CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-905

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-905
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	11/30/2005
PRODUCT:	Valtropin (somatropin, Eutropin)
INTENDED CLINICAL POPULATION:	[redacted]
SPONSOR:	LG Life Sciences, Ltd., Seoul, Korea
DOCUMENTS REVIEWED:	Pharmacology and Toxicology
REVIEW DIVISION: (HFD-510)	Division of Metabolism and Endocrinology Products
PHARM/TOX REVIEWER:	Herman Rhee, Ph.D.
PHARM/TOX SUPERVISOR:	Karen Davis-Bruno, Ph.D.
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PROJECT MANAGER:	Kati Johnson

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Date of review submission to Division File System (DFS): September 18, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval

Preclinical pharmacology and toxicology recommends approval of NDA21-905, based on preclinical findings on Valtropin® (LBD-009) as reviewed in this document.

B. Recommendation for nonclinical studies:

The following preclinical findings should be included in labeling instructions as indicated under "Pharmacology Recommendation Section", which is briefly summarized below.

C. Recommendations on labeling:

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Valtropin® [somatropin (rDNA origin) for injection] is a polypeptide hormone of recombinant DNA origin. The hormone is produced by recombinant DNA technology in yeast cells *(Saccharomyces cerevisiae)*. Valtropin® has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin. The Valtropin™ drug substance is identical in amino acid sequence to pit-hGH and to several commercial rhGH preparations. Pre-clinical data generated from general pharmacology indicate that LBD-009 increased nitrogen retention, lean body mass, increased muscle performance and decreased adipose mass.

Repeat-dose toxicity study indicates that LBD-009 provided growth in rats without remarkable adverse effects in rats and rabbits. The sponsor performed genotoxicity. *In vitro* studies (bacterial mutagenesis [Ames test] and chromosomal aberration), and *in vivo* tests for genotoxicity (mouse micronucleus test) were negative. Long-term studies for carcinogenicity have not been performed. Fertility and early embryonic development studies (Segment I) of Valtropin® in rats were negative. From reproductive toxicity studies performed with reference somatropins, it appears that there is no clear evidence for an increased risk of adverse effects for the embryo or fetus.

Safety evaluation of LBD-009 has been conducted in a series of studies that have addressed general toxicity (single- and repeated-dose) and antigenicity as well as a comprehensive set of safety pharmacology tests. This recent work included a repeat rat subchronic study, a new rat toxicokinetic and three repeat genotoxicity studies, the new data serving to bridge the early and late pharmaceutical development of somatropin. The findings were consistent with earlier studies. LBD-009 has shown the properties and activities typical of a recombinant somatropin preparation. It appears that the nonclinical safety profile supports its use in growth hormone deficiency in the indications in this submission.

B. Pharmacologic activity

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH. Direct comparison of the activity of Valtropin™ and the positive control Humatrope® in the rat weight gain and tibia length assays has validated the assay and also demonstrated their comparability. It appears that such assays with Valtropin™ in comparison to other well-characterized rhGH preparations confirm its comparable growth activity potential.

In children, hGH leads to increased growth velocity, pubescence and fertility. The identity and biological activity of LBD-009 is established by similar preparations on the market. These include biological testing, with the rat weight gain assay, within the routine controls for release of each batch of drug substance. A direct comparison of LBD-009 or Valtropin™ and Humatrope® against growth hormone standard in the rat weight gain and tibia length assays establishes their comparability.

C. Nonclinical safety issues relevant to clinical use

None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-905
Review number: 01
Sequence number/date/type of submission: 000/11/30/2005/Commercial
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: LG Life Sciences, Ltd./ Parexel International, Waltham, MA 02451 Tel(781-487-9900)
Manufacturer for drug substance: [redacted] b(4)

Reviewer name: Herman Rhee, Ph.D.
Division name: **Metabolism and Endocrine Product**
HFD #: **510**
Review completion date: 9/13/2006

Drug:

Trade name: Vatropin or Eutropin
Generic name: Somatropin
Code name: K-249, LBD-009
Chemical name: rH-Growth hormone
CAS registry number: NA
Molecular formula/molecular weight: $C_{990}H_{1528}N_{262}O_{300}S_7$/22,125 Daltons

Structure: The primary structure is identical to natural, pituitary derived human GH and to Somatropin expressed in E. coli (Hymatrope, Genotropin or Nutropin) or in mammalian cells(Saizen).

