

Animal Number	Week	Sex	AUC for Galanthamine (hr(ng/ml)) Individual	Mean ± Std. Dev.
32 40 mg/kg/day				
461	50	M	22499	
462			20269	
463			NS[c]	18209 ± 5687
464			20243	
465			9827	
486	50	F	11420	
487			18343	
488			14311	13999 ± 3158
489			11923	
490			NS	

[a] NF = None found at 2 or 6 hr. In the calculation of means, the AUC was treated as zero.

[b] NC = The 2- and/or 6-hour sample was unavailable or unanalyzed. The animal was omitted from the calculation of mean AUC's.

[c] NS = No samples.

[Notebook Reference: NB-1531, 10/28/93 - 10/29/93, pp. 20 - 21]

TWO YEAR CARCINOGENICITY IN RATS :

1.0 Study Identification

1.2 Test Facility

Department of Toxicology
Janssen Research Foundation
2340 Beerse, Belgium

1.3 Study Number

4101

1.4 Study Date

12/96-12/98

1.5 Volume Numbers

1.47-1.51

1.6 Date of Submission

9/29/99

1.7 GLP/ QA

Yes

2.0 Study Protocol Design and Methods

2.1 Study Type

Gavage

2.2 Species / Strain

Rat/SPF Wistar,

2.3 Number of Animals per Group

60/sex

2.4 Animal Housing

Individual

2.5 Drug Batch Number

a) 00242268 (first year)
b) MR 113675PFP091

2.6 Drug Purity /Stability

Stability determination and periodic concentration checks showed no problems.

2.7 Dosing

2.7.1 Doses

0, 2.5, 10, and 40 --> 20 --> 30 mg/kg

(40 mg/kg given day 1 ; no drug given for next 3 days; 20 mg/kg then given through week 4 [males] or 10 [females], 30 mg/kg then given for remainder of study).

2.7.2 Basis of Dose Selecton

Toxicity seen in 3 month study. (See below).

2.8 CAC Concurrence on Dose Selection

Yes (Meeting of 1/27/98).

2.12 Dual Controls Employed

Yes

2.13 Interim Sacrifice

No

2.14 Satellite TK Groups

No. (Samples taken from main study groups; see below).

3.0 Study Results and Frequency of Monitoring

3.1 Clinical Observations

a) Tremors in MD (first 2-3 weeks) and HD (throughout study).

b) Wet urogenital region in MD F and HD of both sexes, mainly first few weeks.

c) Crusty nose in HD F, week 1.

d) Subcutaneous tissues mass incidence statistically significantly increased in MD and HD M. Increased in LD and MD F (not statistically significant) but not in HD F. Incidences as follows:

	C	LD	MD	HD
M	12/60	17/60	24/60	23/60
F	10/60	20/60	19/60	12/60

The text states that the significant increase in males "could be attributed to a number of ... masses which were small (< 1 cm) and disappeared before the death of the resprective animals, indicating that they were not of neoplastic origin. The increases were therefore not considered revelant."

(In a 3 month rangefinding study, in addition to tremors, urogential staining, and salivation, 40 mg/kg caused deaths of 1 in 10 rats and 80 mg/kg caused deaths in 4 of 9 rats).

3.2 Mortality

(See attatched tables and figures).

Three M and 12 F died shortly after the first dose (40mg/kg), after which doses were lowered as noted above. (The above animals that died were replaced. The tables and figures do not include the animals that died after the first dose).

There were no clear drug effects aside from the above. Although mortality at HD M was above controls during the 2nd half of the study, mortality at MD M was below controls to a similar degree. Mortality was also below controls in MD F.

3.3 Body Weight

(See attatched figures)

Weight gain decreased in all groups but LD M. Weights near end of study (% of control) were as follows:

	M	F
LD	-	97
MD	92	89
HD	80	89

3.4 Food Consumption

Decreased at MD and HD, throughout study except at MD M (decreased at 1 week and after 10 months).

3.6 Hematology

(Performed at 6, 12, 18, and 24 months, and in decedents).

a) Very slight decreases in RBC, Hb, and Hct seen in HD M and all F groups at 1 or more time points. MCV and MCH usually concomitantly slightly increased (except in LD F). Sporadic very slight decreases in MCHC in HD M and MD and HD F. Thrombocytes slightly increased in HD M and sporadically in LD and MD M.

b) Total WBC were very slightly, sporadically, and equivocally increased across most dose groups. Not a clear drug effect (not D-R, increases in individual groups not maintained over time). Associated with slight increases in lymphocytes and occasionally neutrophils, and occasionally with slight decreases in eosinophils and monocytes.

3.7 Clinical Chemsitry

(Performed at 6, 12, 18, and 24 months, and in decedents).

Several apparently drug-related effects were seen; however they were slight in magnitude (except for somewhat greater effects on triglycerides and phospholipids) and did not increase in magnitude over time. They were primarily seen at HD, occasionally extending to MD and less frequently LD. Effects included increases in chloride, inorganic phosphate, and (first year only) total bilirubin, and decreases in total protein, albumin, calcium, cholesterol, triglycerides, phospholipids, ALT, and AST.

Other parameters measured: sodium, potassium, glucose, BUN, creatinine, alkaline phosphatase.

3.8 Organ Weights

Several changes in absolute or relative weights seen which were secondary to decreased bodyweights. Decreases in both absolute and relative weights were seen for spleen in HD M and MD and HD F, and for liver in HD F.

3.9 Gross Pathology

a) Obesity - decreased in MD and HD M

b) Pituitary tissue masses - decreased in HD F, and (not statistically significantly) in MD and HD M.

c) In mammary gland, decreased incidences of stimulation, inspissated secretion, and tissue mass in HD F.

d) Uterus - incidence of tissue mass in cervix in HD F 6/60 vs 0/60 controls. Incidence of uterine cyst 0/60 in HD F vs 6/60 controls. Dilated uterus in 5/60 HD F vs 0/60 controls

e) Lungs - tissue mass in 3/60 HD M and 4/60 HD F; none in all other groups. Text states "histopathological examination of these tissue masses revealed purulent inflammatory changes most probably of infectious origin."

3.10 Histopathology

(Some organs routinely examined at all doses; some only in C and HD. [See attatched list]).

a) Neoplastic findings

(Summary tables attached [Note that the denominators shown are not always correct, for example the denominator for organs which were not routinely examined at LD and MD were given as 60]).

1) Decreased incidence of pituitary adenomas in all groups but LD F.

2) Decrease in mammary tumors (adenocarcinomas and fibroadenomas) in HD F.

3) Decreased incidence of HD animals with benign tumors at any site, due to above.

4) Uterine / cervical tumors

The incidence of uterine adenocarcinoma was 4/60, 3/60, 9/60, and 9/60 in C, LD, MD, and HD, resp. Cervical sarcoma was seen in 3 HD only. (Cervix was not routinely examined histologically in any group ; 6, 2, 4, and 9 in C, LD, MD, and HD, resp. were examined histologically, presumably based on gross findings in cervix). Following the attached overall tumor incidence tables are the sponsor's tables showing incidences and statistical results of various combinations ("Text Tables" B and C). Note that spot checking showed an "adenocarcinoma" in the cervix of an HD which does not appear in any of the incidence tables. The animal with this finding [# H 830] also had an adenocarcinoma in uterus; perhaps it was decided to only count this animal once. In this case, the incidence values for "uterus or cervix - adenocarcinoma or carcinoma" [Text Table B, last line] would be correct). The sponsor states that the p values for trends for uterine adenocarcinomas (.0366) and for overall uterine / cervical adenocarinoma or carcinoma (.0343) were not below the FDA cutoff point of 0.005. The p value for trend for cervical sarcoma (.0141) was said to be below the FDA cutoff for rare tumors (presumably .025), although the p value for combined incidence of sarcomas in cervix, uterus, and vagina (.0386) was above this cutoff point.

The time of discovery of the first uterine adenocarcinoma was slightly earlier in the drug groups compared to control (month 24, 19, 20, and 22 in C, LD, MD, and HD resp.); however almost all of these tumors were seen near the end of the study and a conclusion of a difference in latency across groups cannot be clearly made. The 3 cervical sarcomas at HD were detected in rats dying months 17 and 25, and 1 at termination.

b) Non-neoplastic findings

The sponsor's tables of those findings which were stastically significant are attatched. Following these tables is a table showing results of various of quantitative measurements made in the female genital tract. Salient results are summarized as follows:

1) Female genital tract

Effects in ovary, uterus, and vagina were said to reflect increased cyclic activity (hypothesized to be due to a reduction in the age - related rise in serum prolactin; prolactin level results shown later). Such effects in ovaries included decreased absence of corpora lutea, increased eosinophilic stained (regressive) corpora lutea, decreased presence of clear interstitial tissue, decreased glanulosa - theca cell hyperplasia, decreased presence of prominent sex cord cells , decreased Sertoli - like cells and tertiary follicles, and (not shown in tables) decrease in papillary cysts. In vagina, an increase in desquamation and a decrease in mucification were seen. In uterus, increased granulocytic infiltration of the endometrium and (not shown in tables) decreased cystic uterus were seen.

The above changes were mainly seen at HD, with some trends of slight effects at MD (and, in the case of granulocytic infiltration of endometrium, also at LD).

2) Mammary Gland

Decreased activity at HD F. Decreased tubulo-acinar development in all M groups.

3) Kidneys

Decrease in chronic renal disease and other findings at HD of both sexes

4) Liver

In males, decreases in eosinophilic focal cellular changes, ductal fibrosis, and vacuolated cell placques/ foci were seen at HD.

In females, decreases in ductal fibrosis were seen at MD and HD, and a decrease in ductal proliferation was seen at HD. The latter was associated with an increase in oval cell proliferation, "accepted to be an early stage of bile duct proliferation." Increases were seen in dense hepatocytic cytoplasm and parenchymal pigmentation at MD and HD F; these were said to be associated with body weight reduction.

5) Thyroid

Decreased C - cell hyperplasia at HD

6) Pancreas

Decreased incidence of "large islets" in HD M and MD and HD F

7) Heart

Decreased incidence of fibrosis in HD M

8) Adrenal

Decreased incidence of cortical focal cellular changes, cortical hyperplasia, and ectasia in HD F

9) Bone marrow / spleeen

Slight increases in incidence of diffuse hyperplasia and granulopoiesis in bone marrow in HD M and HD F (bone marrow not examined at LD and MD), and in granulopoiesis and hyperplaisa of red pulp in MD and HD F. (Above not shown in table).

10) Lungs

Slight increase in focal macrophages and foamy cells in HD F. (Foamy cell incidence not shown in table)

11) Extraorbital lacrimal gland

Decreased atrophy in HD M.

12) Salivary gland (parotid)

Increased incidence of focally large basophilic acini in HD F.

3.11 Toxicokinetics

Samples were taken on day 182 from 2/sex/group at 0.25, 3, and 24 hr. post-dose, from an additional 2/sex/group at 0.5 and 6 hr. post-dose, and from an additional 2/sex/group at 1 and 12 hr. post-dose. Samples were taken on day 398 at 1, 8, and 24 hr. post - dose, from a different 2/sex/group at each time point. Additional samples were taken 0.5 hr. after dosing on additional days as indicated in the attatched results.

AUC values increased roughly in proportion to dose, were similar on days 182 and 398, and were about 1.5-2x greater in F than in M. Levels of norgalantamine were not measured.

Plasma levels of galantamine and norgalantamine were measured on day 76 of a 3 month rangefinding study at doses of 10, 20, and 40--> 80 mg/kg. At the 10mg/kg dose, AUCs for galantamine were similar to those in the 2 year study. AUCs for norgalantamine were about 1/10 (M) and 1/20 (F) those of galantamine.

3.12 Plasma prolactin levels

Although not indicated in the study protocol, plasma prolactin levels were apparently measured, presumably at termination. The time after dosing or time of day when samples were taken was not stated.

Results are shown in attached tables and figures. (Separate results for animals with and without pituitary adenomas). It is difficult to draw firm conclusions due to the large inter-animal variability seen, although it does appear that levels in HD F were lower than controls.

T 1

EXPERIMENT: 4101
26-Month Carcinogenicity Study
C113675 - OR/GAV - RAT

! M O R T A L I T Y !
! Incidence per dosage group !
! Cumulative per lunar month !

	Males											
	Dosage group (mg/kg)											
	Control			Low:2.5			Medium:10			High:30		
Lunar Month	X / N	%		X / N	%		X / N	%		X / N	%	
1.	0 / 60	0.0		0 / 60	0.0		0 / 60	0.0		1 / 60	1.7	
2.	0 / 60	0.0		0 / 60	0.0		0 / 60	0.0		1 / 60	1.7	
3.	0 / 60	0.0		1 / 60	1.7		0 / 60	0.0		1 / 60	1.7	
4.	0 / 60	0.0		1 / 60	1.7		0 / 60	0.0		2 / 60	3.3	
5.	0 / 60	0.0		1 / 60	1.7		0 / 60	0.0		2 / 60	3.3	
6.	1 / 60	1.7		2 / 60	3.3		0 / 60	0.0		2 / 60	3.3	
7.	2 / 60	3.3		3 / 60	5.0		0 / 60	0.0		4 / 60	6.7	
8.	2 / 60	3.3		3 / 60	5.0		1 / 60	1.7		5 / 60	8.3	
9.	9 / 60	15.0		3 / 60	5.0		1 / 60	1.7	*	6 / 60	10.0	
10.	9 / 60	15.0		6 / 60	10.0		3 / 60	5.0		8 / 60	13.3	
11.	9 / 60	15.0		6 / 60	10.0		3 / 60	5.0		8 / 60	13.3	
12.	9 / 60	15.0		7 / 60	11.7		3 / 60	5.0		10 / 60	16.7	
13.	9 / 60	15.0		8 / 60	13.3		4 / 60	6.7		12 / 60	20.0	
14.	9 / 60	15.0		10 / 60	16.7		4 / 60	6.7		12 / 60	20.0	
15.	10 / 60	16.7		10 / 60	16.7		6 / 60	10.0		13 / 60	21.7	
16.	12 / 60	20.0		11 / 60	18.3		7 / 60	11.7		15 / 60	25.0	
17.	12 / 60	20.0		12 / 60	20.0		7 / 60	11.7		20 / 60	33.3	
18.	12 / 60	20.0		12 / 60	20.0		8 / 60	13.3		21 / 60	35.0	
19.	12 / 60	20.0		12 / 60	20.0		8 / 60	13.3		22 / 60	36.7	
20.	13 / 60	21.7		16 / 60	26.7		9 / 60	15.0		22 / 60	36.7	
21.	16 / 60	26.7		18 / 60	30.0		9 / 60	15.0		24 / 60	40.0	
22.	16 / 60	26.7		19 / 60	31.7		9 / 60	15.0		26 / 60	43.3	
23.	19 / 60	31.7		20 / 60	33.3		11 / 60	18.3		26 / 60	43.3	
24.	22 / 60	36.7		21 / 60	35.0		11 / 60	18.3	*	28 / 60	46.7	
25.	25 / 60	41.7		21 / 60	35.0		13 / 60	21.7	*	31 / 60	51.7	
26.	26 / 60	43.3		22 / 60	36.7		15 / 60	25.0		32 / 60	53.3	
27.	27 / 60	45.0		22 / 60	36.7		15 / 60	25.0	*	32 / 60	53.3	

