

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 020926**

**PHARMACOLOGY REVIEW(S)**

Sponsor: Geltex Pharmaceuticals Inc, Waltham, MA

**PHARMACOLOGY TEAM LEADER COMMENTS ON LABELING CHANGES REQUESTED  
BY ASSOCIATE DIRECTOR FOR PHARMACOLOGY/TOXICOLOGY**

**DRUG:** RenaGel

**INDICATION:** Control of hyperphosphatemia in patients with end stage renal failure.

**REQUESTS FROM ASSOCIATE DIRECTOR OF PHARM/TOX:**

The following comments were received from the Associate Director for Pharmacology/Toxicology regarding the RenaGel label on October 30, 1998:

1) Why does the labeling under clastogenesis say "a small but statistically..." This is a positive response that is several fold the control and 1/5 the response of the positive control. It should be described as "positive" for chromosomal aberrations in CHO cells.

2) Although I agree that this may be a case for using mg/kg as the dose comparison, it should be clearly described as such in the repro section of the label.

**RESPONSE OF PHARMACOLOGY TEAM LEADER (HFD-510):**

I agree with Dr. DeGeorge's comments.

Regarding point #1, Results from genetic toxicology reports should be listed as positive, negative or equivocal. Descriptive terms such as "weak" or "small" should not be included in the label. Therefore, under the Carcinogenesis, mutagenesis, impairment of fertility section, the statement regarding the results of the CHO assay should be revised as follows:

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Regarding point #2, The basis of comparison to human exposures should be specified in the label. Therefore, in the Pregnancy category section, the phrase \_\_\_\_\_ should be added in each parenthetical section describing exposure relative to human dose. Thus, two statements in the Pregnancy section should be:

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**TO BE COMMUNICATED TO SPONSOR:**

For consistency in labeling, the following statements should be modified:

1. Results from genetic toxicology reports should be listed as positive, negative or equivocal. Descriptive terms such as "weak" or "small" should not be included in the label. Therefore, under the Carcinogenesis, mutagenesis, impairment of fertility section, the statement regarding the results of the CHO assay should be revised as follows:

"In an in vitro mammalian cytogenetics test with metabolic activation, sevelamer caused a ~~small~~ **statistically significant** increase in the number of structural chromosome aberrations..."

2. The basis of comparison to human exposures should be specified in the label. Therefore, in the Pregnancy category section, the phrase "based on mg/kg" should be added in each parenthetical section describing exposure relative to human dose. Thus, two statements in the Pregnancy section should be:

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cc: IND Arch  
HFD510  
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**ISI**

Ronald W. Steigerwalt, Ph.D.  
Pharmacology Team Leader

10/30/98

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RENAGEL NDA 20,926

NDA 20,926

Sponsor: Geltex Pharmaceuticals Inc., Waltham, MA  
Date submitted: November 3, 1997  
Drug: RenaGel<sup>®</sup> (proprietary/trade name)  
Sevelamer hydrochloride (generic name, USAN)  
Other names used: RenaStat (previous name), GT16-026A (code name),  
PB-94 (internal name at Chugai Pharmaceuticals, Japan)  
Chemical name: allylamine polymer with 1-chloro-2,3-epoxypropane,  
hydrochloride (IUPAC)  
Category: Phosphate binder  
Indication: Control of hyperphosphatemia in patients with end stage  
renal failure  
Dosage form: Capsule  
Strengths: 403 mg  
Route of administration: Oral  
Maximum clinical dose: 15g/day (300 mg/kg)  
Treatment duration: Indefinite  
Related IND: IND \_\_\_\_\_ RenaGel capsules, Geltex Pharmaceuticals,  
Inc. \_\_\_\_\_  
Meetings: Pre-NDA meeting \_\_\_\_\_

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LIST OF STUDIES

The Nonclinical Pharmacology and Toxicology section of this NDA (section 5) contains three subsections:

Nonclinical Pharmacology (subsection 5.2)

Nonclinical Pharmacokinetics (subsection 5.3)

Nonclinical Toxicology (subsection 5.4)

A list of studies is appended to this review (APPENDIX I)

The draft and revised labeling are attached to this review (APPENDIX II)

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INTRODUCTION

In patients with chronic renal failure control of serum phosphorus (P) concentration is perturbed because of the loss of functional nephrons. When the glomerular filtration rate (GFR) falls, phosphate excretion is reduced and secretion of PTH rises in response to a positive P balance. The increased level of PTH stimulates the excretion of P in the residual nephrons. However, when GFR drops below 25% of normal, the elevated PTH cannot further increase P excretion and hyperphosphatemia develops.

Due to loss of functional renal tissue, calcitriol (1,25-(OH)<sub>2</sub>-vitD<sub>3</sub>) levels also fall, causing Ca malabsorption in the intestine and hypocalcemia. The ensuing hypocalcemia further stimulates PTH secretion and leads to secondary hyperparathyroidism (HPT). The chronic elevation of PTH causes osteitis fibrosa which leads to bone pain and fractures. Limiting P absorption in renal failure is needed to prevent hyperphosphatemia, inhibit PTH secretion and suppress secondary HPT.