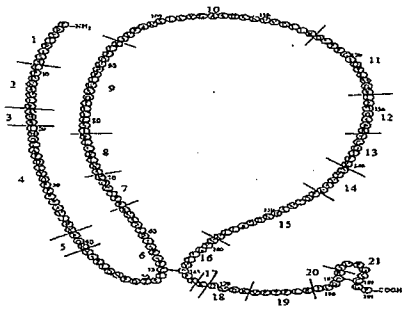

Figure 3.2.S.3.1-1: The primary structure of rhGH showing tryptic cleavages sites

Relevant INDs/NDAs/DMFs: [redacted], IND62376, IND69726, NDA20280, and NDA21538 b(4)

Drug class: recombinant human growth hormone

Intended clinical population: Children with short stature, Turner's syndrome, and replacement therapy for growth hormone deficiency (GHD) in adults and children.

Clinical formulation: 5 mg Somatropin, 10 mg glycine, 45 mg D-mannitol, 2.98 mg dibasic sodium phosphate and 0.22 mg monobasic sodium phosphate: Diluent vial has 5 ml water for injection with 0.3% m-cresol as a preservative as shown below. The proposed human dose is 0.06 mg/kg (1.5 IU/kg).

Table 2.4-1: Compositions of Eutropin™ Injection and Valtropin™

Composition (per Vial)	Valtropin™ 15 IU Formulation[A]	Eutropin™ Injection 4 IU Formulation
Somatropin	5 mg	1.33 mg
Mannitol	45 mg	5 mg
Glycine	10 mg	20 mg
Sodium Phosphate, Monobasic, [redacted]	0.22 mg	-
Sodium Phosphate, Dibasic, [redacted]	2.98 mg	ca.1.6 mg[B]

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[A] According to batch formula, 1N sodium hydroxide and 1N hydrochloric acid are used to adjust pH to [redacted]
[B] Adjusted to pH of approximately [redacted] with buffer.

Route of administration: Subcutaneous injection

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-905 are owned by LG Life Sciences, Ltd. or are data for which LG Life Sciences, Ltd. has obtained a written right of reference. Any information or data necessary for approval of NDA 21-905 that LG Life Sciences, Ltd. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that LG Life Sciences, Ltd. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 21-905.

Studies reviewed within this submission:

1. A 28-Day Subcutaneous Repeated Toxicity Study of Valtropin in rats

2. A 28-Day Comparative Toxicokinetic and Toxicity Study with LB03002 (SR-hGH) and hGH in Juvenile Rhesus Monkeys

3. A 90-Day Subcutaneous Repeated Toxicity Study of LBD-009 (recombinant human growth hormone without N-methionine) in Mice

4. A 90-Day Subacute and Subcutaneous Toxicity Test of LBD-009 in Rats

5. 26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002 (Sr-rhGH) in Cynomolgus Monkeys with an 8-Week Recovery Period

6. Reproductive and developmental toxicology:

a. Fertility and early embryonic development in rats
b. Teratogenicity study of LBD-009 in rats
c. Teratogenicity Study of LBD-009 in Rabbits
d. Peri and postnatal toxicity study of LBD-009 in rats

7. Local tolerance: Valtropin Effect on Skin Irritation in Rabbits

8. Special toxicology studies: Antigenicity study:

a. Valtropin Effect on Antigenicity in Mice and Rats
b. Valtropin Effect on Antigenicity in Guinea pigs
c. Valtropin Effect on Antigenicity in Guinea pigs (Anaphylactic Shock)
d. Biological Activity of Valtropin: Rat weight gain assay

Studies <u>not</u> reviewed within this submission:

1. All acute single dose and some repeated dose toxicology studies which were reviewed under IND 62,376(Eutropin) as attached.

2. Genotoxicity studies that were reviewed under IND 62,376 as attached.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Valtropin® [somatropin (rDNA origin) for injection] is a polypeptide hormone of recombinant DNA origin. The hormone is produced by recombinant DNA technology in yeast cells *(Saccharomyces cerevisiae)*. Valtropin® has 191 amino acid residues and a molecular weight of 22,125 daltons. The amino acid sequence of the product is identical to that of human growth hormone (hGH) of pituitary origin.

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH. Direct comparison of the activity of Valtropin™ and the positive control Humatrope® in the rat weight gain and tibia length assays has validated the assay and also demonstrated their comparability. It appears that such assays with Valtropin™ in comparison to other well-characterized rhGH preparations confirm its comparable growth activity potential.