Significance computed by Chi-square test (two tailed) : * P < .05 ** P < .01 *** P < .001
X : Number of animals dead or sacrificed at stated period
N : Total number of animals

T 2

EXPERIMENT: 4101
24-Month Carcinogenicity Study
8113675 - OR/GAV - RAT

MORTALITY
Incidence per dosage group
Cumulative per lunar month

Females

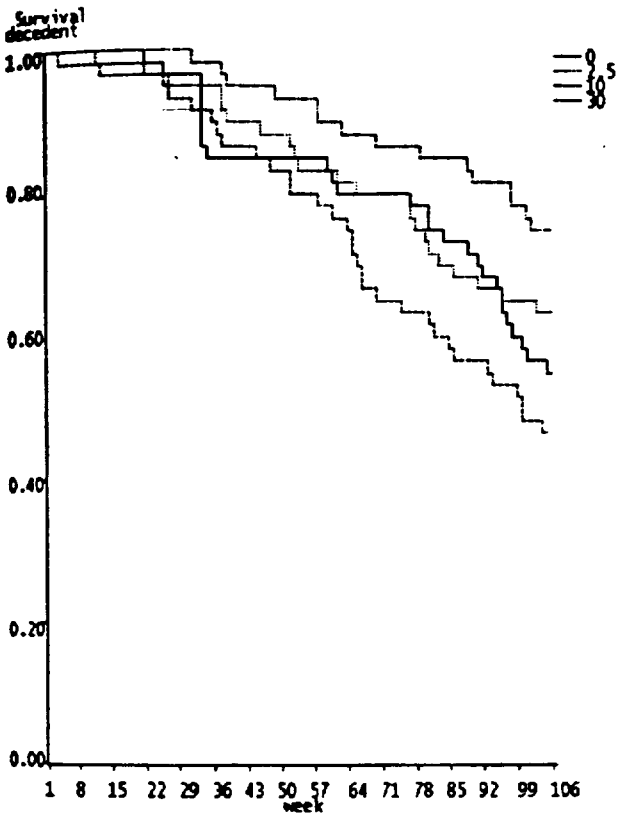
Lunar Month	Control X / N	Control %	Low:2.5 X / N	Low:2.5 %	Medium:10 X / N		Medium:10 %	High:30 X / N	High:30 %
1.	0 / 60	0.0	0 / 60	0.0	0 / 60		0.0	1 / 60	1.7
2.	0 / 60	0.0	0 / 60	0.0	0 / 60		0.0	1 / 60	1.7
3.	0 / 60	0.0	0 / 60	0.0	0 / 60		0.0	2 / 60	3.3
4.	0 / 60	0.0	0 / 60	0.0	0 / 60		0.0	2 / 60	3.3
5.	0 / 60	0.0	0 / 60	0.0	0 / 60		0.0	3 / 60	5.0
6.	2 / 60	3.3	1 / 60	1.7	0 / 60		0.0	3 / 60	5.0
7.	2 / 60	3.3	1 / 60	1.7	0 / 60		0.0	3 / 60	5.0
8.	3 / 60	5.0	1 / 60	1.7	0 / 60		0.0	3 / 60	5.0
9.	4 / 60	6.7	1 / 60	1.7	0 / 60		0.0	3 / 60	5.0
10.	4 / 60	6.7	2 / 60	3.3	0 / 60		0.0	3 / 60	5.0
11.	4 / 60	6.7	2 / 60	3.3	0 / 60		0.0	3 / 60	5.0
12.	4 / 60	6.7	3 / 60	5.0	0 / 60		0.0	3 / 60	5.0
13.	4 / 60	6.7	4 / 60	6.7	1 / 60		1.7	4 / 60	6.7
14.	6 / 60	10.0	5 / 60	8.3	1 / 60		1.7	4 / 60	6.7
15.	8 / 60	13.3	5 / 60	8.3	1 / 60	*	1.7	4 / 60	6.7
16.	9 / 60	15.0	6 / 60	10.0	3 / 60		5.0	5 / 60	8.3
17.	9 / 60	15.0	7 / 60	11.7	4 / 60		6.7	6 / 60	10.0
18.	10 / 60	16.7	7 / 60	11.7	4 / 60		6.7	8 / 60	13.3
19.	10 / 60	16.7	8 / 60	13.3	5 / 60		8.3	8 / 60	13.3
20.	10 / 60	16.7	10 / 60	16.7	6 / 60		10.0	8 / 60	13.3
21.	10 / 60	16.7	13 / 60	21.7	7 / 60		11.7	8 / 60	13.3
22.	14 / 60	23.3	14 / 60	23.3	8 / 60		13.3	12 / 60	20.0
23.	20 / 60	33.3	17 / 60	28.3	10 / 60		16.7	19 / 60	31.7
24.	22 / 60	36.7	19 / 60	31.7	12 / 60		20.0	21 / 60	35.0
25.	26 / 60	43.3	21 / 60	35.0	15 / 60		25.0	25 / 60	41.7
26.	29 / 60	48.3	26 / 60	43.3	16 / 60	*	26.7	26 / 60	43.3
27.	29 / 60	48.3	26 / 60	43.3	17 / 60	*	28.3	27 / 60	45.0

Significance computed by Chi-square test (two tailed) : * P < .05 ** P < .01 *** P < .001
X : Number of animals dead or sacrificed at stated period
N : Total number of animals

Table 1

STUDY 4101 : 24 MONTH RAT ORAL GAVAGE STUDY OF R113675 (GALANTAMINE)
Kaplan-Meier plot of survival

Male

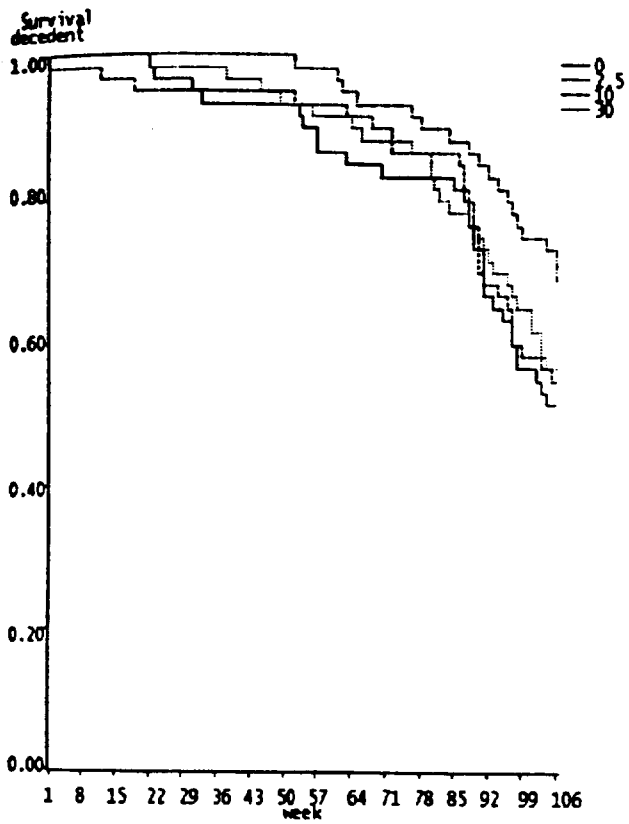


Run on: 12-MAY-99

Table 1

STUDY 4101 : 24 MONTH RAT ORAL GAVAGE STUDY OF R113675 (GALANTAMINE)
Kaplan-Meier plot of survival

Female



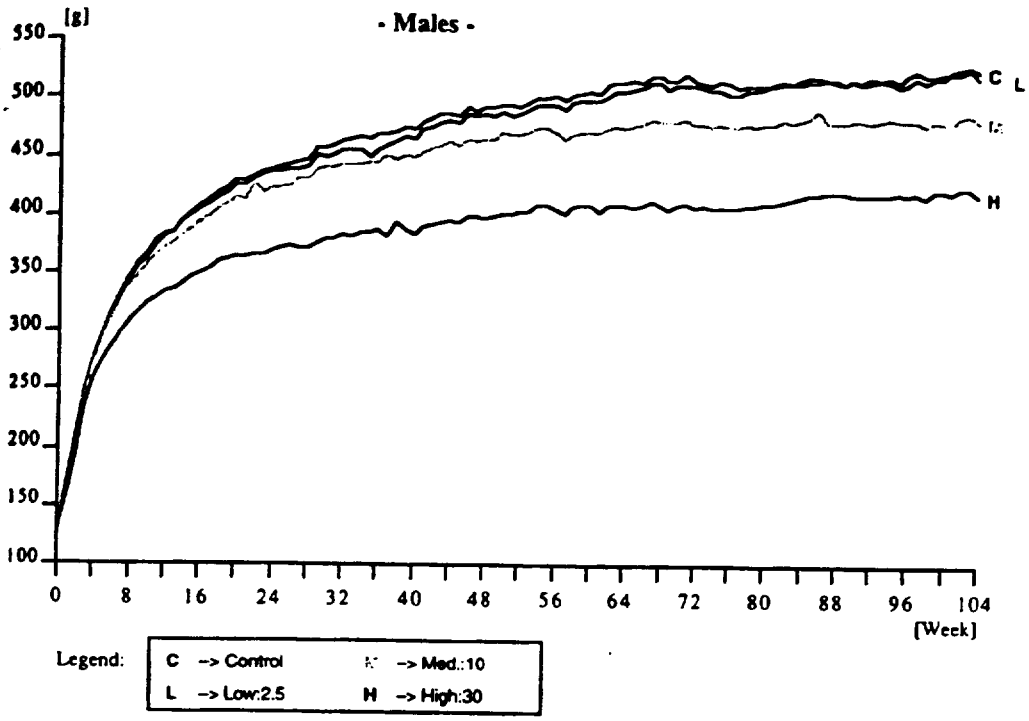
Run on: 12-MAY-99

(galantamine) Tablets
Application 21-169

T 14

BODY WEIGHT
Mean values per dosage group in g

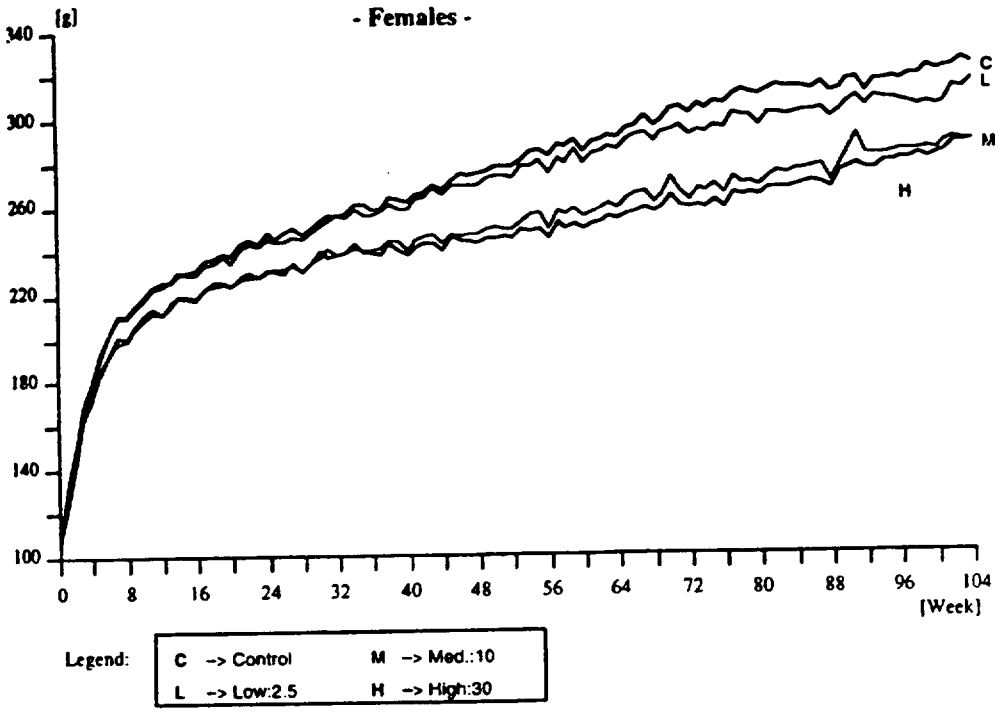
Experiment: 4101
24-Month Carcinogenicity Study
RJ13675 - OR/GAV - RAT



T 26

BODY WEIGHT
Mean values per dosage group in g

Experiment: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT



2.5.5. HISTOPATHOLOGY

Histological examination was performed by experienced anatomo-pathologists of the Janssen Research Foundaton and a peer review was carried out by an independent consultant For histopathological examination, organs and tissues were trimmed, embedded within 3 months after prelevation (with exception of animals C27, L134, L135, M209, M325, C553, M731, H805, H846, H855), sectioned, stained or others as needed) and mounted by a procedure as much standardized as possible. The technical preparation of the organs and tissues was carried out at
The following organs and tissues were examined as planned in the protocol:

Control and all dosed animals

- adrenal glands (medulla, cortex)
- brain
- kidneys
- liver (2 samples)
- lungs (2 samples)
- lymph node(s) (mesenteric)
- mammary gland
- ovaries
- pancreas
- peripheral nerve (sciatic nerve)
- pituitary gland
- prostate
- salivary gland (mandibular)
- seminal vesicles and coagulating glands
- spinal cord (thoracal)
- spleen
- testes and epididymides
- thymus
- thyroid glands and parathyroid tissue
- uterus
- vagina
- any organ or tissue, suspected for neoplasm

(continued)

Histopathology (organs examined) continued

Controls and high dosed animals

- aorta
- bone (sternum and stifle joint) with bone marrow
- caecum
- colon
- duodenum
- esophagus
- extraorbital lacrimal gland
- external ear
- eye
- heart
- ileum
- jejunum
- nasal turbinates (nose)
- rectum
- salivary gland (parotid)
- skeletal muscle (psoas)
- stomach (forestomach, glandular stomach)
- trachea
- urinary bladder

Tissues from animals found dead or from animals sacrificed during the study were also submitted for histological examination. A limited number of tissues from rats which died during the study could not be evaluated histologically because of autolysis. No single animal was completely lost for histological examination because of too far an advanced autolysis.