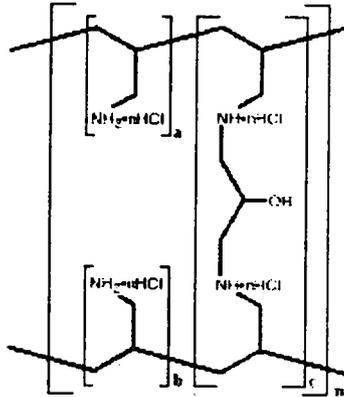
Lowering serum P also produces an increase in serum calcitriol in patients with only moderate renal failure. The calcitriol increases intestinal Ca absorption, causes mild hypercalcemia and suppresses PTH secretion. However, in severe renal failure, exogenous calcitriol must be added to correct for calcitriol deficiency. The exogenous calcitriol administration has side effects of hypercalcemia and hyperphosphatemia. Patients with renal failure require low protein diet therapy. In addition, treatment with calcitriol, other vitamin D analogues and phosphate binders may be indicated. Phosphate binders available are aluminum hydroxide and calcium salts (e.g., calcium acetate, PhosLo<sup>®</sup>). However, the latter have the risk of aluminum toxicity and hypercalcemia with metastatic calcification. Thus, Sponsor has developed a non-aluminum, non-calcium phosphate binder for use in chronic or end stage renal failure (ESRF).

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**CHEMISTRY**

Sevelamer HCl is a crosslinked poly(allylamine hydrochloride) polymer, or a non-absorbed polymeric phosphate binder:

Structure:



Where:

- a, b = number of primary amine groups    a - b = 9
- c = number of crosslinking groups    c = 1
- n = fraction of protonated amines    n = 0.4
- m = large number to indicate extended polymer network

Molecular formula:  $(C_3H_7 \cdot nHCl)_{812z} (C_9H_{18}N_{20} \cdot nHCl)_{94z}$  (z = large number)

Appearance: white to off-white powder

Phosphate binding: \_\_\_\_\_  
 index: \_\_\_\_\_ fold on weight basis \_\_\_\_\_)

Drug product: 403 mg sevelamer hydrochloride, \_\_\_\_\_ stearic acid, \_\_\_\_\_  
 colloidal silicon dioxide

Particle size: \_\_\_\_\_ the rest broadly centered around 230 um, with \_\_\_\_\_

CLINICAL INFORMATION

Two controlled and four uncontrolled clinical efficacy trials were carried out. Primary efficacy endpoint in all patient studies was change in serum phosphorus concentration. Secondary endpoint were serum calcium, PxCa product, PTH, and serum lipid profile. Renagel was found to be efficacious in reducing serum phosphorus, and equally potent as calcium-based phosphate binders. Renagel does not cause hypercalcemia, lowers the CaxP product, reduces serum PTH and lowers serum LDL cholesterol. The effect on cholesterol is due to the binding of cholesterol-derived bile acids and subsequent increase in biliary secretion by Renagel. There was one adverse event with a significant dose trend (cough increase).

The recommended starting dose is 2-4 capsules (403 mg per capsule) with each meal (3x/day). The average dose required in clinical trials was 3-4 capsules/meal, ie, 9-12 capsules/day = 3.6-4.8g/day = 72 - 96 mg/kg/day.

Maximum clinical dose is 15 g/day = 0.3 g/kg/day.

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## NONCLINICAL PHARMACOLOGY

### Primary Efficacy Studies

#### *1. In vitro binding of Renastat to phosphate*

Polymer absorbs phosphate with saturable binding characteristics.

Binding at pH7, at 5mM phosphate concentration (Renagel concentration of 0.1g/20ml solution) was appr. 3 mmolP/gRenagel.

Binding of P to calcium acetate (PhosLoR) was ca. 6 mmoles/g.

#### *2. Studies to evaluate the effects of Renastat on fecal phosphorus excretion in normal rats.*

##### Methods

Wistar rats, fed ad libitum with renastat/cellulose diet for 3 days. Feces were then collected for 48h. Chow content: P: 0.28%. Renastat or cellulose: 11.7%.

##### Results

Excretion:

Controls 18 mg P/g feces

Renastat 34 mg P/g feces

(16 mg P/g feces excreted in form bound to Renastat)

Thus, Renastat increases fecal P excretion.

#### *3. A study to evaluate the effects of Renastat and calcium carbonate on fecal phosphorus excretion in normal rats.*

##### Methods

Wistar rats, fed ad libitum with renastat/cellulose diet for 3 days. Feces were then collected for 72. Diet content P: 0.28%, Renastat, calcium carbonate or cellulose: 11.7%.

##### Results

Excretion: controls 15 mg P/g feces vs Renastat 27 mg/g vs calcium carbonate 19 mg/g.

Increase in fecal P excretion (in %):

Renastat 77%

CaCO<sub>3</sub> 23%

Thus, Renastat increases fecal P excretion more efficaciously than CaCO<sub>3</sub> in this system.

#### *4. A pilot study to evaluate the test article in a model of renal secondary hyperparathyroidism and hyperphosphatemia in rats.*

##### Methods:

Partially nephrectomized rat model: right kidney removed, left renal artery ligated so that targeted 33% of left kidney tissue was necrotic. Rats in experimental group (A) received successive diets with

Day -18 to 1 0.7%P,

Day 1 to 13 1.4% P,

Day 14 to 23 0.7% P-5% Renagel,

Day 24 to 28 0.54% P-7.5% Renagel,

Day 29 0.7%P

Day 29 to 34 1.4% P,

Day 35 to 48 0.39% P-10% Renagel.