In children, hGH leads to increased growth velocity, pubescence and fertility. The identity and biological activity of LBD-009 are established by similar preparations on the market. These include biological testing, with the rat weight gain assay, within the routine controls for release of each batch of drug substance. A direct comparison of LBD-009 or Valtropin™ and Humatrope® against growth hormone standard in the rat weight gain and tibia length assays establishes their comparability.

2.6.2.2 Primary pharmacodynamics

Human growth hormone is a non-glycosylated, single chain, 191 amino acid, 22-Kilo-Dalton (kD) protein with two intramolecular disulphide bonds. Approximately 75% of pit-hGH is in this form and about 5-10% in a 20-KD form, formed by alternate splicing of messenger ribonucleic acid (RNA). All the effects of human growth hormone (hGH) are the result of its binding to a specific cell receptor which is widely distributed throughout the body. The mature receptor is a transmembrane glycoprotein containing a large N-terminal extracellular domain, which is responsible for binding of hGH, and a C-terminal cytoplasmic domain.

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH. Direct comparison of the activity of Valtropin™ and the positive control Humatrope® in the rat weight gain and tibia length assays has validated the assay and also demonstrated their comparability. It appears that such assays with Valtropin™ in comparison to other well-characterized rhGH preparations confirm its comparable growth activity potential.

Mechanism of action:

Growth hormone receptor activation is initiated by the binding of hGH to two hGH receptors, to form a ligand-binding-site-occupied receptor dimer. Receptor dimerisation leads to signal transduction, which is predominantly mediated by the non-receptor tyrosine kinase, Jak2. It appears that the actions of hGH are either direct or mediated through insulin-like growth factors (IGF) -1 and -2 (IGF-1 and IGF-2), of which IGF-1 appears to be the more important because serum levels of IGF-1 are known to reduced in hGH deficiency. IGF-2 may not play a dominant role in the action of growth hormone.

Drug activity related to proposed indication:

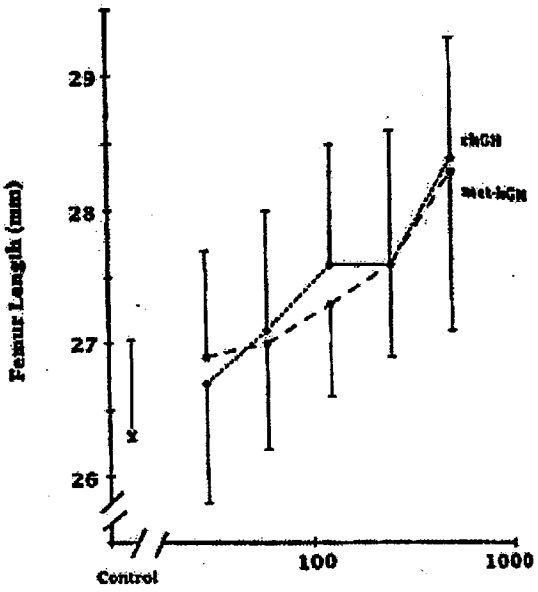
The sponsor provided the following summary table for the pharmacodynamic effects of LBD009. Rat weight was noted and tibia growth was observed after subcutaneous administration of growth hormone at doses of 2, 4, and 8 µg/day. LBD009 were dosed daily for 27-29 days with 30, 60, 125, 250 or 500 µg/kg/day of rhGH or met-rhGH to hyposectomized rats. Body weights were recorded throughout treatment with a clear dose-related increase observed. At the end of dosing animals were sacrificed and the tibias and femurs removed. Femur length was measured and, again, a clear dose-related increase in length was demonstrated as shown below.

Table 2.6.2-3: Evaluation of primary pharmacodynamics of LBD009

Parameter	Test Animal/Material	Dose/route	Effect	Study No.
Weight gain assay	Rats	2, 4, 8 µg/day, s.c.	Increase in weight gain comparable to other rhGH products.	RCH-HG-007 [3.2.S.3.1]
Tibia growth assay	Rats	2, 4, 8 µg/day, s.c.	Increase in tibia length comparable to other rhGH products.	RCH-HG-007 [3.2.S.3.1]
Blood glucose	Adrenalectomised rats	80 IU/kg, i.v. (32 mg/kg)[b]	20% decrease 20 min. after injection, normal after 40 and 60 min., decrease after 120 min.	Lee et al. 1992[a] [4.3.2.28]
Glucose tolerance	Rat	40 IU/kg, i.v. (16 mg/kg)	Significant increase in blood glucose 12-30 min. after injection; decrease in glucose tolerance	Lee et al. 1992[a] [4.3.2.28]
Lipolysis	Rat Epididymal fat pads	2 IU/ml (0.8 mg/ml)[b]	Slight inhibition (33% not significant) of glycerol release in an *in vitro* assay	Lee et al. 1992[a] [4.3.2.28]
Epinephrine-induced lipolysis	Rat epididymal fat pads	2 IU/ml (0.8 mg/ml)[b]	55% inhibition of glycerol release in an *in vitro* assay	Lee et al. 1992[a] [4.3.2.28]