T 111

EXPERIMENT: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Males				
	Dosage group (mg/kg)				(a)
	Control	Low:2.5	Medium:10	High:30	P (1-sided) for trend
Adrenal glands : Adenoma, cortical	0 / 60	0 / 60	3 / 60	0 / 60	(b) 0.1897
Adrenal glands : Phaeochromocytoma	1 / 60	5 / 60	3 / 60	0 / 60	(b) 0.7547
- Phaeochromocytoma, benign	1 / 60	5 / 60	2 / 60	0 / 60	(b) 0.8165
- Phaeochromocytoma, malignant	0 / 60	0 / 60	2 / 60	0 / 60	(b) 0.2372
Brain : Astrocytoma	0 / 60	2 / 60	0 / 60	0 / 60	(b) 0.7367
- Astrocytoma, benign	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6740
- Astrocytoma, malignant	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6717
Epididymides : Mesothelioma, benign	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9201
External ear : Carcinoma	0 / 60	0 / 60	1 / 60	1 / 60	(c) 0.1628
Hematopoietic system : tumor	4 / 60	5 / 60	2 / 60	1 / 60	(b) 0.9415
- Lymphosarcoma	0 / 60	2 / 60	1 / 60	0 / 60	(b) 0.5915
- Lymphoid leukemia	2 / 60	0 / 60	0 / 60	1 / 60	(b) 0.7683
- Thymoma	2 / 60	3 / 60	1 / 60	0 / 60	(b) 0.9359
- Thymoma, predominantly epithelial, benign	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3071
- Thymoma, predominantly lymphocytic, benign	2 / 60	2 / 60	0 / 60	0 / 60	(b) 0.9697
- Thymoma, predominantly lymphocytic, malignant	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6740
Large intestine, colon : Adenocarcinoma, polypous	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3071
Liver : Hepatocytic neoplasia	2 / 60	3 / 60	2 / 60	1 / 60	(b) 0.7309
- Hepatocarcinoma	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3071
- Hepatocellular adenoma	2 / 60	3 / 60	1 / 60	1 / 60	(b) 0.8024
Lungs : Primary lung tumor	1 / 60	0 / 60	1 / 60	0 / 60	(b) 0.7277
- Primary lung tumor, adenoma	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3071
- Primary lung tumor, carcinoma	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9072
Lymph node(s), bronchial : Hemangiosarcoma	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6740
Lymph node(s), mesenteric : Hemangioma	3 / 60	1 / 60	1 / 60	2 / 60	(b) 0.6687
Mouth : Carcinoma, squamous cell	0 / 60	0 / 60	0 / 60	1 / 60	(c) 0.2025
Pancreas : Adenoma, endocrine	2 / 60	5 / 59	2 / 60	2 / 60	(b) 0.6275
Pancreas : Adenoma, endocrine-exocrine (mixed)	1 / 60	0 / 59	0 / 60	0 / 60	(b) 0.8629
Pancreas : Adenocarcinoma, endocrine	1 / 60	0 / 59	0 / 60	0 / 60	(b) 0.9201
Pancreas : Adenoma, exocrine	1 / 60	0 / 59	1 / 60	0 / 60	(b) 0.7389
Parathyroid gland(s) : Adenoma	0 / 59	0 / 59	1 / 58	0 / 58	(b) 0.3004
Pituitary gland : Adenoma	19 / 60	10 / 59	8 / 59	7 / 57	(b) 0.9959
Prostate : Adenoma, papillary	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9201
Salivary gland, parotid gland : Adenocarcinoma	0 / 60	0 / 60	0 / 60	1 / 60	(c) 0.1944
Seminal vesicles : Carcinoma, scirrhous	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.5869
Skin : Papilloma, squamous cell	0 / 60	0 / 60	2 / 60	0 / 60	(b) 0.2372
Soft tissue : Fibrohistiocytic sarcoma	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9201
Soft tissue : Fibrosarcoma	0 / 60	0 / 60	0 / 60	1 / 60	(c) 0.2308
Soft tissue : Fibroma	0 / 60	1 / 60	0 / 60	1 / 60	(b) 0.2330
Soft tissue : Hemangioma	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9180
Soft tissue : Lipoma	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6740
Stomach, forestomach : Sarcoma	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.2991
Testes : Leydig cell tumor, benign	2 / 60	3 / 60	1 / 60	2 / 60	(b) 0.5487
Testes : Mesothelioma, benign	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.8629
Thyroid glands : C-cell neoplasia	4 / 60	1 / 58	3 / 60	2 / 60	(b) 0.6582
- C-cell adenoma	4 / 60	1 / 58	3 / 60	1 / 60	(b) 0.8176
- C-cell carcinoma	0 / 60	0 / 58	0 / 60	1 / 60	(c) 0.1944
Thyroid glands : Follicular adenocarcinoma	2 / 60	1 / 58	1 / 60	0 / 60	(b) 0.8988
Thyroid glands : Follicular adenoma	4 / 60	4 / 58	5 / 60	2 / 60	(b) 0.6478
Urinary bladder : Papilloma, transitional cell	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.8596

(a) Age-adjusted analysis, taking into account the context of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted Cochran-Armitage trend test

EXPERIMENT: 4101
24-Month Carcinogenicity Study
B113675 - OR/GAV - RAT

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Dosage group (mg/kg)				(a)
	Control	Low:2.5	Medium:10	High:30	P (1-sided) for trend
Females					
Adrenal glands : Adenoma, cortical	0 / 59	1 / 60	0 / 60	0 / 60	(b) 0.6966
Adrenal glands : Phaeochromocytoma	0 / 59	1 / 60	0 / 60	1 / 60	(b) 0.2786
- Phaeochromocytoma, benign	0 / 59	1 / 60	0 / 60	0 / 60	(b) 0.6966
- Phaeochromocytoma, malignant	0 / 59	0 / 60	0 / 60	1 / 60	(c) 0.2534
Bone : Osteosarcoma	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6812
Brain : Granular cell tumor, benign	1 / 60	0 / 60	1 / 60	0 / 60	(b) 0.7069
Brain : Meningioma, benign	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6966
Brain : Oligodendroglioma, benign	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3388
Cervix : Carcinoma	1 / 60	0 / 60	0 / 60	2 / 60	(b) 0.2320
- Carcinoma, adenosquamous	0 / 60	0 / 60	0 / 60	2 / 60	(c) 0.0607
- Carcinoma, squamous cell	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9258
Cervix : Sarcoma	0 / 60	0 / 60	0 / 60	3 / 60	(c) 0.0139 *
External ear : Carcinoma	0 / 60	0 / 60	0 / 60	1 / 60	(c) 0.2500
Hematopoietic system : tumor	2 / 60	1 / 60	1 / 60	2 / 60	(b) 0.5355
- Thymoma, predominantly epithelial, benign	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3388
- Thymoma, predominantly lymphocytic, benign	2 / 60	1 / 60	0 / 60	2 / 60	(b) 0.6104
Kidneys : Carcinoma, transitional cell	1 / 60	1 / 60	0 / 60	0 / 60	(b) 0.8898
Liver : Hepatocytic neoplasia	1 / 59	1 / 60	1 / 60	2 / 59	(b) 0.2900
- Hepatocarcinoma	0 / 59	1 / 60	0 / 60	0 / 59	(b) 0.6966
- Hepatocellular adenoma	1 / 59	0 / 60	1 / 60	2 / 59	(b) 0.1934
Lymph node(s), mesenteric : Hemangioma	0 / 60	0 / 60	2 / 60	0 / 58	(b) 0.2776
Mammary gland : Adenocarcinoma	7 / 60	5 / 59	4 / 59	2 / 60	(b) 0.9718
Mammary gland : Adenoma, adenofibroma, fibroadenoma	8 / 60	5 / 59	5 / 59	2 / 60	(b) 0.9802
Mammary gland : Fibroma	0 / 60	1 / 59	0 / 59	1 / 60	(b) 0.2798
Nose : Carcinoma, adenosquamous	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6891
Ovaries : Adenoma	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9258
Ovaries : Granulosa-theca cell tumor, benign	0 / 60	1 / 60	0 / 60	2 / 60	(b) 0.1027
Pancreas : Adenoma, endocrine	0 / 59	3 / 59	1 / 58	0 / 59	(b) 0.6917
Pituitary gland : Adenoma	34 / 60	36 / 60	26 / 58	16 / 58	(b) 1.0000
Skin : Carcinoma, squamous cell	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3373
Skin : Kerato-acanthoma	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.6966
Soft tissue : Sarcoma	0 / 60	0 / 60	0 / 60	1 / 60	(c) 0.2500
Thyroid glands : Follicular adenoma	3 / 59	4 / 60	3 / 60	1 / 60	(b) 0.8585
Thyroid glands : C-cell neoplasia	4 / 59	3 / 60	2 / 60	3 / 60	(b) 0.8228
- C-cell adenoma	3 / 59	3 / 60	1 / 60	3 / 60	(b) 0.7667
- C-cell carcinoma	1 / 59	0 / 60	1 / 60	0 / 60	(b) 0.7293
Uterus : Adenocarcinoma	4 / 60	3 / 60	9 / 60	9 / 60	(b) 0.0299 *
- Adenocarcinoma, papillary	0 / 60	0 / 60	2 / 60	0 / 60	(b) 0.2766
- Adenocarcinoma, polypous	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9258
Uterus : Adenoma, papillary	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3321
Uterus : Carcinoma	2 / 60	1 / 60	1 / 60	0 / 60	(b) 0.8930
- Carcinoma, adenosquamous	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.8920
- Carcinoma, poorly differentiated	0 / 60	0 / 60	1 / 60	0 / 60	(b) 0.3371
- Carcinoma, squamous cell	0 / 60	1 / 60	0 / 60	0 / 60	(b) 0.5977
Uterus : Polyp	4 / 60	7 / 60	9 / 60	6 / 60	(b) 0.2669
- Polyp, stromal	4 / 60	7 / 60	8 / 60	5 / 60	(b) 0.3900
- Polyp, glandular	0 / 60	0 / 60	1 / 60	1 / 60	(b) 0.1056
Uterus : (Fibro)sarcoma	1 / 60	0 / 60	1 / 60	1 / 60	(b) 0.4184
- Fibrosarcoma	1 / 60	0 / 60	0 / 60	0 / 60	(b) 0.9258
- Sarcoma	0 / 60	0 / 60	1 / 60	1 / 60	(b) 0.1054
Vagina : Polyp, stromal	0 / 60	0 / 60	2 / 60	0 / 60	(b) 0.2776
Vagina : Sarcoma	0 / 60	0 / 60	2 / 60	0 / 60	(b) 0.2705

(a) Age-adjusted analysis, taking into account the context of observation (Peto monograph, WHO, IARC, Lyon, 1980, pp. 311-426); dose levels 0, 1, 2, 3. P-values are either asymptotic (b) or "exact" (c).
(b) Asymptotic p-value of Peto's trend statistic (no correction for continuity).
(c) "Exact" p-value of the age-adjusted Cochran-Armitage trend test

EXPERIMENT : 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

TUMOR BEARING MALES

Lunar month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)
			Age adjusted test for positive dose-related trend (a)					
			Animals bearing FATAL tumor(s)					
16	1 / 50	0 / 50	0 / 54	0 / 47	-1.488	1.215	-1.350	
17	0 / 48	0 / 49	0 / 53	1 / 45	1.513	1.204	1.379	
20	1 / 48	3 / 48	1 / 52	0 / 38	-2.151	5.723	-0.899	
21	3 / 47	1 / 44	0 / 51	0 / 38	-4.778	4.686	-2.207	
22	0 / 44	1 / 42	0 / 51	0 / 36	-0.457	1.173	-0.422	
23	2 / 44	0 / 41	0 / 51	0 / 34	-2.882	2.315	-1.895	
24	1 / 41	0 / 40	0 / 49	1 / 34	0.073	2.312	0.048	
25	2 / 38	0 / 39	0 / 49	1 / 32	-1.424	3.363	-0.777	
26	0 / 35	1 / 39	1 / 47	0 / 29	0.067	2.190	0.045	
27	1 / 34	0 / 38	0 / 45	0 / 28	-1.462	1.104	-1.392	
All					-12.988	25.283	-2.583	0.995
(c)	11 / 60	6 / 60	2 / 60	3 / 60				
			Animals bearing only INCIDENTAL tumor(s)					
1 - 20	0 / 11	0 / 13	0 / 8	0 / 21	0.000	0.000	0.000	
21 - 22	0 / 0	1 / 1	0 / 0	0 / 4	-1.600	0.640	-2.000	
23 - 27	4 / 5	2 / 2	1 / 5	2 / 4	-3.500	5.775	-1.456	
Terminal	20 / 33	24 / 38	25 / 45	12 / 28	-9.250	39.127	-1.479	
All					-14.350	45.542	-2.126	0.983
(c)	24 / 49	27 / 54	26 / 58	14 / 57				
			Animals bearing FATAL and / or INCIDENTAL tumor(s)					
Total					-27.338	70.825	-3.248	0.999
(c)	35 / 60	33 / 60	28 / 60	17 / 60				

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

EXPERIMENT : 4101
26-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

TUMOR BEARING FEMALES

Lunar month	Control (b)	Low (b)	Medium (b)	High (b)	Trend	Variance	z-value	p-value (1-tailed)
	Age adjusted test for positive dose-related trend (a)							
	Animals bearing FATAL tumor(s)							
14	1 / 56	0 / 56	0 / 59	0 / 56	-1.507	1.237	-1.355	
16	1 / 52	0 / 55	1 / 59	1 / 56	0.392	3.632	0.206	
17	0 / 51	1 / 54	1 / 57	1 / 55	1.396	3.643	0.732	
18	1 / 51	0 / 53	0 / 56	1 / 54	-0.056	2.449	-0.036	
19	0 / 50	1 / 53	1 / 56	0 / 52	-0.043	2.421	-0.027	
20	0 / 50	2 / 52	1 / 55	0 / 52	-0.565	3.641	-0.296	
21	0 / 50	2 / 50	1 / 54	0 / 52	-0.573	3.683	-0.298	
22	4 / 50	1 / 47	1 / 53	3 / 52	-1.767	10.880	-0.536	
23	5 / 46	2 / 46	2 / 52	4 / 48	-1.906	14.963	-0.493	
24	2 / 40	2 / 43	2 / 50	2 / 41	-0.230	9.060	-0.076	
25	4 / 38	0 / 41	3 / 48	2 / 39	-1.771	10.078	-0.558	
26	3 / 34	4 / 39	1 / 45	1 / 35	-4.765	9.815	-1.521	
27	0 / 31	0 / 34	1 / 44	0 / 34	0.434	1.155	0.403	
All (c)	21 / 60	15 / 60	15 / 60	15 / 60	-10.960	76.657	-1.252	0.895
	Animals bearing only INCIDENTAL tumor(s)							
1 - 22	0 / 7	0 / 7	0 / 2	0 / 6	0.000	0.000	0.000	
23 - 26	1 / 1	2 / 4	0 / 0	1 / 5	-2.600	3.440	-1.402	
27	0 / 0	0 / 0	0 / 0	1 / 1	0.000	0.000	0.000	
Terminal	24 / 31	28 / 34	33 / 43	19 / 33	-10.532	31.745	-1.869	
All (c)	25 / 39	30 / 45	33 / 45	21 / 45	-13.132	35.185	-2.214	0.987
	Animals bearing FATAL and / or INCIDENTAL tumor(s)							
Total (c)	46 / 60	45 / 60	48 / 60	36 / 60	-24.092	111.842	-2.278	0.989

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

Tumour-increasing effects of treatment

For only two tumours, uterine adenocarcinomas and cervix sarcomas, was there any evidence whatsoever of a positive effect of treatment, as judged by a one-tailed trend with $p<0.05$. Results relating to these two tumours (and associated tumour groupings) are summarized in text-tables B and C and discussed in the sections below.