Control group (A) received Cellulose instead of Renagel. Model is expected to respond to P challenge with hyperphosphatemia/hypocalcemia, and/or increased PTH.

#### Results

Surgery - Left kidney mass appeared reduced by \_\_\_\_\_ on Day49. Thus, remaining kidney mass (% of total) was \_\_\_\_\_

BW - BW gain slightly reduced in Renagel group

Serum chemistry -

BUN and creatinine increased over time in both groups, not significantly different from each other. There was no significant effect of dietary P or Renagel on serum P.

Serum Cl was increased significantly by Renagel.

Serum PTH was decreased (by ca.50%) by 10% Renagel combined with 0.39%P, not affected by <10%Renagel combined with >0.39% P.

Urinalysis -

Renagel increased urine Ca and Cl concentration. Diet P level appeared inversely related to urinary Cl and Ca.

#### Conclusion

Model was not able to evaluate efficacy of test article in preventing hyperphosphatemia, since this did not develop. Model did show reduction in serum PTH by Renagel. Taken together, model was not very convincing.

### ***5. The effects of Renastat on the mass balance of phosphorus excretion in normal rats fed a high phosphorus diet***

#### Methods

Female CD rats fed ad libitum with renastat/cellulose diet for 4 days. Feces were then collected for 72h. Diet: 0.8% P plus 8% or 12% Renastat (control 12% cellulose).

#### Results

Ratio fecal:urinary P was 0.17 (controls) vs. 0.24 (8% Renastat) vs. 0.34 (10% Renastat).

Urinary P excretion (mg/3 days) was 1192 (controls) vs. 698 (8%R) vs 450 (12%R).

Fecal P excretion was 202 vs. 168 vs. 153, with no statistically significant differences.

Total P excretion: 1394 vs. 866 vs. 603. Thus, Renastat decreased P intake or interfered with fecal P determination. Results consistent with inhibition of P absorption by Renastat.

### ***6. The effect of Renagel on urinary phosphorus excretion in normal rats.***

#### ***Published article***

#### Methods

Female SD rats fed ad libitum for 4 days. Urine was collected for 48h (day 3+4) or 24h (day 4) Diet contents: 0.8% P, and 0, 0.5, 1, 3, 9% Renagel.

#### Results

In vitro binding: Polymer (0.1g/20ml) binds 2.6 mmoles phosphate/g polymer, at estimated physiological phosphate concentration of 5 mM. Saturated capacity is in order of 7 mmoles/g (in >50 mM phosphate solution). Binding peaks (is maximal) around pH 7. Explanation of pH dependence: (A) Below pH 7 amines in polymer are protonated and thus in binding state. Above pH 7 polymeric amines convert to uncharged form, limiting potential binding sites. (B) Below pH 7, phosphate in

solution is primarily  $\text{H}_2\text{PO}_4^-$  (monoanion), while above pH 7 it is  $\text{HPO}_4^{2-}$  (dianion), which may be bound stronger to the polymer.

Total urinary P excretion: 300 mg (controls). Renagel (0.5, 1, 3, 9%) decreased urinary P excretion by 57%, 66%, 88%, 96%. Result indicates inhibition of P absorption by Renagel.

Smaller size Renagel particles cause larger inhibition of urinary P excretion. Thus, particle size inversely related to efficacy.

### **Secondary Efficacy Studies**

*The effects of Renagel on bile acid mass excretion in fat-fed hamsters.*

**Background:** Renagel can bind bile acids. Because absorption of cholesterol from the gut is highly dependent on the presence of bile acids, Renagel can inhibit cholesterol absorption and lower serum cholesterol levels.

**Results:**

Renagel	Fecal bile acid content (uM/g)
0% (controls)	0.85
0.2%	1.8
0.4%	4
0.6%	5.7

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Thus, Renagel produces an increase in bile acid excretion

### **Safety Pharmacology Studies**

At oral doses up to 2000 mg/kg PB-94 had no effect on behavioral, neurological or autonomic profiles in male mice.

Oral doses up to 2000 mg/kg had also no effect on spontaneous motor activity or body temperature, and no anesthetic potential, anticonvulsive or analgesic actions in male mice.

Intragastric or intraduodenal doses of 2000 mg/kg did not affect respiratory or cardiovascular systems in anaesthetized male beagle dogs.

Test compound had no effect on the spontaneous contraction in the guinea pig isolated ileum or rat gastric fundus preparations at 0.05 and 0.5 mg/ml. However, 5mg/ml PB-94 increased the resting tension of ileum and gastric fundus. Supernatant from 5 mg/ml suspension also increased resting tension, somewhat less than suspension itself. PB-94 had no effect on tension in the everted ileum preparation at concentrations up to 5 mg/ml. It also had no effect on contractile responses of ileum or gastric fundus to ACh, histamine,  $\text{BaCl}_2$ , 5-HT. Results suggest that a soluble component in the PB-94 suspension (HCl?) causes contraction when applied to GI serosa. No control was done to confirm suggestion.