[a] study conducted in compliance with Good Laboratory Practice Regulations issued by the Ministry of Health and Social Affairs, Korea (October 1987.KGLP)

[b] with 2.5 IU being equivalent to 1 mg



Mean (±SD) femur length of hypophysectomized rats after 27-29 daily injections vs. dose of rhGH (●), Met-hGH (■), or placebo (X).
n = 8-9 g rats/group.

Source: Moore et al. 1988 [4.3.2.33]

Figure 2.6.2-3: **Dose-related effects of recombinant human growth hormone (Genentech Inc) and Protropin® (met-hGH) on femur length in hypophysectomised rats**

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2.6.2.3 Secondary pharmacodynamics

The sponsor summarized some of secondary pharmacodynamic effects of growth hormone in a table form, which were largely negative as shown below.

Table 2.6.2-6: Evaluation of secondary pharmacodynamics of LBD009

Parameter	Test Animal/Material	Dose/route	Effect
Isolated organs			
Smooth muscle	Guinea pig ileum	3×10^{-4} IU/ml (1.2×10^{-4} mg/ml)[b]	No effect
Smooth muscle	Guinea pig trachea	1×10^{-3} IU/ml (4×10^{-4} mg/ml)[b]	No effect
Smooth muscle	Rat fundus	1×10^{-3} IU/ml (4×10^{-4} mg/ml)[b]	No effect
Smooth muscle	Rat uterus	1×10^{-3} IU/ml (4×10^{-4} mg/ml)[b]	No effect

Source: Lee et al. 1992[a] [4.3.2.28]

[a] study conducted in compliance with Good Laboratory Practice Regulations issued by the Ministry of Health and Social Affairs, Korea (October 1987.KGLP)

[b] with 2.5 IU being equivalent to 1 mg

2.6.2.4 Safety pharmacology

Neurological effects:
When administered to mice as single subcutaneous administrations of 20 and 40 IU/kg (ca. 8 and 16 mg/kg, respectively), LBD-009 had no effect on locomotor activity, rotarod activity, acetic acid induced writhing or the convulsions induced by strychnine or pentylenetetrazole. It had no effect on rat body temperature at the same doses as summarized in a table below.

Cardiovascular effects:
Subcutaneous administration of LB03002 at 0.2, 0.6 and 2 mg/kg to conscious, telemetered cynomolgus monkeys had no notable effect on arterial blood pressure (systolic, diastolic and mean), heart rate or the lead II ECG variables (RR, PR, QT and QTc interval and QRS duration), waveform or rhythm, when compared to vehicle at selected time points over the 22-24 h post-dose. Intravenous injection of LBD-009 at 5, 10 or 20 IU/kg (ca. 2, 4, or 8 mg/kg) to anesthetized rabbits did not affect blood pressure, heart rate or respiration as shown below. The table below also shows that LBD009 had little or no effect on rectal temperature, analgesic as well as anticonvulsant effects.

Table 2.6.2-7: Safety pharmacology evaluation of LBD009

Parameter	Test Animal/Material	Dose/route	Dose in mg/kg[b]	Effect
Nervous system				
Central nervous system	Mouse	20 IU/kg, s.c. 40 IU/kg, s.c.	8 16	No effect No effect
Rectal temperature	Rat	20 IU/kg, s.c. 40 IU/kg, s.c.	8 16	No effect No effect
Writhing test	Mouse	20 IU/kg, s.c. 40 IU/kg, s.c.	8 16	No effect No effect
Anticonvulsant effect	Mouse	20 IU/kg, s.c. 40 IU/kg, s.c.	8 16	No effect No effect
Cardiovascular System				
Valtropin™ SR: Cardiovascular function	Monkey	-	0.2 0.6 2.0	No effect
Respiratory System				
Respiration and blood pressure	Rabbit	5 IU/kg, i.v. 10 IU/kg, i.v. 20 IU/kg, i.v.	2 4 8	No effect No effect No effect