Uterine adenocarcinomas

Uterine adenocarcinomas were seen in 25 animals, 1 (in a control) being classified as polypoid, 2 (both at 10 mg/kg/day) being classified as papillary, with the other 22 not being further classified. Nine cases were seen at 30 mg/kg/day and at 10 mg/kg/day as compared with 3 at 2.5 mg/kg/day and 4 in the control groups, and as a result the exact trend test was significant (one-tailed $p = 0.0366$). This p-value is not below the cut-off of 0.005 regarded by the FDA as critical for common tumours, and cannot be regarded as providing convincing evidence of a true treatment effect.

TEXT-TABLE B : Summary of findings for carcinomas and adenocarcinomas of the uterus and cervix

	Dose level (mg/kg/day) 0	2.5	10	30	Trend	Trend2[1]
Uterus - adenocarcinoma						
Incidence	4	3	9	9		
Exact one-tailed p-value		0.8604	0.2375	0.1453	0.0366	0.0744
Uterus - carcinoma						
Incidence	2	1	1	0		
Exact one-tailed p-value		0.9219	0.8976	1.0000	0.9292	0.7731
Uterus - adenocarcinoma or carcinoma						
Incidence	6	4	10	9		
Exact one-tailed p-value		0.9138	0.3768	0.3384	0.1168	0.1432
Cervix - squamous or adeno-squamous carcinoma						
Incidence	1	0	0	2		
Exact one-tailed p-value		1.0000	1.0000	0.5192	0.1472	1.0000
Uterus or cervix - adenocarcinoma or carcinoma						
Incidence	6	4	10	11		
Exact one-tailed p-value		0.9138	0.3768	0.1831	0.0343	0.1432

[1] Trend omitting the top dose group

Text-table B also includes results of analyses of related tumours of the genital tract. No evidence of a trend was seen for uterine carcinomas, seen in 4 animals, or for carcinomas of the cervix, seen in 3 animals. Similar conclusions to those for uterine adenocarcinomas were reached in an analysis of the overall incidence of adenocarcinoma or carcinoma in the uterus or cervix. This analysis, based on 31 animals with tumour, gave an exact one-tailed p value of 0.0343, which again cannot be regarded as convincingly demonstrating a true treatment effect.

Cervix sarcomas

TEXT-TABLE C : Summary of findings for sarcomas in the uterus, vagina and cervix

	Dose level (mg/kg/day) 0	2.5	10	30	Trend	Trend2[1]
Uterus - sarcoma (including fibrosarcoma)						
Incidence	1	0	1	1		
Exact one-tailed p-value		1.0000	0.8149	0.7671	0.4007	0.6256
Vagina - sarcoma						
Incidence	0	0	2	0		
Exact one-tailed p-value		1.0000	0.1643	1.0000	0.5214	0.0814
Cervix - sarcoma						
Incidence	0	0	0	3		
Exact one-tailed p-value		1.0000	1.0000	0.1355	0.0141	No cases
Uterus, vagina or cervix						
Incidence	1	0	3	4		
Exact one-tailed p-value		1.0000	0.3065	0.2060	0.0386	0.1163

[1] Trend omitting the top dose group

Sarcomas were seen in the uterus in 3 animals, in the vagina in 2 animals and in the cervix in 3 animals. There was no evidence of a treatment relationship for sarcomas of the uterus or the vagina. However, all 3 cervix sarcomas occurred in the 30 mg/kg/day group, so that the exact trend test p-value was 0.0141, which is just below the cut-off regarded by the FDA as critical for rare tumours (occurring in less than 1% of control animals), but above the cut-off regarded as critical for common tumours. When results for the combined incidence of sarcomas in the genital tract were analysed, there was also some evidence of a trend (one-tailed p = 0.0386).

EXPERIMENT: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

HISTOPATHOLOGY
Incidences of non-tumorous changes
that are statistically different from control

MALES

Organ or Tissue - Observation		Dosage group (mg / kg)			
		Control	Low:2.5	Med.:10	High:30
Extraorbital lacrimal gland	*Number examined:*	*60*	*16*	*19*	*60*
- focal or follicular atrophy		40	16	18	25 *
Heart	*Number examined:*	*60*	*1*	*3*	*60*
- fibrosis		26	0	0	10 **
Kidneys	*Number examined:*	*60*	*60*	*60*	*60*
- chronic disease		18	24	18	6 *
- hyaline cast(s)		5	8	6	14 *
Liver	*Number examined:*	*60*	*60*	*60*	*60*
- ductal fibrosis		6	5	7	0 *
- eosinophilic focal cellular changes		22	22	21	7 **
- vacuolated cell plaques/foci		35	38	42	20 *
Mammary gland	*Number examined:*	*60*	*60*	*60*	*59*
- female aspect (tubulo-acinar development)		11	5	3 *	3 *
Nose	*Number examined:*	*60*	*3*	*4*	*56*
- blood in lumen		13	0	0	4 *
- inflammation		7	0	1	0 *
Pancreas	*Number examined:*	*60*	*59*	*60*	*60*
- large islets		22	25	30	11 *
Pituitary gland	*Number examined:*	*60*	*59*	*59*	*57*
- focal cellular changes		0	4	7 **	0
Salivary gland, mandibular gland	*Nr examined:*	*60*	*60*	*60*	*60*
- edema		20	26	32 *	14
Spleen	*Number examined:*	*60*	*60*	*60*	*60*
- diffuse atrophy		16	3 **	5 *	14
Thymus	*Number examined:*	*56*	*57*	*60*	*56*
- congestion		6	8	7	16 *
Thyroid glands	*Number examined:*	*60*	*58*	*60*	*60*
- C-cell hyperplasia, diffuse		36	40	34	17 ***

Significance versus Control computed by the Fisher Exact test (two tailed) : * P < .05 ** P < .01 *** P < .001
Statistics are only performed if more than 50 % of the animals of the group are examined

EXPERIMENT: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

HISTOPATHOLOGY
Incidences of non-tumorous changes
that are statistically different from control

FEMALES

Organ or Tissue - Observation	Dosage group (mg / kg)			
	Control	Low:2.5	Med.:10	High:30
Adrenal glands *Number examined:*	*59*	*60*	*60*	*60*
- cortical focal cellular changes	23	20	16	11 *
- cortical hyperplasia	9	9	8	2 *
- ectasia	38	31	43	14 ***
Kidneys *Number examined:*	*60*	*60*	*60*	*60*
- chronic disease	11	11	5	1 **
- diffuse hyperplasia (transitional epithelium)	37	34	28	18 ***
- inflammation (pelvis)	8	0 **	1 *	1 *
- minerals (pelvis)	50	50	47	28 ***
Liver *Number examined:*	*59*	*60*	*60*	*59*
- dense hepatocytic cytoplasm	6	5	23 ***	28 ***
- ductal fibrosis	12	12	3 *	2 **
- large vacuolization	7	2	0 **	1
- oval cell proliferation	1	2	7	12 **
- pigmentation in the parenchyma	3	3	25 ***	26 ***
- proliferation of ducts	17	26	17	6 *
- RES aggregates	15	6 *	9	5 *
- small vacuolization	6	2	0 *	4
Lungs *Number examined:*	*60*	*60*	*60*	*60*
- focally macrophages	1	8 *	7	7
Mammary gland *Number examined:*	*60*	*59*	*59*	*60*
- accumulated content	35	30	33	10 ***
- fibrosis	25	27	22	5 ***
- focal hyperplasia	21	17	19	8 **
- glandular development	47	52	50	29 **
- inspissated material	15	18	15	3 **
- secretion present	46	46	44	22 ***
Nose *Number examined:*	*60*	*3*	*3*	*60*
- inflammatory cells (nasolacrimal duct)	12	0	0	3 *
Ovaries *Number examined:*	*60*	*60*	*60*	*60*
- absence of corpora lutea	21	24	19	4 ***
- clear interstitial tissue	53	46	51	37 **
- granulosa-theca cell hyperplasia	7	7	2	0 *
- prominent sex cord cells	21	28	16	10 *
Pancreas *Number examined:*	*59*	*59*	*58*	*59*
- large islets	23	17	8 **	9 **
Salivary gland, parotid gland *Number examined:*	*60*	*3*	*2*	*60*
- focally large basophilic acini	1	2	0	8 *
Thyroid glands *Number examined:*	*59*	*60*	*60*	*60*
- C-cell hyperplasia, diffuse	36	38	28	18 ***
- C-cell hyperplasia, focal	15	10	9	6 *

Significance versus Control computed by the Fisher Exact test (two tailed) : * P < .05 ** P < .01 *** P < .001
Statistics are only performed if more than 50 % of the animals of the group are examined

EXPERIMENT: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

HISTOPATHOLOGY
Incidences of non-tumorous changes
that are statistically different from control

FEMALES

Organ or Tissue - Observation		Dosage group (mg / kg)			
		Control	Low:2.5	Med.:10	High:30
Vagina	*Number examined:*	*60*	*60*	*60*	*60*
- desquamation		7	10	11	22 **
- mucified aspect		44	45	37	32 *

Significance versus Control computed by the Fisher Exact test (two tailed) : * P < .05 ** P < .01 *** P < .001
Statistics are only performed if more than 50 % of the animals of the group are examined

EXPERIMENT: 4101
24-Month Carcinogenicity Study
R113675 - OR/GAV - RAT

HISTOPATHOLOGY
Non-tumorous changes
Mean scores per dosage group

FEMALES

Organ or Tissue - Observation	Dosage group (mg / kg)			
	Control	Low:2.5	Med.:10	High:30
Ovaries *Number examined:*	*57*	*54*	*55*	*48*
- abscence of corpora lutea	0.30	0.37	0.31	0.06 **
	(0.06)	(0.07)	(0.06)	(0.04)
- amount of interstitial tissue	3.79	3.76	3.82	3.10 ***
	(0.11)	(0.12)	(0.12)	(0.11)
- atretic follicles	1.05	1.02	1.02	0.92 *
	(0.05)	(0.02)	(0.05)	(0.05)
- basophilic-stained corpora lutea	0.12	0.06	0.20	0.27
	(0.04)	(0.03)	(0.05)	(0.06)
- clear interstitial tissue	1.37	1.52	1.58	1.40
	(0.09)	(0.08)	(0.09)	(0.11)
- eosinophilic-stained (regressive) corpora lutea	1.40	1.26	1.53	2.73 ***
	(0.16)	(0.17)	(0.19)	(0.19)
- generations of corpora lutea	1.70	1.65	2.11	3.17 ***
	(0.18)	(0.19)	(0.21)	(0.15)
- Sertoli-like cells	0.84	1.11	0.67	0.50 *
	(0.11)	(0.13)	(0.09)	(0.08)
- tertiary follicles	0.72	0.76	0.64	0.52 *
	(0.07)	(0.07)	(0.07)	(0.07)
Uterus *Number examined:*	*52*	*54*	*55*	*46*
- dilated lumen	1.87	1.83	2.02	2.09
	(0.14)	(0.11)	(0.10)	(0.16)
- granulocytic infiltration (endometrium)	0.19	0.46 *	0.51 *	0.78 **
	(0.06)	(0.09)	(0.10)	(0.16)
- height of the epithelium	2.37	2.56	2.51	2.46
	(0.11)	(0.09)	(0.09)	(0.10)
Vagina *Number examined:*	*56*	*54*	*53*	*49*
- cornification	0.21	0.22	0.38	0.41
	(0.06)	(0.06)	(0.07)	(0.10)
- mucification	1.32	1.39	1.15	0.98
	(0.13)	(0.11)	(0.12)	(0.12)
- thickness of the epithelium	2.50	2.76	2.81	2.88
	(0.11)	(0.14)	(0.16)	(0.18)

Significance versus Control computed by Mann-Whitney U test (two tailed) : * P < .05 ** P < .01 *** P < .001
Standard Error is shown between brackets
Statistics are only performed if more than 50 % of the animals of the group are examined

Table 5-3: **Mean (n = 2) plasma concentrations (ng/ml) and some pharmacokinetic parameters of galantamine in SPF Wistar rats measured on day 182 of a twenty-four-month carcinogenicity study (Exp. No. 4101) on aqueous solutions of galantamine hydrobromide (R113675) at 2.5, 10 and 30 mg base-eq./kg/day.**

Time (h)	2.5 mg/kg/day		10 mg/kg/day		30 mg/kg/day	
	Males	Females	Males	Females	Males	Females
0.25	312	576	936	1404	2816	3033
0.5	254	474	1138	999	2104	3776
1	232	410	920	1426	3166	3740
3	67	226	438	650	1508	2458
6	60	93	261	475	919	1583
12	14	15	89	87	332	502
24	< 10	< 10	< 10	13	24	32[1]
C_{max} (ng/ml)	312	576	1138	1426	3166	3776
T_{max} (h)	0.25	0.25	0.5	1	1	0.5
$AUC_{0-24\,h}$ (ng.h/ml)	1001	1913	4848	7216	16491	24832

[1] n = 1.