### **Drug Interaction Studies (Vol. 1.11)**

Oral administration of single doses of Renagel (100 mg/kg) to male Beagle dogs had no significant effects on the parameters  $T_{\max}$ ,  $C_{\max}$  and AUC of drug after simultaneous oral

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dosing with thyroxin, digoxin, estrone, propranolol, tetracycline, verapamil, quinidine, valproic acid, vit D3, or warfarin. However,  $T_{max}$  values for estrone and propranolol were increased, although statistically non-significant (3.8x, 1.5x). The increase for estrone was biologically significant:  $T_{max}$  in control animals was  $1.3 \pm 1.2h$  (0.5-4h), in Renagel group  $5.0 \pm 4.2h$  (0.5-12h).

Dog data (single dose of drug X + simultaneous single dose of 100 mg/kg Renagel)

Test article	drug dose (mg/kg)	Tmax (h)	Cmax (ug eq/ml)	AUC (ug eq.h/ml)	AUC(+R)/AUC(-R)
digoxin -/+R	0.023	3.1/2.6	3.9/3.1	39/37	.95
estrone -/+R	0.1	1.3/5	21.7/22.8	187/271	1.4
propranolol -/+R	1	2.8/4.2	1.2/1.1	21/21	1.0
thyroxine -/+R	0.009	7.9/8.6	5.6/5.2	137/139	1.01
tetracycline -/+R	23.7	1.2/1.6	1.5/1.5	31/26	.84
valproic acid -/+R	14.1	2/2.4	27/28	434/429	.99
quinidine -/+R	14.3	2.1/3.4	5.1/4.6	56/54	.96
verapamil -/+R	9.72	7.5/5	4/4	116/164	.70
Vit D3 -/+R	0.10	3.4/2.9	241/181	3289/3064	.93
warfarin -/+R	0.52	6.9/7.9	1.9/2	45/45	1.0

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**NONCLINICAL PHARMACOKINETICS**

**1. Degradation of PB-94 in gastrointestinal contents**

**Methods:** Dual-labeled ( $^3\text{H}$ )[ $^{14}\text{C}$ ]PB-94 was incubated with buffer, or with the suspended GI contents of 3 rats, under sterile, anaerobic or aerobic conditions. Eluted radioactivity in the supernatant of centrifuged suspensions was determined.

$^{14}\text{C}$  label was inserted in crosslinking chain (epichlorohydrine moiety),  $^3\text{H}$  label in longitudinal backbone (polyallylamine moiety) of polymer. Method of radiolabeling or of preparation of radiolabeled substance not given. Sponsor/testing facility \_\_\_\_\_

**Results:**

**Data**

Table 1. Proportion of Radioactivity in Supernatant and Its Increase after Incubation of [ $^{14}\text{C}$ ] PB-94 with Gastrointestinal Contents

Suspension of Contents	Radioactivity in Supernatant (%)			
	0h	5h	24h	48h
Anaerobic (Increase)	0.12 ± 0.00 0.00	0.18 ± 0.00 0.05	0.35 ± 0.05 0.22	0.44 ± 0.04 0.31
Aerobic (Increase)	0.13 ± 0.03 0.00	0.18 ± 0.01 0.05	0.23 ± 0.00 0.10	0.24 ± 0.01 0.12
Sterile (Increase)	0.11 ± 0.03 0.00	0.17 ± 0.01 0.05	0.25 ± 0.00 0.14	0.23 ± 0.01 0.13
Buffer Solution (Increase)	0.16 ± 0.01 0.00	0.19 ± 0.00 0.01	0.21 ± 0.01 0.03	0.21 ± 0.00 0.05

Upper row represents the mean of three ± S.D. values. Lower row represents the difference from the mean at 0h.

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Table 2. Proportion of Radioactivity in Supernatant and Its Increase after Incubation of [ $^3\text{H}$ ] PB-94 with Gastrointestinal Contents

Suspension of Contents	Radioactivity in Supernatant (%)			
	0h	5h	24h	48h
Anaerobic (Increase)	0.14 ± 0.01 0.00	0.37 ± 0.04 0.21	0.47 ± 0.03 0.31	0.52 ± 0.03 0.36
Aerobic (Increase)	0.15 ± 0.02 0.00	0.31 ± 0.01 0.15	0.26 ± 0.03 0.11	0.45 ± 0.01 0.30
Sterile (Increase)	0.13 ± 0.01 0.00	0.22 ± 0.03 0.13	0.24 ± 0.02 0.11	0.31 ± 0.01 0.18
Buffer Solution (Increase)	0.18 ± 0.01 0.00	0.13 ± 0.01 0.03	0.17 ± 0.03 0.17	0.18 ± 0.03 0.16

Upper row represents the mean of three ± S.D. Lower row represents the difference from the mean at 0h.

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**Conclusion:**

When incubated in rat gastrointestinal contents, PB-94 is degraded to a very small extent into soluble fragments containing nonlinked or linked parts of longitudinal and

crosslinking chains. The degradation is enhanced by non-live gastrointestinal contents and by gastrointestinal microflora, the latter through both aerobic and anaerobic processes. Maximal degradation is <0.5% in 48h.

**2. Disposition and excretion of cross-linked polymer hydrogel (CPH) [<sup>14</sup>C]GT16-026A in rats.** January 1994. Lot nr. 17,012.

Methods

SD male rats, fasted, single dose of 100 mg/kg <sup>14</sup>C-Renagel, oral gavage. Rats were fed immediately after dosing. Samples of urine/feces/blood/tissues were taken at specified intervals up to 96h (3 rats killed at 4, 8, 12, 24, 32, 48, 72h for blood and tissue collection, 6 rats at 96h for total recovery). Unbound radioactivity in test article measured by washing with 3 solvents. Sponsor (Geltex Inc) supplied <sup>14</sup>C-labeled test article to contract lab). Method of radiolabeling not given.