Source: Lee et al. 1992[a] [4.3.2.28]

[a] study conducted in compliance with Good Laboratory Practice Regulations issued by the Ministry of Health and Social Affairs, Korea (October 1987.KGLP)

[b] with 2.5 IU being equivalent to 1 mg

2.6.3.4 **Safety Pharmacology**

Test Article: LBD009

Organ Systems Evaluated	Species/ Strain	Method of Administration	Doses (IU/kg)	Doses (mg/kg)[1]	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Nervous system								
Central nervous system (rotarod, motor activity, hexabarbital-induced sleep time)	Mouse/ddY	Subcutaneous	20, 40	8, 16	Male 8-10/group	No effect	Yes[2]	Lee et al. 1992 [4.3.2.28]
Rectal temperature	Rat/Sprague Dawley	Subcutaneous	20, 40	8, 16	Male 6/group	No effect	Yes[2]	Lee et al. 1992 [4.3.2.28]
Analgesia (writhing test)	Mouse/ddY	Subcutaneous	20, 40	8, 16	Male 7/group	No effect	Yes[2]	Lee et al. 1992 [4.3.2.28]
Anticonvulsant effect	Mouse/ddY	Subcutaneous	20, 40	8, 16	Not given 6-8/group	No effect	Yes[2]	Lee et al. 1992 [4.3.2.28]
Cardiovascular system								
Cardiovascular parameters	Monkey/Cyno-molgus	Subcutaneous	-	Valtropin™ SR 0.0, 0.2, 0.6 and 2.0 mg/kg s.c. crossover	Male n=4	No effect on arterial blood pressure, heart rate or ECG parameters	Yes[3]	DHJH1002 [4.2.1.3.1]
Respiratory system								
Respiration and blood pressure	Rabbit/New Zealand	Intravenous	5, 10, 20	2, 4, 8	Male Not given	No effect	Yes[2]	Lee et al. 1992 [4.3.2.28]

[1] with 2.5 IU being equivalent to 1 mg
[2] study conducted in compliance with Good Laboratory Practice Regulations issued by the Ministry of Health and Social Affairs, Korea (October 1987.KGLP)
[3] study conducted in compliance with the OECD Principles of Good Laboratory Practice (ENV/MC/CHEM (98)17)

Pulmonary effects:
Please see tables above.
Renal effects: N/A
Gastrointestinal effects: N/A
Abuse liability: N/A
Other: None.

2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The pharmacokinetics of LBD-009 have been studied in the rat after subcutaneous administration, and in the rabbit after intravenous and subcutaneous administration. For the rat, the pharmacokinetics of the subcutaneous dose was studied as part of a repeat-dose toxicity study, using doses of 0.2 and 2.0 IU/kg (ca. 79 and 788 µg/kg). These results suggest that at very high, repeat subcutaneous doses, a higher systemic

exposure may be obtained, possibly due to changes such as saturation of protein binding, or the influence of injection site irritation upon the absorption of subsequent doses. For the rabbit, a single report includes method of analysis (radioimmunoassay; RIA), plasma levels, urinary excretion and tissue distribution. Due to the nature of biological preparation, the sponsor did not perform the separate metabolism studies for LBD-009. The pharmacokinetic data for the rat and rabbit are discussed below.

2.6.4.2 Methods of Analysis

The assay of LBD-009 in the rabbit study was by RIA, based on a polyclonal guinea-pig anti-hGH antibody and a rabbit anti-guinea pig immunoglobulin G (IgG) antibody. Concentrations of LBD009 in biological samples were measured by radioimmunoassay, utilizing ^{125}I-labelled hGH as tracer, a polyclonal anti-hGH antibody from guinea pig and an anti-guinea pig IgG from rabbit as secondary antibody. A regression curve for hGH standard over the range 0.5 µU/ml–1 mU/ml (197 pg/ml–394 ng/ml) was constructed, from which the concentration of LBD009 in each sample was determined.

2.6.4.3 Absorption

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The absorption of LBD-009 has been studied in the rat after subcutaneous administration, and in the rabbit after intravenous and subcutaneous administration. Male and female [redacted] IGS rats were administered control vehicle or Valtropin™ at a dose level of 0.2 or 2 IU/kg/day (corresponding to 79 and 788 µg/kg/d, respectively). Ten rats/sex/group were designated for the study and the dose volume was 2 ml/kg. The only clinical observation was crust and/or local hair loss at the injection site, observed in all groups, and the expected increase in body weight in some groups. The pharmacokinetics of absorption was studied by taking blood samples from tail veins at pre dose, 1, 2, 4, 8, 12, and 24 hours post dose on days 1 and 14. Serum concentrations of hGH were measured by a validated immunoassay method as shown below.