Table 5-4: **Mean (n = 2) plasma concentrations (ng/ml) and $AUC_{0\text{-}24\ h}$-values (ng.h/ml) of galantamine in SPF Wistar rats measured on day 398 of a twenty-four-month carcinogenicity study (Exp. No. 4101) on aqueous solutions of galantamine hydrobromide (R113675) at 2.5, 10 and 30 mg base-eq./kg/day.**

Time (h)	2.5 mg/kg/day		10 mg/kg/day		30 mg/kg/day	
	Males	Females	Males	Females	Males	Females
1	184	389	746	1350	1625	3924
8	24.9	58.5	135	312	707	873
24	< 5.0	< 10	11.1	< 7.5	30.6	32.3
$AUC_{0\text{-}24\ h}$ (ng.h/ml)	910	1982	4702	7986	15046	26167

Table 5-5: **Mean (n = 2) 0.5-h plasma concentrations (ng/ml) of galantamine in SPF Wistar rats measured during a twenty-four-month carcinogenicity study (Exp. No. 4101) on aqueous solutions of galantamine hydrobromide (R113675) at 2.5, 10 and 30 mg base-eq./kg/day.**

		2.5 mg/kg/day		10 mg/kg/day		30 mg/kg/day	
Day	Time (h)	Males	Females	Males	Females	Males[1]	Females[2]
29	0.5	184	409	939	1025	1983	2057
91	0.5	258	410	975	1397	2515	3329
182	0.5	254	474	1138	999	2104	3776
Css	(ng/ml)[3]	232	431	1017	1140	2201	3553
SD		42	37	106	223	279	-[4]

[1] From day 0 till day 3, the male rats of the 40-mg/kg dose level were not dosed (except Rat No. 803 on day 1 at 40 mg/kg). From day 4 of the study onwards, the 40-mg/kg dose level was reduced to 20 mg/kg. From day 28 of the study onwards, the 20-mg/kg dose level was increased up to 30 mg/kg.

[2] From day 0 till day 3, the female rats of the 40-mg/kg dose level were not dosed. From day 4 of the study onwards, the 40-mg/kg dose level was reduced to 20 mg/kg. From day 70 of the study onwards, the 20-mg/kg dose level was increased up to 30 mg/kg.

[3] Calculated from day 29 onwards, except for the 30-mg/kg dose level in females where the Css was calculated from day 91 onwards.

[4] Not calculated.

Prolactin levels

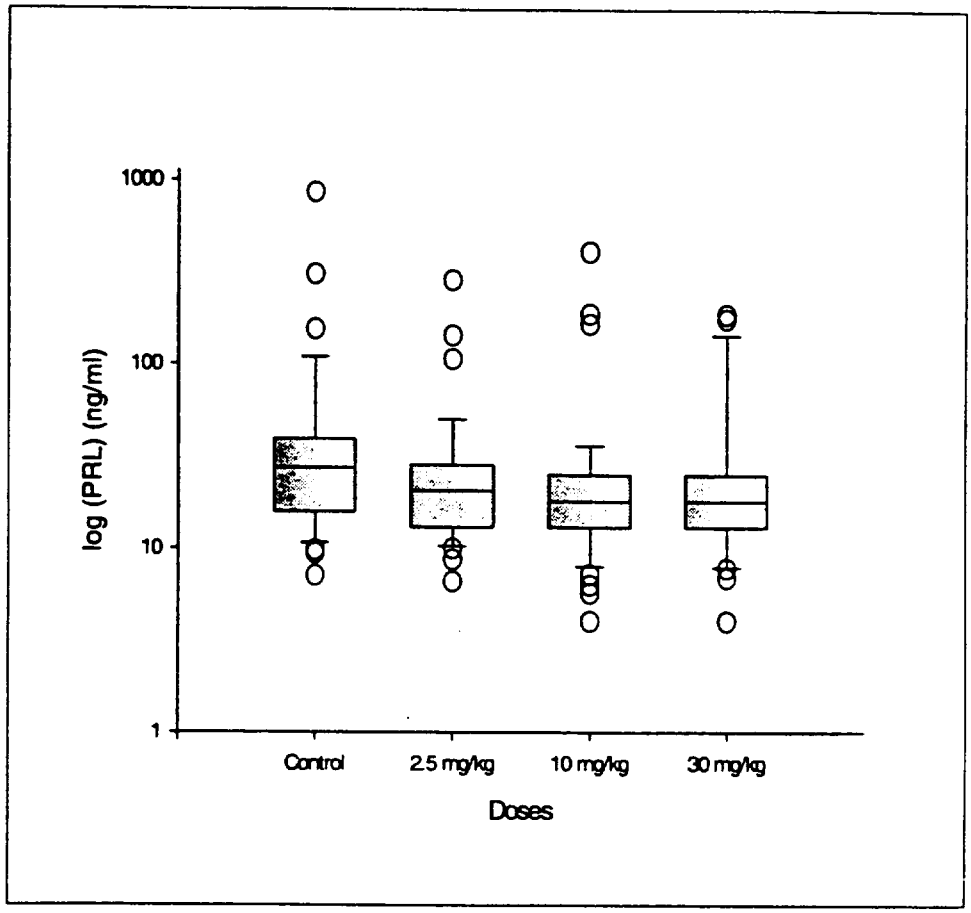


Fig. 1 and table 1:
Effects of chronic oral administration of R113675 on the serum prolactin levels in all terminally sacrificed male rats. The results are expressed as median, 10, 25, 75 and 90 percentiles. Open circles represent outlyers.

Dosage group (mg/kg)	Control	2.5	10	30
median	**27**	**20.5**	**18**	**18**
mean	65.4	33.6	34.5	36.2
stand. dev.	152.8	49.3	67.1	51.7
standard error	26.6	8	10.1	9.9
number of samples	33	38	44	27
p-value		0.1698	0.0251	0.0929
Sign			*	

Statistical significance computed by Mann-Whitney U-test (two-tailed)
* $p < 0.05$

18 w

Prolactin levels

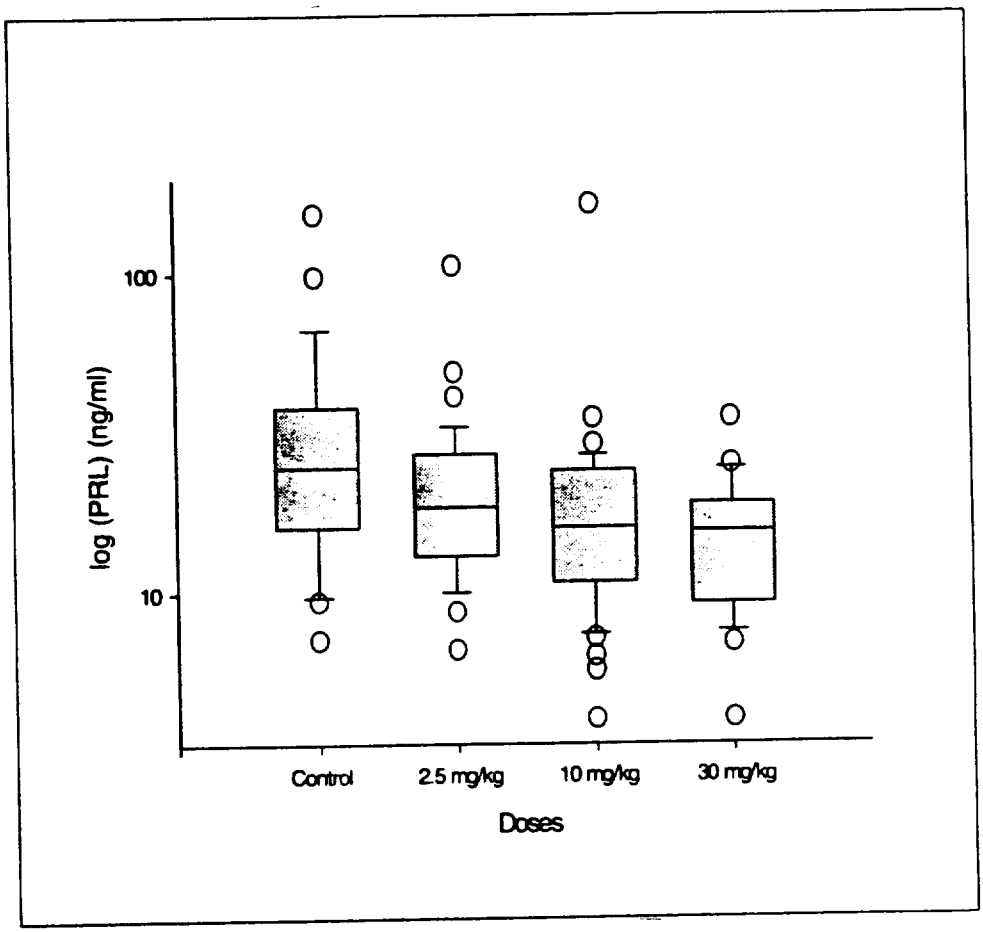


Fig. 2 and table 2 :
Effects of chronic oral administration of R113675 on the serum prolactin levels in terminally sacrificed male rats without pituitary neoplasia. The results are expressed as median, 10, 25, 75 and 90 percentiles. Open circles represent outlyers.

Dosage group (mg/kg)	Control	2.5	10	30
median	24.5	18.5	16	16
mean	34.4	22.6	20.9	16
stand. dev.	33.4	17.4	25.4	7.4
standard error	7.1	3	4.2	1.6
no. of samples	22	34	37	21
p-value		0.1223	0.0129	0.0058
Sign			*	**

Statistical significance computed by Mann-Whitney U-test (two-tailed)
* $p < 0.05$, ** $p < 0.01$

Prolactin levels

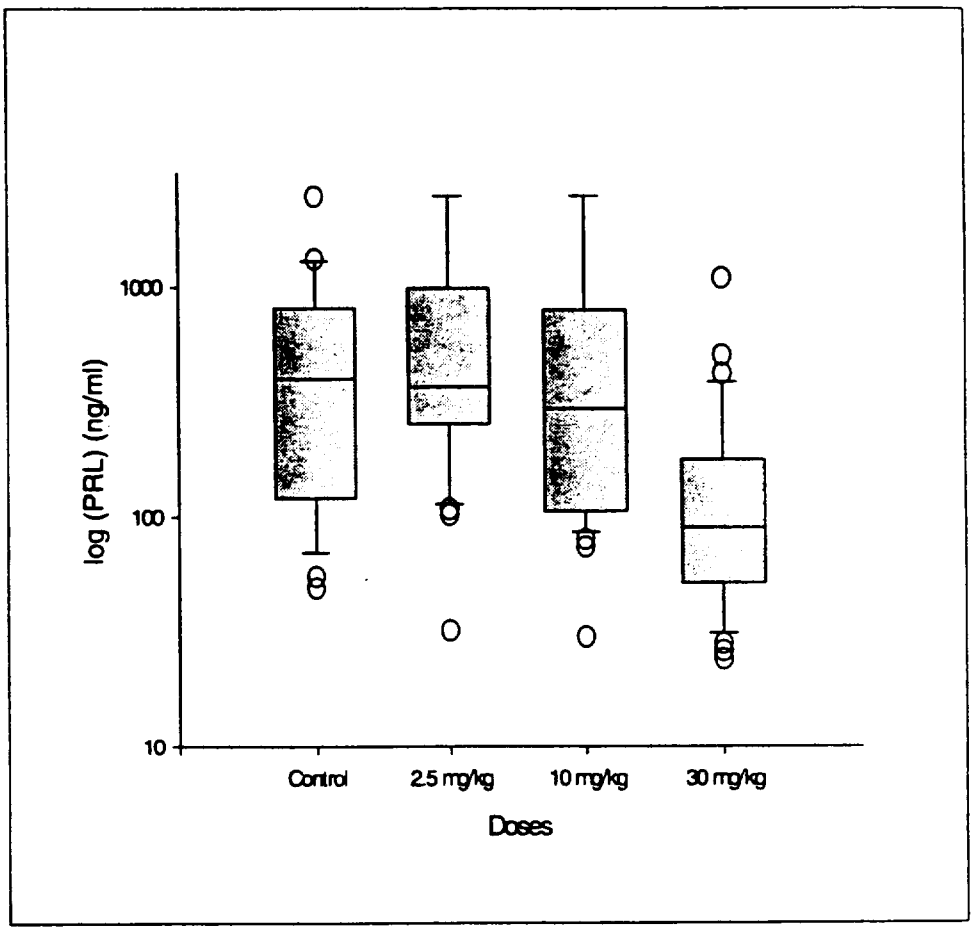


Fig. 3 and table 3 :
Effects of chronic oral administration of R113675 on the serum prolactin levels in all terminally sacrificed female rats. The results are expressed as median, 10, 25, 75 and 90 percentiles. Open circles represent outlyers.

Dosage group (mg/kg)	Control	2.5	10	30
median	399	367.5	294	90
mean	573.8	761.2	715.8	166.7
stand. dev.	636.2	798	867.7	206.6
standard error	114.3	136.9	132.3	36
number of samples	31	34	43	33
p-value		0.3242	0.9781	0.0001
Sign				***

Statistical significance computed by Mann-Whitney U-test (two-tailed)
*** $p < 0.01$

Prolactin levels

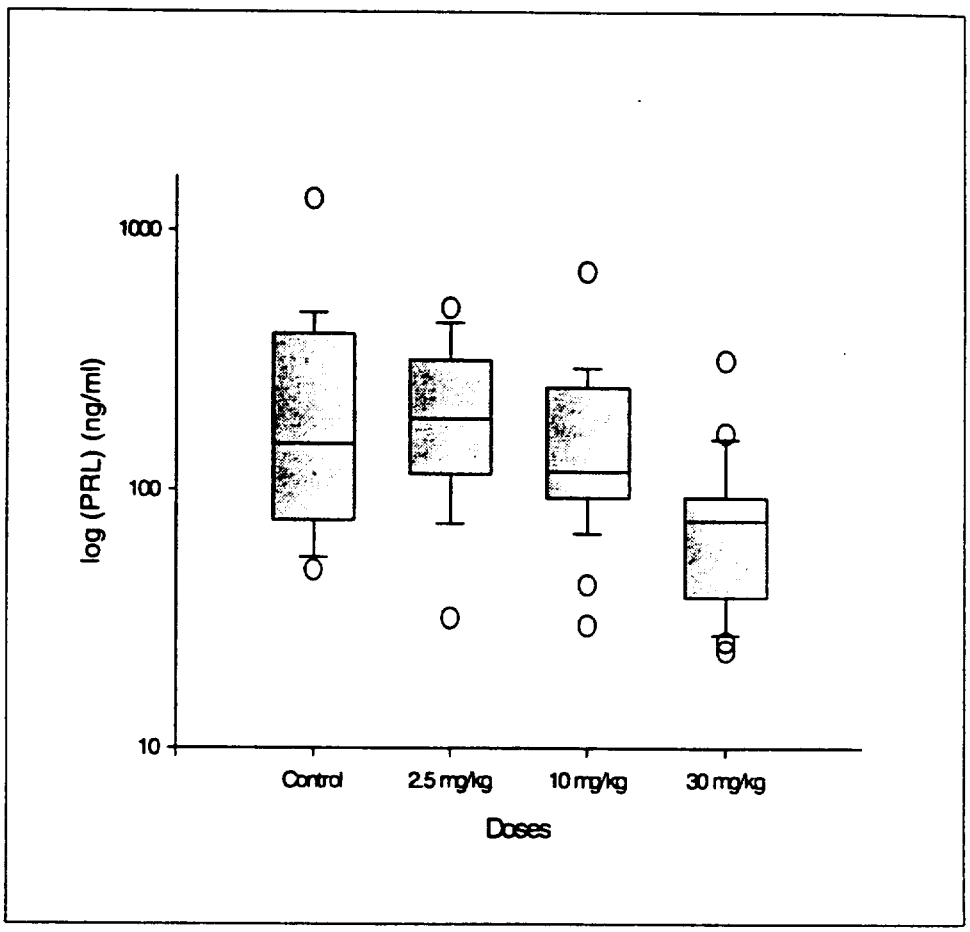


Fig. 4 and table 4 :
Effects of chronic oral administration of R113675 on the serum prolactin levels in terminally sacrificed female rats without pituitary neoplasia. The results are expressed as median, 10, 25, 75 and 90 percentiles. Open circles represent outlyers.