Results

Washing removed 0.01% of radioactivity (1.5mg/15g), ie. 0.01% of dose is unbound.

Fecal excretion (% of dose)

12h	81.7%
24h	94.0%
48h	94.7%
96h	94.7%

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Radioactivity in GI tract peaked at 4h time point in all GI parts (stomach, cecum, small and large intestine).

Total GI tract activity:

4h	96.7
8h	39.4
12h	14.7
24h	1.2
32h	2.5
48h	0.3
72h	0.06

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Recovery at 96h (% of dose)

feces	94.7%
urine	<0.08%
cagewash	<0.05%
GI contents	<0.05%

## Tissue radioactivity at 4h-96h postdose (LOQ 0.01 ug eq/g)

Organ	Tmax	Cmax (ug eq/g)	Cmax (% of dose)	Period in which radioactivity was present
liver	8	0.22	0.013	4-96h
spleen	8	0.17	<0.005	4-72h
kidney	4	0.86	0.007	4-96h
blood	8-12	0.04	0.003	8-96h

Report states "The highest mean fraction of dose observed in the liver or kidney was 0.01%; this amount corresponds to the percentage of unbound radioactivity."

This statement is misleading: if 0.01% of dose is present in liver *and* kidney at eg 4h this adds up to 0.02%. Also, other organs would contribute too, thus % of dose in total tissues is larger than unbound radioactivity.

Conclusion

Fecal excretion of  $^{14}\text{C}$ -renagel is at least 94% of dose. Urinary excretion <0.1% of dose. Combined maximal radioactivity in liver, kidney, spleen, blood <0.03% of dose. Thus, absorption is extremely low.

### 3. Pharmacokinetics studies of PB-94 (II): Absorption and distribution in male rats after a single oral administration of [ $^{14}\text{C}$ ]PB-94

Methods

SD male rats, fasted, single dose of 250mg/kg  $^{14}\text{C}$ -PB-94, oral gavage, fed immediately after dose administration. Samples of blood and tissues taken at specified intervals up to 72h; total of 31 tissues, GI contents and carcass evaluated. Whole body autoradiography at 4 time points, up to 72h.

Sponsor \_\_\_\_\_ supplied  $^{14}\text{C}$ -labeled test article \_\_\_\_\_ to testing facility \_\_\_\_\_ Labeled compound was synthesized using \_\_\_\_\_ as crosslinker. Addendum report on synthesis and evaluation of  $^{14}\text{C}$ -PB-94 included. Particle size was as specified \_\_\_\_\_ Specific radioactivity of test substance, and radiochemical purity of test substance and dosing formulation were determined. Radiochemical purity of test substance was determined as % radioactivity in centrifugate of solution of \_\_\_\_\_ in 10ml water.

Results

Specific radioactivity test substance: 130 kBq/mg

Radiochemical purity test substance: 99.96%

Radiochemical purity dosing formulation: 99.96%.

From addendum report:

Water-soluble radioactivity: 0.031%

Dialytic components  $M_w < 25000$ : \_\_\_\_\_

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Radioactivity in blood:

<0.14 ug eq/ml (=detection limit) at all sampling times

Whole body autoradiography:

6-12h: radioactivity in gastric and intestinal contents, inhomogeneous distribution

24h-48h: activity in intestinal contents

72h: no activity at any site

Radioactivity in tissues:

	tissue	activity (ugeq/g)	tissue	% of dose
6h	cecum	9.64		NC
	large intestine	3.82		NC
	Harderian gland	0.59		<0.005
	liver	0.55		0.01
	brown fat, mandibular gland, stomach, small intestine, kidney, pancreas, spleen	0.10-0.29	mandibular gland, stomach, kidney, pancreas, spleen	<0.005
	brown fat, small intestine			NC
	carcass			0.05
	content of stomach			0.06
	content of small intestine			0.75
	content of cecum			18.1
	content of large intestine			41.3
	content GI tract			60.2
	other tissues	BDL		BDL
12h	large intestine	1.63		NC
	liver	0.4		0.01
	Harderian	0.67		<0.005
	cecum	0.51		NC
	brown fat, stomach, kidney, small intestine, spleen, mandibular, thymus	0.08-0.25	stomach, kidney, spleen, mandibular, thymus	<0.005
	carcass		brown fat, small intestine	NC
	content of cecum			0.12
	content of large intestine			3.72
	content GI tract			5.09
				8.81
24h	Harderian gland	0.4		<0.005
	liver, brown fat, cecum, stomach	0.09-0.26	liver brown fat, cecum stomach	0.01 NC <0.005
	carcass			0.02
	content GI tract (cecum +large intestine)			0.19
48h	brown fat, liver, Harderian	0.14-0.21	liver, Harderian brown fat	<0.005 NC
	carcass			0.013
	content GI tract			<0.02

72h	brown fat, liver, fat  carcass content GI tract	0.10-0.21	liver fat brown fat	<0.005 <0.005 NC 0.02 <0.02
6-72h	other tissues (incl. blood, plasma)	BDL	other tissues	BDL