The pharmacokinetic data in the rat after repeat subcutaneous doses showed that exposure in terms of C_{max} and AUC_t values generally increased proportionately with dose after a single dose. For the lower dose (79 µg/kg/d), repeat subcutaneous administration for 14 days resulted in a lower C_{max}, and a generally similar AUC_t. However, with repeat administration of the high dose (788 µg/kg/d), both C_{max} and AUC_t increased disproportionately with dose. These results suggest that at very high, repeat subcutaneous doses, a higher systemic exposure may be obtained, possibly due to changes such as saturation of protein binding, or the influence of injection site irritation upon the absorption of subsequent doses.

The absorption after a subcutaneous dose of LBD-009 was also determined in the rabbit. Subcutaneous doses were studied by means of injection of 197 µg/kg LBD-009, in a volume of approximately 2 ml, into the dorsal side of the neck of 10 rabbits. Blood samples were collected from the carotid artery shortly before dosing and up to 720 minutes post-dose. The extracted plasma was frozen at -60°C pending analysis. Urine was also collected for 24 h post-dose and frozen prior to analysis. Maximum plasma

levels (C_{max}) of approximately 40–50 ng/ml were achieved at 3 to 4 h post subcutaneous dose. The mean AUC from time 0 to 480 minutes after s.c. administration was 14,400 ng·min/ml. Extrapolation of the AUC from 480 minutes to infinity was not possible because the terminal plasma concentration phase was not well defined. Comparison of these data with the mean AUC from time zero to infinity ($AUC_{0-\infty}$) value of 18,400 ng·min/ml calculated following i.v. bolus administration of 79 µg/kg to rabbits suggests substantial bioavailability, equivalent to approximately 80%, upon s.c. administration of LBD-009.

Table 2.4-2: Pharmacokinetic Parameters for LBD009 in Rats After Single and Repeat Subcutaneous Doses of 0.2 and 2.0 IU/kg/d (Study P167 [4.2.3.2.7])

		0.2 IU/kg/d (approx. 79 µg/kg/d [1])			2 IU/kg/d (approx. 788 µg/kg/d [1])		
		C_{max} (ng/ml)	T_{max} (h)	AUC_t (ng*h/ml)	C_{max} (ng/ml)	T_{max} (h)	AUC_t (ng*h/ml)
Males	Day 1	18.5	1	28.6	197	1	343
	Day 14	7.7	2	33.5	796	2	4367
Females	Day 1	9.2	1	17.6	143	1	296
	Day 14	0.7	2	n.c.	946	2	3339

[1] For one unit being equivalent to 394 µg LBD-009
n.c.= not calculated

Table 2.4-3: Pharmacokinetic Parameters for LBD-009 in Rabbits Following Single intravenous Bolus Doses of 79, 197, 788, and 1,970 µg/kg (Lee et al. 1993 [4.3.2.27])

Parameter (units)	Parameter value (mean ± SD)			
Dose ([1] µg/kg)	79	197	788	1,970
$t_{1/2}$ (min)	9.30 ± 2.06	16.8 ± 4.75***	22.2 ± 6.74***	25.8 ± 6.78***
MRT (min)	11.6 ± 1.74	21.7 ± 2.92**	26.7 ± 7.32**	37.9 ± 7.44***
V_{ss} (ml/kg)	166 ± 31.8	218 ± 27.4**	342 ± 73.0***	556 ± 46.0***
CL_T (ml/min/kg)	14.2 ± 5.61	10.2 ± 0.79	14.3 ± 0.788	14.7 ± 3.13
CL_R (ml/min/kg)	0.0419 ± 0.0386	0.00929 ± 0.0483	0.00714 ± 0.143	0.0162 ± 0.0455
CL_{NR} (ml/min/kg)	13.9 ± 6.62	10.1 ± 0.710	14.2 ± 0.781	14.2 ± 2.10
$AUC_{0-\infty}$ (ng min/ml)	18,400	-	-	-

** $p \leq 0.01$, *** : $p < 0.001$ when compared to values for the 79 µg/kg dose.
[1] For one unit being equivalent to 394 µg LBD-009
Mean pharmacokinetic parameters were determined from individual plasma concentration measurements from 8 rabbits at each dose.