Dosage group (mg/kg)	Control	2.5	10	30
median	150	187	118	76
mean	282.3	221.2	176.3	84.5
stand. dev.	325.4	144.5	139.6	65
standard error	84	43.6	29.1	13.6
number of samples	15	11	23	23
p-value		0.795	0.5402	0.003
sign				**

Statistical significance computed by Mann-Whitney U-test (two-tailed)
** $p < 0.01$

TWO YEAR CARCINOGENICITY IN MICE:

1.0 Study Identification

1.2 Test Facility

Department of Toxicology
Janssen Pharmaceutica N.V.
2340 Beerse, Belgium

1.3 Study Number

4199

1.4 Study Date

3/97-3/99

1.5 Volume Numbers

1.41-1.45

1.6 Date of Submission

9/29/99

1.7 GLP/QA

Yes

2.0 Study Protocol Design and Methods

2.1 Study type

Gavage

2.2 Species/Strain

Mouse/

2.3 Number of Animals per Group

60/ sex

2.4 Animal Housing

Individual

2.5 Drug Batch Number

a) 00242268
b) MR 113675 PFP091 (last 2 months)

2.6 Drug Purity / Stability

Stability determination and periodic concentration checks showed no problems.

2.7 Dosing

2.7.1 Doses

0, 2.5, 5, 10 mg/kg

(HD lowered to 5 mg/kg after first dose, increased to 7.5 mg/kg after 10 days, and increased to 10 mg/kg after a further 2 weeks).

2.7.2 Basis of Dose Selection

Toxicity seen in 3 month rangefinding study. (See below)

2.8 CAC Concurrence on Dose Selection

Yes. (Meeting of 1/27/98)

2.12 Dual Controls Employed

No.

2.13 Interim sacrifices

No.

2.14 Satellite TK Groups

10/ sex/ dose

3.0 Study Results and Frequency of Monitoring

3.1 Clinical Observations

a) Slight sedation at HD
b) Decreased incidence of "bad condition" in all M groups, not clearly D-R
c) Decreased incidence of skin irritation in all M groups
d) Decreased incidence of s.c. tissue masses in HD M

(In a 3 month rangefinding study, 20 mg/kg caused 50% lethality, and tremors, sedation, and decreased weight gain; 40 mg/kg caused 100% lethality after the first dose).

3.2 Mortality

(See attatched tables and figures)

a) M- mortality slightly greater than controls at MD and HD, months 16-20; thereafter mortality was greater in controls; at termination mortality was slightly below controls in all drug groups (not D-R)

b) F- 3 of the first 10 treated HD (10 mg/kg) died on day 1, after which dosing regimen was altered as noted above. Mortality was below controls in all dose groups, not D-R (LD-during much of study; MD- only very late in study; HD-during 2nd year)

3.3 Body Weight

(See attatched figures)

D-R decreases at all doses (but generally not statistically significant in LD F). Weights near end of study (% of control) were as follows:

	M	F
LD	97	93
MD	90	92
HD	90	87

3.4 Food Consumption

a) M- Slight decrease in all M groups, week 1, not D-R. Thereafter, no clear drug effect. (Sporadic, slight decreases at MD and HD, and sporadic, very slight increases at LD).

b) F- No clear drug effect. (Very slight/ sporadic decreases at HD).

3.6 Hematology

(Performed at 6, 12, and 24 months, and in decedents where possible).

a) In HD M, Hb slightly increased at months 6, 12, and 24 (not progressive with time); RBC also increased at 6 and 24 months and Hct also increased at 24 months.

b) Total WBC slightly and sporadically decreased at MD and HD. Lymphocytes, and occasionally other cell types (N,B,E,M), concomitantly slightly decreased.

c) Thrombocytes slightly increased at HD at 24 months.

3.7 Clinical Chemistry

(Performed at 24 months, and in decedents where possible).

a) At 24 months, potassium slightly decreased in HD M, and BUN slightly decreased in all M groups (not D-R).

b) Other parameters measured: ALT, AST, AP, total bilirubin, total protein , albumin, cholesterol, triglycerides, phospholipids, glucose, Na, Cl, Ca, inorganic phosphate, creatinine.

3.8 Organ Weights

Several changes in absolute or relative weights seen which were secondary to decreased bodyweights. In HD M, slight decreases in both absolute and relative weights of liver, heart, and spleen were seen. In MD and HD F, decreased absolute and relative weights of thymus was seen.

3.9 Gross pathology

a) Males

1) Decreased cachexia at HD
2) Decreased swollen kidneys at MD and HD
3) Slightly decreased liver masses, all doses (not D-R)
4) Slightly decreased lung nodules at HD
5) Slight increase in small spleen / decrease in swollen spleen at MD and HD

b) Females

1) Decreased cachexia at MD and HD
2) Slightly decreased liver swelling and masses at HD.
3) Increased ovarian hemorrhagic cysts at MD and HD (but no effect on plain cysts or ovarian hemorrhage).
4) Increased swollen, cystic uterus, and slight increase in uterine tissue masses, at all doses (not D-R). Slight increase in uterine cysts at MD and HD.
5) Slight decrease in swollen thymus at MD and HD
6) Slight decrease in swollen spleen at all doses.

3.10 Histopathology

(Some organs routinely examined at all doses; some only in C and HD [See attached list]).

There were no clearly drug- related increases in neoplastic or non-neoplastic findings. There was a trend toward a slight decrease in chronic kidney pathology at HD. Summary tables for neoplastic findings attatched. (Note that the denominators shown are not always correct in that the denominators for organs which were not routinely examined at LD and MD, e.g. brain and thyroids, were given as 60 in these groups). There was an apparent slight decrease in the number of tumor- bearing M at HD, but note that mortality effects (see above) may at least in part account for this. (The table also shows a slight decrease in this parameter in MD M, but since not all organs were routinely examined in this group, comparison with controls is meaningless).

3.11 Toxicokinetics

Samples taken on day 183, from 2/sex/group at 1, 2, 4, 6, and 10 hours post-dose. Results shown in attatched table. Levels of galantamine were roughly

proportional to dose, and were somewhat lower in F. Levels of norgalantamine were not measured.

Plasma levels of both galantamine and norglantamine were measured on day 90 of a 3 month rangefinding study; results are attatched. (Note that levels were expressed in different units than in the 2 year study above). At the dose of 10 mg/kg, levels in the 3 month study were 2 (AUC) - 3 (C max) fold lower that those in the 2 year study. At this dose, AUCs of norgalantamine were ~ 1/5 (M) and 1/2 (F) those of galantamine.

T 3

Experiment: 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE

MORTALITY
Incidence per dosage group (cumulative)

Males Dosage Group (mg / kg)												
Lunar Month	Control			Low:2.5			Med:5			High:10		
	X/N	S	%	X/N	S	%	X/N	S	%	X/N	S	%
0	0/60		0.0	0/60		0.0	0/60		0.0	0/60		0.0
1	2/60		3.3	1/60		1.7	2/60		3.3	1/60		1.7
2	3/60		5.0	2/60		3.3	4/60		6.7	2/60		3.3
3	3/60		5.0	3/60		5.0	4/60		6.7	3/60		5.0
4	4/60		6.7	3/60		5.0	4/60		6.7	6/60		10.0
5	4/60		6.7	3/60		5.0	4/60		6.7	7/60		11.7
6	5/60		8.3	4/60		6.7	6/60		10.0	7/60		11.7
7	6/60		10.0	4/60		6.7	7/60		11.7	7/60		11.7
8	6/60		10.0	4/60		6.7	7/60		11.7	7/60		11.7
9	6/60		10.0	5/60		8.3	8/60		13.3	7/60		11.7
10	6/60		10.0	5/60		8.3	8/60		13.3	7/60		11.7
11	6/60		10.0	6/60		10.0	8/60		13.3	7/60		11.7
12	7/60		11.7	6/60		10.0	8/60		13.3	7/60		11.7
13	7/60		11.7	6/60		10.0	8/60		13.3	9/60		15.0
14	7/60		11.7	7/60		11.7	8/60		13.3	10/60		16.7
15	7/60		11.7	7/60		11.7	8/60		13.3	12/60		20.0
16	7/60		11.7	7/60		11.7	10/60		16.7	16/60		26.7
17	8/60		13.3	8/60		13.3	13/60		21.7	16/60		26.7
18	11/60		18.3	9/60		15.0	15/60		25.0	18/60		30.0
19	13/60		21.7	12/60		20.0	16/60		26.7	18/60		30.0
20	16/60		26.7	13/60		21.7	16/60		26.7	20/60		33.3
21	18/60		30.0	16/60		26.7	19/60		31.7	21/60		35.0
22	22/60		36.7	18/60		30.0	20/60		33.3	23/60		38.3
23	25/60		41.7	21/60		35.0	21/60		35.0	25/60		41.7
24	32/60		53.3	22/60		36.7	24/60		40.0	27/60		45.0
25	35/60		58.3	24/60		40.0	27/60		45.0	32/60		53.3
26	38/60		63.3	27/60		45.0	30/60		50.0	33/60		55.0
27	38/60		63.3	27/60		45.0	30/60		50.0	33/60		55.0

Significance level computed with Chi-Square probability test (two tailed): * $p < .05$ ** $p < .01$ *** $p < .001$
(Significance computed versus the Control dosage group)
X: Number of animals dead or sacrificed at stated period N: Total number of animals S: Significance

(galantamine) Tablets
pplication 21-169

T 4

MORTALITY
Incidence per dosage group (cumulative)

Experiment: 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE

Females
Dosage Group (mg / kg)

Lunar Month	Control X/N	S	%	Low:2.5 X/N	S	%	Med:5 X/N	S	%	High:10 X/N	S	%
0	0/60		0.0	0/60		0.0	0/60		0.0	3/59		5.0
1	3/60		5.0	1/60		1.7	4/60		6.7	5/59		8.5
2	3/60		5.0	1/60		1.7	4/60		6.7	5/59		8.5
3	3/60		5.0	1/60		1.7	5/60		8.3	5/59		8.5
4	3/60		5.0	1/60		1.7	5/60		8.3	5/59		8.5
5	3/60		5.0	1/60		1.7	5/60		8.3	5/59		8.5
6	5/60		8.3	1/60		1.7	6/60		10.0	5/59		8.5
7	6/60		10.0	1/60		1.7	6/60		10.0	5/59		8.5
8	7/60		11.7	1/60		1.7	6/60		10.0	5/59		8.5
9	7/60		11.7	1/60		1.7	6/60		10.0	5/59		8.5
10	9/60		15.0	1/60		1.7	6/60		10.0	5/59		8.5
11	9/60		15.0	2/60		3.3	7/60		11.7	6/59		10.2
12	9/60		15.0	3/60		5.0	7/60		11.7	6/59		10.2
13	9/60		15.0	3/60		5.0	8/60		13.3	6/59		10.2
14	10/60		16.7	3/60		5.0	9/60		15.0	6/59		10.2
15	12/60		20.0	6/60		10.0	13/60		21.7	8/59		13.6
16	12/60		20.0	7/60		11.7	13/60		21.7	8/59		13.6
17	14/60		23.3	10/60		16.7	17/60		28.3	11/59		18.6
18	16/60		26.7	14/60		23.3	17/60		28.3	11/59		18.6
19	17/60		28.3	14/60		23.3	18/60		30.0	12/59		20.3
20	22/60		36.7	16/60		26.7	19/60		31.7	14/59		23.7
21	27/60		45.0	22/60		36.7	23/60		38.3	17/59		28.8
22	29/60		48.3	26/60		43.3	27/60		45.0	20/59		33.8
23	33/60		55.0	29/60		48.3	28/60		46.7	23/59		39.0
24	40/60		66.7	31/60		51.7	29/60		48.3	27/59	•	45.8
25	42/60		70.0	36/60		60.0	30/60	•	50.0	31/59		52.5
26	45/60		75.0	40/60		66.7	33/60	•	55.0	36/59		61.0

Significance level computed with Chi-Square probability test (two tailed): * $p < .05$ ** $p < .01$ *** $p < .001$
(Significance computed versus the Control dosage group)
X: Number of animals dead or sacrificed at stated period N: Total number of animals S: Significance

Table 1

STUDY 4199 : 24 MONTH MOUSE ORAL GAVAGE STUDY OF R113675 (GALANTAMINE)
Kaplan-Meier plot of survival