BDL = below detection limit (0.06-0.43 ug eq/g, or 0.00002-0.015%)

NC= not calculated

### Conclusion

Radioactivity (% of dose) after single dose in rat

	6h	12h	24h	48h	72h
content of: stomach + small intestine	0.81	<0.01	<0.01	<0.01	<0.01
content of: cecum + large intestine	59.4	8.81	0.19	<0.01	<0.01
Total content GI tract	60.2	8.81	0.19	<0.02	<0.02
liver	0.01	0.01	0.01	<0.005	<0.005
carcass	0.05	0.12	0.02	0.01	0.02
GI tissues (small intestine, large intestine, cecum)	NC	NC	NC	NC	NC
brown fat	NC	NC	NC	NC	NC
blood	BDL	BDL	BDL	BDL	BDL
all other tissues	BDL	BDL	BDL	BDL	BDL

Distribution to GI tissues and brown fat not calculated (NC), others below detection level (BDL)

Of the tissue radioactivities that were calculated the largest activity at any time is in the carcass at 12h (0.12% of dose). GI tissue and brown fat activities were not calculated, but assuming their respective weights are  $\leq$  liver weight their combined activity is maximal  $\leq$ 0.3% (at 6h). On a similar basis, the largest activities in all tissues combined is maximal <0.4% (at 6h), and <0.21% (at 12h).

#### **4A. Pharmacokinetics studies of PB-94 (III): Excretion in male rats after a single oral administration of [<sup>14</sup>C]PB-94**

##### Methods

SD male rats, fasted, single dose of 250mg/kg <sup>14</sup>C-PB-94, oral gavage, fed immediately after dose administration. First group: Urine, feces, expired air collected from 0-12, 12-24, 24-48, 48-72h after administration. Second group: Bile, urine, feces collected from 0-12, 12-24, 24-48 h post dosing.

Sponsor \_\_\_\_\_ supplied <sup>14</sup>C-labeled test article \_\_\_\_\_ to testing facility \_\_\_\_\_  
Labeled compound was synthesized using \_\_\_\_\_ as crosslinker. Radiochemical purity of test substance and dosing formulation were determined. Radiochemical purity of test substance = % radioactivity in centrifugate of solution of [<sup>14</sup>C]PB-94 in water = 100%-radioactivity in supernatant.

##### Results

Radiochemical purity test substance: \_\_\_\_\_

Radiochemical purity dosing formulation: \_\_\_\_\_

Excretion and content of [<sup>14</sup>C]-radioactivity (% of dose), first group

	urine	feces	expired air	GI content	GI tract	carcass
0-12h	0.05	20	0.07			
0-24h	0.06	91	0.08			
0-48h	0.06	103	0.08			
0-72h	0.06	103	0.08			
72h				0.01	ND	ND

ND= no radioactivity detected

Excretion and content of [<sup>14</sup>C]-radioactivity (% of dose), second group

	urine	feces	bile	GI content	GI tract	carcass
0-12h	0.02	9.28	0.00			
0-24h	0.06	44	0.003			
0-48h	0.08	96	0.003			
48h				4.15	0.02	0.1

ND= no radioactivity detected

Conclusion

Virtually all orally dosed PB-94 radioactivity is excreted in feces. Expressed as sum of radioactivity excreted in urine, expired air, and bile + radioactivity present in carcass, absorption of [<sup>14</sup>C]PB-94 is 0.14-0.18%. This is a little more than expected on basis of radiochemical purity of dosing formulation as determined from % of water-soluble activity (0.05%). This suggests that (1) there is some uptake of the polymer, and/or (2) there is a very small degree (<0.23%) of degradation in GI tract.

**4B. Pharmacokinetics studies of PB-94 (V): Excretion in male rats after a single oral administration of [<sup>3</sup>H]PB-94**

Methods

SD male rats, fasted, single dose of 250mg/kg [<sup>3</sup>H]-PB-94, oral gavage, fed immediately after dose administration.

First group: Urine, feces, expired air collected from 0-12, 12-24, 24-48, 48-72h after administration. Second group: Bile, urine, feces collected from 0-12, 12-24, 24-48 h post dosing.

Sponsor \_\_\_\_\_, supplied <sup>3</sup>H-labeled test article \_\_\_\_\_ to testing facility \_\_\_\_\_

<sup>3</sup>H label was located in longitudinal backbone (polyallylamine moiety) of polymer. Method of radiolabeling or of preparation of radiolabeled substance not given. Radiochemical purity of test substance and dosing formulation, determined as % radioactivity in centrifugate of solution in water, and homogeneity of dosing formulation were determined.

Results

Radiochemical purity test substance \_\_\_\_\_

Radiochemical purity dosing formulation: \_\_\_\_\_

Dosing formulation was homogeneous

Excretion and content of [<sup>3</sup>H]-radioactivity (% of dose), first group

	urine	feces	expired air	GI content	GI tract	carcass
0-12h	0.01	34	0.00			
0-24h	0.02	103	0.00			
0-48h	0.03	107	0.01			
0-72h	0.04	108	0.01			
72h				0.01	0.01	0.2

ND= no radioactivity detected

Excretion and content of [<sup>3</sup>H]-radioactivity (% of dose), second group

	urine	feces	bile	GI content	GI tract	carcass
0-12h	0.01	17.4	0.01			
0-24h	0.01	55	0.01			
0-48h	0.03	87	0.03			
48h				5.71	0.02	0.11

ND= no radioactivity detected

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ON ORIGINALConclusion

Virtually all orally dosed PB-94 radioactivity is excreted in feces. Expressed as sum of radioactivity in urine, expired air, bile and carcass, absorption of [<sup>14</sup>C]PB-94 is \_\_\_\_\_

\_\_\_\_\_ This is more than expected on basis of radiochemical purity of dosing formulation as determined from % of water-soluble activity (0.12%). As the previous study, this suggests that there is uptake of the polymer and/or a very small degree (<0.2%) of degradation in GI tract.