2.6.4.4 Distribution
Two hours following subcutaneous administration of 0.5 IU/kg (approx. 197 μg/kg) of LBD-009 to rabbits, the tissue to plasma ratio of extractable hGH was greater than unity in kidney and liver; other tissues measured (stomach, heart, lung, spleen, large intestine, muscle and brain) had ratios of less than unity. Following 14 days administration of radiolabelled rhGH, radioactivity was found in high concentrations in the kidney, blood, liver and skin. Liver and kidney, particularly the latter, play major roles in the metabolism of growth hormone and this is reflected in the concentrations of radioactivity found in these tissues following administration of growth hormone preparations. In both rats and guinea-pigs, autoradiographic studies showed intravenously injected human and bovine tritium-labelled growth hormones to be concentrated in proximal renal tubular cells. It has been demonstrated that rhGH radioactivity was concentrated in liver with skeletal muscle, intestine, bone and fat the other major organs.

2.6.4.5 Metabolism

Metabolism of somatropin is extensive. Iv and sc studies in rabbits revealed <1% unchanged parent excretion in urine with doses up to 2000 μg/kg and 200 μg/kg by route respectively. It has been documented that a reduced metabolic clearance rate of administered hGH in human subjects with either liver or kidney disease, suggesting that under normal circumstances the liver and kidney are the major sites for catabolism of hGH. In the presence of liver or kidney disease, extravascular degradation sites may play more pronounced role. Other report have suggested that one of the functions of human growth hormone binding protein is to restrict the movement of hGH from the vascular compartment and thus protect it from extravascular degradation. Protein-bound hGH persists ten times longer in plasma than monomeric hGH and its volume of distribution is also larger.

2.6.4.6 Excretion

A study with LBD-009 in the rabbit, and assay by RIA, showed the kidneys to excrete only small amounts of unchanged LBD-009 – approximately 0.5% of the administered dose within 24 h. Studies with radiolabelled material in rats showed 82% and 2% of the administered radioactivity were excreted in urine and faeces, respectively, within 48 h of a single injection; corresponding figures for the subcutaneous route were 81 and 3 biliary excretion within 72 h was 15-16% for the two routes of administration. These figures for urinary and faecal excretion remained similar after repeated, 14 days, administration. These data confirm the extensive metabolism of growth hormone, both administered in disease states and released in normal subjects, with only a small proportion of material excreted unchanged. Urinary excretion predominates.

2.6.4.7 Pharmacokinetic drug interactions
No study was conducted by the sponsor.

2.6.4.8 Other Pharmacokinetic Studies
None.

2.6.4.9 Discussion and Conclusions

The sponsor did perform limited studies on rH GH ADME (Absorption, distribution, metabolism and excretion) because the PK parameters of rhGH are well documented in animals as well as in human as published. It appears that the PK profile of the LBD-009 is not significantly different from that of other commercially available rh-GH products, based on published data as well as the sponsor's submitted PK data in single dose, in sc, im, and oral rodent PK studies with LBD-009.

2.6.4.10 Tables and figures to include comparative TK summary

None.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Evaluation of the toxicity profile of LBD-009 has included single- and repeated-dose toxicity, genotoxicity and reproductive toxicity as well as local tolerance and antigenicity. Single dose studies showed that somatropin, whether administered as LBD-009, Valtropin™ SR or Humatrope®, was essentially without effect in these studies and the no-effect-levels were concluded to be the maximum doses administered.
The repeated-dose toxicity studies with LBD-009 have been carried out in the mouse and rat, with further information generated from a sustained release formulation available from studies in the monkey.

Throughout these studies, this preparation of growth hormone was well tolerated at the doses administered up to 10 IU/kg/day (66 times the maximum recommended clinical dose) with few adverse reactions noted. Those observed changes are generally attributable to the pharmacological activity of growth hormone, rather than any toxic effect of the particular preparation. The potential genotoxicity of LBD-009 and Valtropin™ have been evaluated in three standard tests, including *in vitro* gene mutation in bacteria (with and without metabolic activation), *in vitro* chromosome aberrations in Chinese Hamster Ovary (CHO) and Chinese Hamster Lung cell test in mice. None of these studies indicated any genotoxic potential of LBD-009 or Valtropin™. Appropriate positive controls included in all studies demonstrated the expected genotoxic responses and validity of the studies.