Male

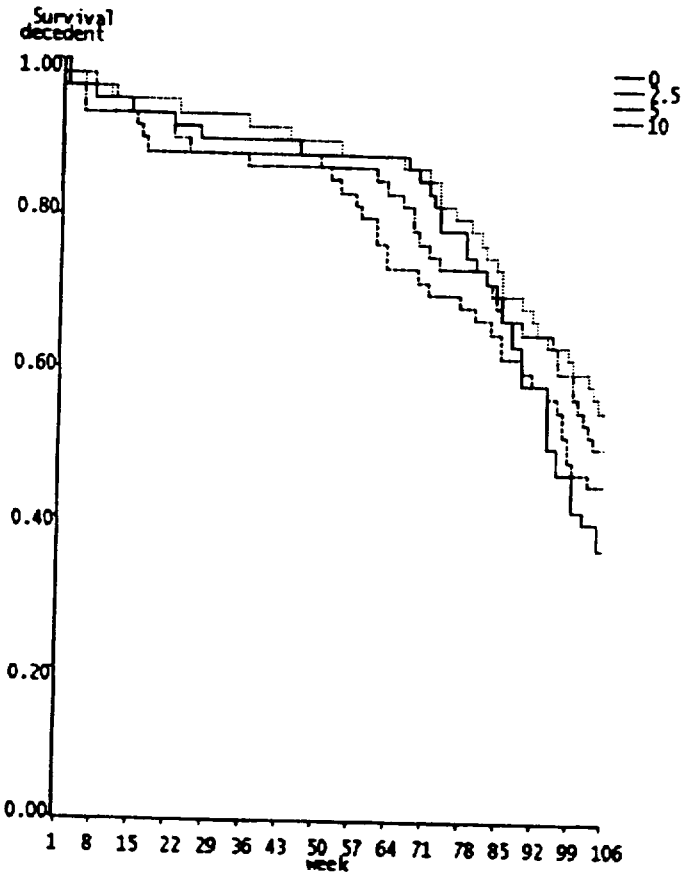


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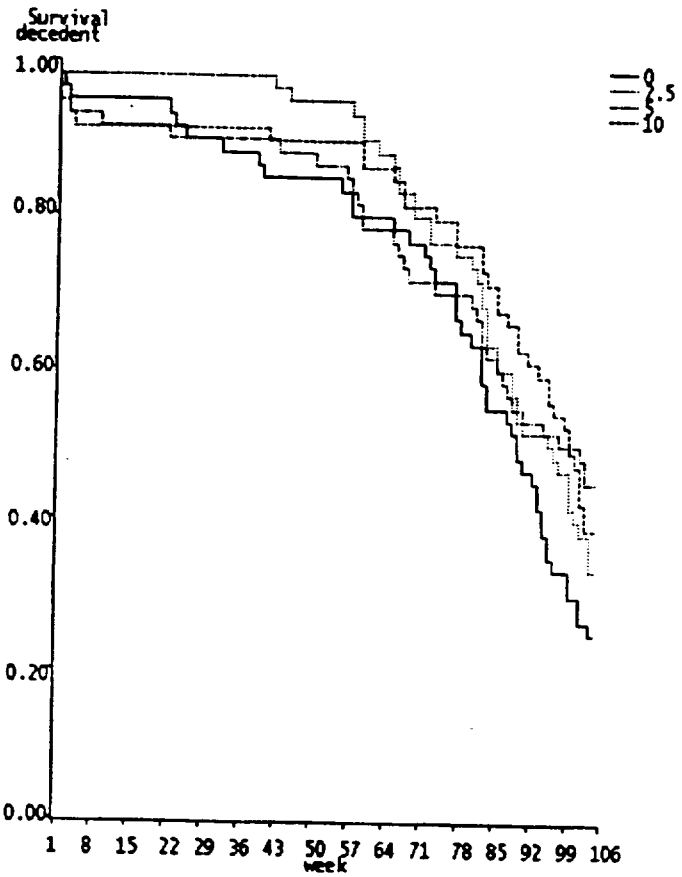
Table 1

STUDY 4199 : 24 MONTH MOUSE ORAL GAVAGE STUDY OF R113675 (GALANTAMINE)
Kaplan-Meier plot of survival

Female



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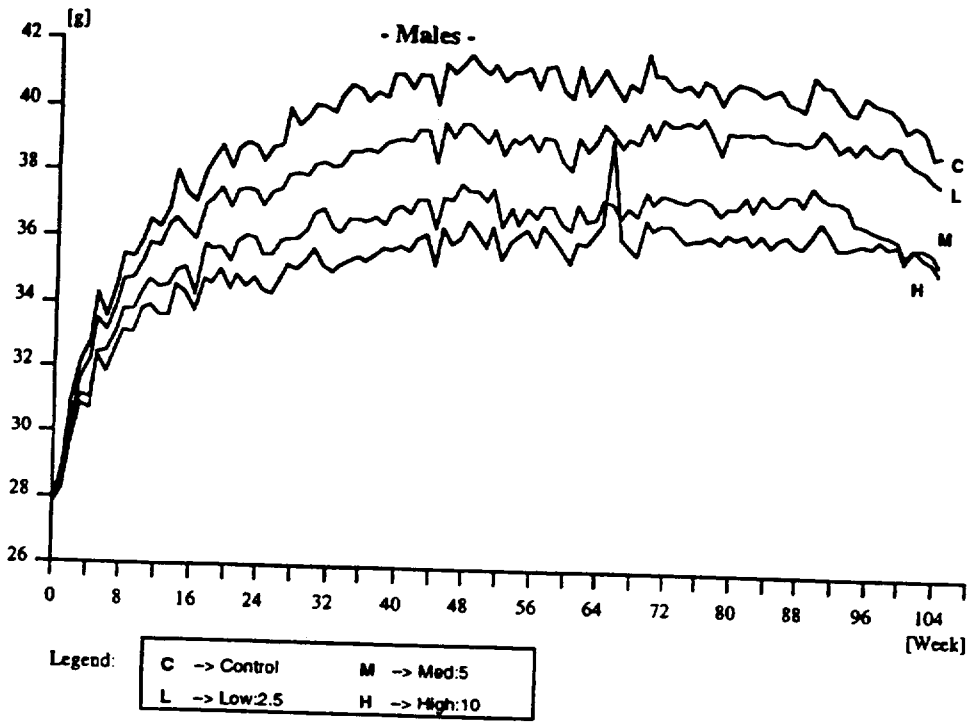
BODY WEIGHT
Mean values per dosage group in g

Experiment: 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE



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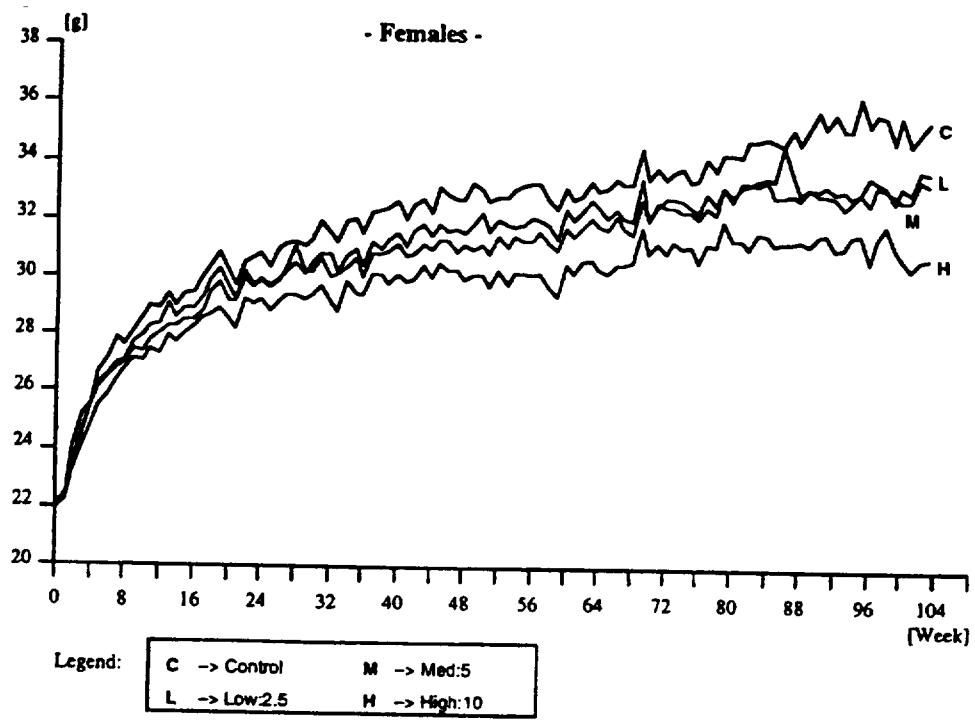
JANSSEN PHARMACEUTICA NV
Department of Toxicology

Experiment: 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE

BODY WEIGHT
Mean values per dosage group in g



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Histopathology Exams

HISTOPATHOLOGY

Histological examination was performed by experienced anatomo-pathologists of the Janssen Research Foundation and a review was carried out by an independent consultant . For histopathological examination, organs and tissues were trimmed, embedded within 3 months after prelevation (with exception of animals Nos. 26, 37, 55, 59, 131, 132, 140, 142, 216, 243, 246, 332, 519, 525, 532, 542, 545, 547, 555, 604, 615, 705, 723, 727, 748, 802, 803, 804, 806, 831, 847), sectioned, stained or others as needed) and mounted by a procedure as much standardized as possible. The technical preparation of the organs and tissues was carried out at .

The following organs and tissues were examined as planned in the protocol:

Control and all dosed animals

- adrenal glands
- gall bladder
- kidneys
- liver
- lungs
- lymph node(s) (mesenteric)
- mammary gland
- ovaries
- pancreas
- pituitary gland
- salivary gland (mandibular)
- spleen
- testes and epididymides
- thymus
- uterus
- vagina
- any organ or tissue, suspected for neoplasm and all gross lesions

Control and high dosed animals

- bone (sternum and stifle joint) with bone marrow
- brain
- esophagus
- heart
- prostate
- seminal vesicles and coagulating glands
- stomach (forestomach, glandular stomach)
- thyroid glands and parathyroid tissue
- trachea
- urinary bladder

A limited number of tissues from mice which died during the study could not be evaluated histologically because of autolysis. No single animal was completely lost for histological examination because of too far an advanced autolysis.

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EXPERIMENT: 4199
24-Month Carcinogenicity Study
B113675 - CR/GAV - MOUSE

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

Organ or tissue : tumor	Males			
	Dosage group (mg/kg)			
	Control	Low:2.5	Medium:5	High:10
Adrenal glands : Adenoma, cortical	2 / 60	0 / 60	0 / 60	0 / 60
Adrenal glands : Phaeochromocytoma, benign	0 / 60	0 / 60	1 / 60	0 / 60
Bone marrow : Hemangioma	1 / 60	0 / 60	0 / 60	0 / 60
Brain : Meningioma, malignant	0 / 60	1 / 60	0 / 60	0 / 60
Coagulating glands : Adenoma	0 / 60	0 / 60	0 / 60	1 / 60
Hematopoietic system : tumor	5 / 60	4 / 60	1 / 60	2 / 60
- Histiocytic sarcoma	1 / 60	2 / 60	0 / 60	0 / 60
- Lymphoid neoplasia	4 / 60	2 / 60	1 / 60	1 / 60
- Lymphoma	3 / 60	1 / 60	1 / 60	1 / 60
- Lymphoma, benign	0 / 60	1 / 60	0 / 60	0 / 60
- Lymphoma, malignant	3 / 60	0 / 60	1 / 60	1 / 60
- Lymphoid leukemia	1 / 60	1 / 60	0 / 60	0 / 60
- Myeloid leukemia	0 / 60	0 / 60	0 / 60	1 / 60
Kidneys : Adenoma	0 / 60	1 / 60	1 / 60	0 / 60
Liver : Hemangioma	1 / 60	0 / 60	2 / 60	0 / 60
Liver : Hepatocytic neoplasia	18 / 60	15 / 60	12 / 60	10 / 60
- Hepatocellular adenoma	12 / 60	15 / 60	8 / 60	7 / 60
- Hepatocarcinoma	7 / 60	1 / 60	7 / 60	3 / 60
Lungs : Primary lung tumor	17 / 60	19 / 60	16 / 60	12 / 60
- Primary lung tumor, adenoma	10 / 60	15 / 60	11 / 60	9 / 60
- Primary lung tumor, adenocarcinoma	7 / 60	4 / 60	6 / 60	4 / 60
Mouth : Papilloma	0 / 60	1 / 60	0 / 60	0 / 60
Pancreas : Endocrine adenoma	1 / 60	0 / 60	0 / 60	0 / 59
Pituitary gland : Adenoma	0 / 59	1 / 59	1 / 59	0 / 60
Skeletal muscle : Hemangiosarcoma	0 / 60	1 / 60	0 / 60	0 / 60
Soft tissue : Malignant neoplasia	1 / 60	0 / 60	0 / 60	0 / 60
- Neurofibrosarcoma	1 / 60	0 / 60	0 / 60	0 / 60
Spleen : Vascular neoplasia	3 / 60	0 / 60	1 / 60	0 / 60
- Hemangioma	1 / 60	0 / 60	0 / 60	0 / 60
- Hemangiosarcoma	2 / 60	0 / 60	1 / 60	0 / 60
Testes : Hemangioma	0 / 60	1 / 60	1 / 60	0 / 60
Testes : Leydig cell tumor, benign	2 / 60	3 / 60	2 / 60	1 / 60
Testes : Schwannoma, benign	0 / 60	1 / 60	0 / 60	0 / 60
Thyroid glands : Follicular adenoma	1 / 60	0 / 60	0 / 60	1 / 60

Significance versus Control computed by the Fisher Exact Test (one tailed)