**5. Pharmacokinetics studies of PB-94 (IV): Absorption, distribution, and excretion in male dogs after single oral administration of [<sup>3</sup>H]PB-94**Methods

Male Beagle dogs, fasted for 16h, single dose of 250mg/kg [<sup>3</sup>H]-PB-94, oral capsule, with 50 ml of water through catheter, fed immediately after dose administration. Samples: Urine, feces, collected from 0-12, 12-24, 24-48, 48-72h after administration. Samples of blood taken at specified intervals up to 72h; Tissues taken at 6h and 72h. Total of 31 tissues, GI contents and carcass evaluated.

Sponsor \_\_\_\_\_, supplied <sup>3</sup>H-labeled test article (from Geltex) to testing facility \_\_\_\_\_. <sup>3</sup>H label was located in longitudinal backbone (polyallylamine moiety) of polymer. Method of radiolabeling or of preparation of radiolabeled substance not given. Radiochemical purity of test substance, determined as % radioactivity in centrifugate of solution in water, was determined.

Results

Radiochemical purity test substance: \_\_\_\_\_

Radioactivity in blood; plasma:

<3.84 ug eq/ml; <1.77 ug eq/ml (below detection limit) at all sampling times

Excretion of [<sup>3</sup>H]-radioactivity (% of dose)

	urine	feces	cage washing
0-24h	0.02	76	
0-48h	0.03	91	
0-72h	0.03	94	
72h			0.00

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ND= no radioactivity detected

Radioactivity in tissues:

	tissue	activity (ugeq/g)	tissue	% of dose	
6h	stomach	44.2 (indiv. values: 0.44-0.93-131)	stomach	NC (!)	
	large intestine	2.53 (5.5-1.3-0.75)	large intestine	NC (!)	
	blood	1.90	blood	0.06	
	skin (white)	1.03	skin (white)	0.07	
	cerebrum	2.0	cerebrum	0.003	
	kidney	0.95	kidney	<0.005	
	small intestine	0.72	small intestine	NC (!)	
			skin (black)	0.05	
			liver	0.01	
			fat	0.06	
			skeletal muscle	0.11	
			mandibular gland, thymus, heart lung, spleen	<0.002	
		plasma, medulla oblongata, spinal cord, mandibular gland, thymus, heart lung, spleen, urinary bladder cerebellum, thyroid gland, trachea, cecum	<0.50  0.5<x<1.0	cerebellum, thyroid gland	<0.002
			other tissues	BLQ	
72h			content of stomach	9.07	
			content of small intestine	8.25	
			content of large intestine	67.29	
			content GI tract	84.61	
		Total Tissues	0.373		
6h, 72h	other tissues (incl. plasma)	BDL	content of stomach	0.11	
			content of small intestine	0.01	
			content of large intestine	0.15	
			content GI tract	0.27	
		other tissues	BLQ		

NC= not calculated

At 72h, there was no detectable activity in any tissue.

Conclusion

Radioactive PB-94 absorbed and excreted in urine over 72h was 0.03% of dose. Activity absorbed and excreted in bile, expired air was not determined. Distribution to GI tissues

was not calculated as % of dose. Distribution to other tissues was <0.4% at 6h, not detectable at 72h.

**6. Pharmacokinetics studies of PB-94 (1): Absorption, distribution and excretion in rats and dogs (Preliminary study)**

Methods

Male rat or dog, fasted, single oral dose of 250mg/kg [<sup>3</sup>H]-PB-94, gavage or capsule, fed immediately after dose administration. Samples: Urine, feces, expired air, bile.

Sponsor \_\_\_\_\_, supplied <sup>14</sup>C-labeled test article to testing facility \_\_\_\_\_

Labeled compound was synthesized using \_\_\_\_\_ as crosslinker.

Radiochemical purity of test substance and dosing formulation were determined as % radioactivity in centrifugate of solution in water.

Results

Mixture containing compound is hard to homogenize (gel). Need to use a slow rotation rate over a long time, and a stirrer bar as long as the containers' diameter.

Radioactivity in blood or plasma:

Below detection limit at all sampling times, in both rat and dog

Excretion of [<sup>14</sup>C]-radioactivity in the rat (% of dose)

	urine	feces	expired air	bile	GI content	GI tract	carcass
0-12h	0.01	40	0.04				
0-24h	0.03-0.05*	81-98.6*	0.05	0.004			
0-48h	0.03-0.05*	101-112*	0.05	0.004			
48h					1.62-27	0.02-0.2*	0-0.53*

\* values from two experiments, n=1 each, other data from n=1

Excretion of [<sup>14</sup>C]-radioactivity in the dog (% of dose)

	urine	feces	expired air
0-12h	0.01-0.52*	80	0.04
0-24h	0.04-0.61*	91-83	0.06
0-48h	0.04-0.81*	99-100	0.06

\* values from two experiments, n=1 each

Conclusion

Excretion is mainly fecal, and a minor % of dose (<1%) is absorbed into the system. Study results were used to decide on method of determining radiochemical purity, specific radioactivity, homogeneity of dosing compound or solution, and method of measuring radioactivity in feces and urine.