24 h

HISTOPATHOLOGY : TUMORS
Incidence per dosage group

EXPERIMENT: 6199
24-Month Carcinogenicity Study
B113675 - OR/GAV - MOUSE

Organ or tissue : tumor	Females			
	Dosage group (mg/kg)			
	Control	Low:2.5	Medium:5	High:10
Adrenal glands : Adenoma, spindle cell	1 / 60	0 / 60	0 / 60	0 / 58
Adrenal glands : Phaeochromocytoma, benign	1 / 60	0 / 60	1 / 60	1 / 58
Bone : Osteoid tumor	0 / 60	0 / 60	1 / 60	1 / 59
- Osteoma	0 / 60	0 / 60	1 / 60	0 / 59
- Osteosarcoma	0 / 60	0 / 60	0 / 60	1 / 59
Bone marrow : Hemangioma	0 / 60	0 / 60	0 / 60	1 / 59
Ear : Chondrosarcoma	0 / 60	0 / 60	0 / 60	1 / 59
Female genital tract :				
- Ovarian tumours :	2 / 59	4 / 58	1 / 60	3 / 58
- Benign epithelial tumours : Adenoma	1 / 59	1 / 58	1 / 60	1 / 58
- Sex cord - stromal tumours	1 / 59	1 / 58	1 / 60	0 / 58
- Granulosa-theca cell tumor	1 / 59	1 / 58	0 / 60	0 / 58
- Granulosa-theca cell tumor, benign	0 / 59	0 / 58	1 / 60	0 / 58
- Granulosa-theca cell tumor, malignant	0 / 59	0 / 58	0 / 60	1 / 58
- Sertoli cell tumor, benign				
- Tumours of oviduct-uterus and uterine cervix-vagina :	3 / 60	1 / 60	0 / 60	1 / 58
- Epithelial tumours	2 / 60	0 / 60	0 / 60	0 / 58
- Benign glandular polyp	1 / 60	1 / 60	0 / 60	1 / 58
- Malignant (adeno)carcinoma	8 / 60	7 / 60	8 / 60	5 / 58
- Mesenchymal tumours	6 / 60	6 / 60	7 / 60	5 / 58
- Benign mesenchymal tumours	4 / 60	5 / 60	3 / 60	3 / 58
- Stromal polyp	2 / 60	1 / 60	4 / 60	2 / 58
- Fibrous and smooth muscle tumours	2 / 60	0 / 60	3 / 60	0 / 58
- Fibroleiomyoma	0 / 60	0 / 60	1 / 60	2 / 58
- Leiomyoma	0 / 60	1 / 60	0 / 60	0 / 58
- Myxofibroma	2 / 60	2 / 60	1 / 60	0 / 58
- Malignant mesenchymal tumours	2 / 60	2 / 60	1 / 60	0 / 58
- Fibrous and smooth muscle tumours	0 / 60	1 / 60	1 / 60	0 / 58
- Fibroleiomyosarcoma	2 / 60	1 / 60	0 / 60	0 / 58
- (stromal) Sarcoma	13 / 60	10 / 60	8 / 60	10 / 59
Hematopoietic system : tumor	6 / 60	5 / 60	2 / 60	6 / 59
- Histiocytic sarcoma	7 / 60	4 / 60	5 / 60	5 / 59
- Lymphoid neoplasia	5 / 60	2 / 60	3 / 60	3 / 59
- Lymphoma, malignant	2 / 60	2 / 60	2 / 60	2 / 59
- Lymphoid leukemia	1 / 60	1 / 60	0 / 60	0 / 59
- Myeloid leukemia	0 / 60	0 / 60	1 / 60	0 / 59
- Erythroleukemia	1 / 60	1 / 60	0 / 60	0 / 59
Lacrimal gland : Adenoma	1 / 60	1 / 60	2 / 60	0 / 59
Liver : Hemangioma	4 / 60	3 / 60	2 / 60	1 / 59
Liver : Hepatocytic neoplasia	1 / 60	0 / 60	0 / 60	0 / 59
- Hepatoblastoma	3 / 60	3 / 60	2 / 60	1 / 59
- Hepatocellular adenoma	1 / 60	0 / 60	0 / 60	0 / 59
- Hepatocarcinoma	11 / 60	7 / 60	9 / 60	8 / 59
Lungs : Primary lung tumor	7 / 60	7 / 60	8 / 60	6 / 59
- Primary lung tumor, adenoma	5 / 60	1 / 60	1 / 60	2 / 59
- Primary lung tumor, adenocarcinoma	1 / 59	0 / 60	0 / 60	0 / 59
Mammary gland : Adenoma	0 / 60	0 / 60	0 / 58	1 / 57
Pancreas : Endocrine adenoma	3 / 57	0 / 59	2 / 56	1 / 56
Pituitary gland : Adenoma	0 / 60	0 / 60	1 / 60	0 / 59
Small intestine : Adenoma	0 / 60	0 / 60	1 / 60	0 / 59
Small intestine : Hemangioendothelial sarcoma	0 / 60	0 / 60	1 / 60	1 / 59
Soft tissue : Benign neoplasia	0 / 60	0 / 60	0 / 60	1 / 59
- Fibrohistiocytoma, benign	0 / 60	0 / 60	1 / 60	0 / 59
- Schwannoma, benign	2 / 60	2 / 60	2 / 60	1 / 59
Soft tissue : Malignant neoplasia	1 / 60	0 / 60	1 / 60	0 / 59
- Hemangiosarcoma	1 / 60	2 / 60	1 / 60	1 / 59
- Sarcoma	1 / 60	0 / 60	0 / 60	0 / 58
Spleen : Vascular neoplasia	1 / 60	0 / 60	0 / 60	0 / 58
- Hemangioma	1 / 60	0 / 60	0 / 60	1 / 59
Thyroid glands : Follicular adenoma	0 / 60	1 / 60	0 / 60	0 / 59
Urinary bladder : Papilloma, transitional cell	1 / 60	0 / 60	0 / 60	0 / 59
Urinary bladder : Sarcoma				

Significance versus Control computed by the Fisher Exact Test (one tailed)

EXPERIMENT : 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE

TUMOR BEARING MALES

Lunar Month	Control (b)	Low:2.5 (b)	Medium:5 (b)	High:10 (b)	Trend	Variance	z-value	p-value (1-tailed)
			Age adjusted test for positive dose-related trend (a)					
			Animals bearing FATAL tumor(s)					
14	0 / 53	1 / 54	0 / 52	0 / 51	-0.481	1.240	-0.432	
16	0 / 53	0 / 53	0 / 52	2 / 48	3.078	2.446	1.968	
17	1 / 53	0 / 53	0 / 50	0 / 44	-1.425	1.214	-1.293	
18	0 / 52	0 / 52	0 / 47	1 / 44	1.574	1.229	1.420	
19	0 / 49	1 / 51	0 / 45	0 / 42	-0.428	1.218	-0.388	
20	0 / 47	1 / 48	0 / 44	1 / 42	1.105	2.448	0.706	
21	0 / 44	1 / 47	0 / 44	0 / 40	-0.457	1.208	-0.416	
22	2 / 42	1 / 44	0 / 41	1 / 39	-1.855	4.809	-0.846	
23	1 / 38	1 / 42	0 / 40	0 / 37	-1.968	2.395	-1.272	
24	6 / 35	0 / 39	2 / 39	0 / 35	-8.000	9.112	-2.650	
25	1 / 28	1 / 38	1 / 36	2 / 33	1.259	5.585	0.533	
26	2 / 25	0 / 36	1 / 33	0 / 28	-2.574	3.299	-1.417	
All (c)	13 / 60	7 / 60	4 / 60	7 / 60	-10.172	36.204	-1.691	0.955
			Animals bearing only INCIDENTAL tumor(s)					
1 - 10	0 / 6	0 / 5	0 / 8	0 / 7	0.000	0.000	0.000	
11 - 18	1 / 4	1 / 3	2 / 7	0 / 8	-2.455	4.144	-1.206	
19 - 25	7 / 14	2 / 9	4 / 9	3 / 10	-2.714	13.925	-0.727	
26	0 / 1	3 / 3	1 / 2	0 / 1	-0.714	1.633	-0.559	
Terminal	17 / 22	24 / 33	17 / 30	13 / 27	-13.304	29.428	-2.452	
All (c)	25 / 47	30 / 53	24 / 56	16 / 53	-19.187	49.130	-2.737	0.997
			Animals bearing FATAL and / or INCIDENTAL tumor(s)					
Total (c)	38 / 60	37 / 60	28 / 60	23 / 60	-29.359	85.334	-3.178	0.999

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

EXPERIMENT : 4199
24-Month Carcinogenicity Study
R113675 - OR/GAV - MOUSE

TUMOR BEARING FEMALES

Tumor month	Control (b)	Low:2.5 (b)	Medium:5 (b)	High:10 (b)	Trend	Variance	z-value	p-value (1-tailed)
			Age adjusted test for positive dose-related trend (a)					
			Animals bearing FATAL tumor(s)					
15	1 / 50	1 / 57	1 / 51	0 / 53	-1.521	3.644	-0.797	
17	2 / 48	0 / 53	1 / 47	0 / 51	-2.523	3.697	-1.312	
18	1 / 46	0 / 50	0 / 43	0 / 48	-1.497	1.255	-1.336	
19	0 / 44	0 / 46	1 / 43	0 / 48	0.475	1.266	0.422	
20	2 / 43	0 / 46	1 / 42	1 / 47	-1.090	4.957	-0.490	
21	2 / 38	1 / 44	2 / 41	2 / 45	0.125	8.336	0.043	
22	2 / 33	1 / 38	1 / 37	0 / 42	-3.347	4.870	-1.517	
23	2 / 31	2 / 34	1 / 33	0 / 39	-3.920	6.138	-1.582	
24	2 / 27	0 / 31	0 / 32	2 / 36	-0.444	4.832	-0.202	
25	2 / 20	2 / 29	1 / 31	2 / 32	-1.688	7.613	-0.612	
26	2 / 18	1 / 24	0 / 30	3 / 28	-0.080	6.481	-0.031	
All					-15.509	53.090	-2.129	0.983
(c)	18 / 60	8 / 60	9 / 60	10 / 59				
			Animals bearing only INCIDENTAL tumor(s)					
1 - 9	0 / 7	0 / 1	0 / 6	0 / 5	0.000	0.000	0.000	
10 - 17	1 / 4	0 / 8	2 / 9	0 / 6	-0.889	2.697	-0.541	
18 - 19	1 / 2	0 / 4	0 / 0	0 / 1	-1.000	0.857	-1.080	
20 - 21	3 / 6	1 / 7	0 / 2	0 / 2	-3.000	3.059	-1.715	
22 - 23	0 / 2	0 / 4	2 / 3	3 / 6	3.667	4.222	1.784	
24 - 26	4 / 6	4 / 8	3 / 4	3 / 6	-0.833	7.566	-0.303	
Terminal	11 / 15	14 / 20	16 / 27	14 / 23	-4.529	21.821	-0.970	
All					-6.585	40.222	-1.038	0.850
(c)	20 / 42	19 / 52	23 / 51	20 / 49				
			Animals bearing FATAL and / or INCIDENTAL tumor(s)					
Total					-22.094	93.312	-2.287	0.989
(c)	38 / 60	27 / 60	32 / 60	30 / 59				

(a) Peto monograph, WHO, IARC, Lyon, 1980, pp. 386 - 387, p. 371 , dose levels 0, 1, 2, 3.
(b) Number observed / number at risk
(c) Number of tumor bearing animals / total number of animals

24 k

Galantamine
(day 183 of 2 year study)

R113675/FK2504

Table 5-3: **Mean (n = 2) plasma concentrations (ng/ml) and some pharmacokinetic parameters of galantamine in SPF Albino Swiss satellite mice measured on day 183 of a twenty-four-month carcinogenicity study (Exp. No. 4199) on aqueous solutions of galantamine hydrobromide (R113675) at 2.5, 5 and 10 mg base-eq./kg/day.**

	2.5 mg/kg/day		5 mg/kg/day		10 mg/kg/day[1]	
Time (h)	Males	Females	Males	Females	Males	Females
1	264	179	401[2]	352	1240	670
2	150	33.2[2]	203	168	502	351
4	69.8	26.2	74.0[2]	37.7	217	88.5
6	24.6[2]	20.9	80.7	12.2	129[2]	7.0
10	6.3	< 5.0	13.8	< 5.0	8.7	19.3
C_{max} (ng/ml)	264	179	401	352	1240	670
T_{max} (h)	1	1	1	1	1	1
AUC_{0-t} (ng.h/ml)	715	302	1123	692	2831	1433
$AUC_{0-24\,h}$ (ng.h/ml)	733	359	1155	711	2844	1448

[1] The satellite mice of the high dosage group (10 mg/kg) were not dosed on day 0 of the study. They were dosed at 5 mg/kg from day 1 of the study onwards. From day 14 of the study onwards, the 5-mg/kg dose level was increased up to 7.5 mg/kg. From day 28 of the study onwards, the 7.5-mg/kg dose level was increased up to 10 mg/kg.

[2] n = 1

Galantamine
(3 month study)

Table 5-3: **Mean (n = 2) plasma concentrations (µg/ml) of galantamine (R113675-base) and some pharmacokinetic parameters obtained in SPF albino Swiss mice on day 90 of a three-month subchronic oral toxicity study (Exp. No. 3818) on aqueous solutions of R113675 at 10, 20 and 40 mg base-eq./kg/day. At the 40-mg/kg dose level, all mice died after the first dose administration.**

	10 mg/kg		20 mg/kg		40 mg/kg	
Time (h)	Males	Females	Males	Females	Males	Females
2	0.401	0.226	0.568 [1]	0.729 [1]	NS [2]	NS
4	0.196	0.107	0.346 [1]	0.278 [1]	NS	NS
8	0.038	0.010 [1]	0.105 [1]	0.028 [1]	NS	NS
24	< 0.010	< 0.010	0.010 [1]	< 0.010 [1]	NS	NS
C_{max} (µg/ml)	0.401	0.226	0.568	0.729	-	-
T_{max} (h)	2	2	2	2	-	-
AUC_{0-t} [3] (µg.h/ml)	1.47	0.793	2.38	2.35	-	-
$AUC_{0-24\,h}$ (µg.h/ml)	1.56	0.812	2.75	2.40	-	-

[1] n = 1.
[2] no sample.
[3] t is the time corresponding to the last measurable concentration above the limit of quantification.

24 m

Norgalantamine
(3 month study)

Table 5-4: **Mean (n = 2) plasma concentrations (µg/ml) of *norgalantamine* (R117455-base) and some pharmacokinetic parameters obtained in SPF albino Swiss mice on day 90 of a three-month subchronic oral toxicity study (Exp. No. 3818) on aqueous solutions of R113675 at 10, 20 and 40 mg base-eq./kg/day. At the 40-mg/kg dose level, all mice died after the first dose administration.**

	10 mg/kg		20 mg/kg		40 mg/kg	
Time (h)	Males	Females	Males	Females	Males	Females
2	0.081	0.088	0.129 [2]	0.203 [2]	NS [3]	NS
4	0.041	0.066	0.077 [2]	0.096 [2]	NS	NS
8	0.020 [1]	< 0.020 [2]	0.023 [2]	< 0.020 [2]	NS	NS
24	< 0.020	< 0.020	< 0.020 [2]	< 0.020 [2]	NS	NS
C_{max} (µg/ml)	0.081	0.088	0.129	0.203	-	-
T_{max} (h)	2	2	2	2	-	-
AUC_{0-t} [4] (µg.h/ml)	0.325	0.414	0.535	0.502	-	-
$AUC_{0-24\,h}$ (µg.h/ml)	0.384	0.493	0.614	0.758	-	-

[1] mean of one value below and one above the limit of quantification.
[2] n = 1.
[3] no sample.
[4] t is the time corresponding to the last measurable concentration above the limit of quantification.

24 h