**7. Open balance study of <sup>14</sup>C-polyallylamine (Renagel™) following oral administration to dogs**

Methods

Beagle dogs (n=3/sex), fasted overnight, given a single oral dose (209 mg/kg) in capsule with 5 ml of water. Animals fed immediately after dosing. Samples of blood, urine, feces up to 48h postdose. Tissues collected at 48h postdose. Aliquots oxidized before analysis. Radioactive stuff supplied to testing facility \_\_\_\_\_ by Sponsor (Geltex). Substance labeled at test facility by sponsors representative by <sup>14</sup>C-methyl-iodide method described. GLP statement included.

Results

Tissue data presented as % of dose. Previous reviewer requested ug eq/g tissue.

Soluble radioactivity in dose mixture (in water and toluene) = \_\_\_\_\_

Blood: Radioactivity \_\_\_\_\_

Excretion of [<sup>14</sup>C]-radioactivity in the dog (% of dose)

	urine*	feces
0-12h	0.03	29
0-24h	0.03*	50
0-48h	0.07*	98

\* 12-24h sample missing, values underestimated

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Radioactivity in tissues:

	tissue	activity (ugeq/g)	% of dose
48h	liver	1.5	0.023
	spleen	0.62	0.002
	stomach	0.83	0.003
	duodenum	5.7	0.04
	jejunum	0.54	0.003
	ileum	0.52	0.003
	cecum	1.3	0.002
	colon	0.78	0.002
	rectum	1.0	0.002
	content of stomach	1.7	0
	content of small intestine	2.3	0.003
	content of large intestine	31	0.06
	blood	0	0
	kidney, lymph nodes	ND	0

ND = not detected

1. Content of GI tract, GI tissues and other tissues at 48h was small and highly variable among the animals.
2. For most tissues, there was only 1 animal with detectable activity at this site. Highest activity was seen in duodenal tissue (avg. 0.04%), mostly due to 1 f animal with a 0.2% of dose in this tissue. This animal also had 0.1% in liver.
3. Largest % of dose was seen in content of large intestinal (avg. 0.06%). This site was positive for 5/6 animals.

Conclusion

Major part of radioactive dose excreted with feces (98%). Conclusion on amount of absorption not possible from data.

**8. Absorption, distribution and excretion of radioactivity in Sprague-Dawley rats following oral administration via gavage of a single dose of [<sup>3</sup>H]-labeled Renagel (GT16-026A) with and without unlabeled Renagel pre-treatment via feed for one month**

Methods

Male SD Rats (n=6) received single [<sup>3</sup>H]-labeled dose (250 mg/kg), via gastric intubation, with or without pretreatment with multiple doses of unlabeled Renagel (6 g/kg/day) in the diet for 28 days. Samples of urine, feces, tissues at 72h. Radioactive material supplied to testing facility \_\_\_\_\_ by Sponsor (Geltex).

Results

Recovery of [<sup>3</sup>H]-activity 0-72h

regimen	urine	feces
single dose	0.05	97.6
repeated dose 29 days	0.05	105

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Radioactivity in tissues:

	tissue	activity (ugeq/g)	% of dose
72h	blood	0.25/0.2*	0.01/0.01
	skeletal muscle	0.27/0.24	0.05/0.05
	liver	0.31/0.24	0
	kidney	0.24/0.26	0
	spleen, skeletal muscle, stomach, large intestine, small intestine, cecum, rectum	0.14-0.26/0.14-0.24	0
	lymph nodes	0.02/0.00	0
	Total Tissues		0.06/0.06

\*Values for single dose/multiple dose regimens

Tissue contents not significantly different with single or multiple dose regimens.

Conclusion

Excretion and tissue distribution appears similar after single or 28-day multiple dosing.

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NONCLINICAL TOXICOLOGY

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GENERAL TOXICITY

SINGLE DOSE STUDIES RAT AND DOG

Study Number	Species	Dosing schedule	Dosing Route	Feeding status	Doses (g/kg)	N/s ex/ grp	Parameters	Findings
TX-95-117	rat	single dose	oral gavage	Fasted, fed 3h postdose	0, 1, 2	5	signs, BW, gross pathology	No changes in BW, no signs, no pathology effects. NOAEL > 2 g/kg
TX95-118	dog	single dose	oral (gelatin capsule)	Fasted overnight, fed 3h postdose	2.4	1	Signs, BW, FC, WC, hematology, blood chemistry, gross pathology	Signs: Vomiting in LDf, and HDm.f Vomit (PB-94) re-administered. Swollen PB observed in feces at 1 day postdose. BW, WC: Transient increase in HD. at 1 day postdose. Hematology: Slight decrease in HDm of RBC, Hb, platelet count, Hc at 2 days post dose. Clin chem: Increase in free fatty acids, decrease in triglycerides and Fe 2 days post dose in MD, HD, and 14 days post dose in HD. Pathology: No abnormalities NOAEL < 2g/kg

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