The reproductive toxicity of LBD-009 has been investigated in a standard range of studies conducted with LBD-009, including fertility, embryo toxicity, and peri/post-natal development. These studies showed that LBD-009 had few effects on parameters indicative of reproductive toxicity, in common with other somatropin preparations. Additional toxicity studies including studies in juvenile animals, local tolerance, and antigenicity showed little or no potential for toxicity, and a profile that is consistent with that know for other marketed somatropin drug products. These studies have shown low potential for toxicity, with the observed effects as a consequence of the pharmacological activity of growth hormone. These nonclinical safety testing results have been compared with and are consistent with the safety profile of other hGH drugs on the market in the US, and they demonstrate that the safety concern for LBD-009 for clinical use in man is low.

Antigenicity of LBD-009 was also studied in the mouse and guinea pig, and in the monkey with Valtropin™ SR, and together these studies did not indicate significant antigenic potential under repeat-dose use. Such reactions to treatment were not observed in rats at the same dose levels and no data on repeated-dose studies with other somatropins in mice have been found in the literature, precluding discussion of these findings within this context. However, detection of anti-rhGH antibodies has been seen in animals and human with other related products.

Statistical significances in these rodent studies with LBD-009 were calculated relative to the saline control group, rather than the vehicle group, which might have been considered more appropriate. Nevertheless, mean values in the two control groups are essentially similar, with only sporadic occurrences of differences, and the calculation of statistical differences in this way does not affect the validity of the conclusions drawn in the reports.

General toxicology:

The repeated-dose toxicity studies with LBD-009 have been carried out in the mouse and rat, with further information regarding the drug substance with a sustained release formulation available from studies in the monkey. Throughout these studies, this preparation of growth hormone was well tolerated at the doses administered (up to 10 IU/kg/day, approx. 4 mg/kg/d, 66 times the maximum recommended clinical dose) with few adverse reactions noted. Those changes, which were observed are generally attributable to the pharmacological activity of growth hormone, rather than any toxic effect of the particular preparation. Generally these findings are restricted to hematology and clinical chemistry changes. Similar observations can be made and conclusions drawn on the effects of Humatrope® and of the other somatropin preparations. It appears that Valtropin™ possesses a profile of effects in repeated-dose toxicity studies similar to that of other marketed somatropin preparations, and adequate for confirmation of safety for the proposed use in man.

Somatropin, whether administered as LBD-009, Valtropin™ SR or Humatrope®, was essentially without effects in these studies. Thus, the no-effect-levels (NOEL) were considered to be the maximum doses administered. Other somatropin preparations such as saizen, norditropine, serostime or biotropin had also little or no effects after a single dose over a similar range of doses to those evaluated for LBD-009 in laboratory animals.

Subcutaneous administration of LBD-009 to rodents produced greater effects in mice than in rats. Female mice receiving 10 IU/kg/day (approx. 4 mg/kg/d) showed decreased activity, decreased respiratory rate, difficulty in breathing and comatose state during the 2nd and 3rd weeks of dosing, symptoms which recovered spontaneously by the 4th week of dosing. Moreover, two female animals in this high-dose group died during this period; at autopsy, they had a dark-red congestion of the duodenum, jejunum, ileum and caecum probably as a result of failure of circulation. The sponsor considered that that these symptoms and deaths were due to immune reactions to foreign proteins, although their data in monkey does not support this contention.

Genetic toxicology:

The potential genotoxicity of LBD-009 has been evaluated in three standard tests, including *in vitro* gene mutation in bacteria (with and without metabolic activation), *in vitro* chromosome aberrations in Chinese Hamster Ovary (CHO) cells, and in an *in vivo* micronucleus test in mice. None of these studies indicated any genotoxic potential of

LBD-009. Appropriate positive controls included in all studies demonstrated the expected genotoxic responses and validity of the studies. The bacterial gene mutation study in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 investigated LBD-009 at concentrations up to 1.6 IU/plate (corresponding to 0.64 mg/plate), with and without metabolic activation by the microsomal fraction (S9 mix) from livers of Aroclor 1254-induced rats livers.

The same maximum concentration was used to evaluate the potential for causing chromosome aberrations in CHO cells, again with and without metabolic activation. Cells were incubated with test compound for 5 h, washed and resuspended before harvesting 12 or 24 h after the start of incubation. The micronucleus test was performed in ICR mice with 40, 80 or 160 IU/kg (ca. 0, 16, 32, 64 mg/kg) of LBD-009 administered were recovered from the femur 24 h after the final dosing. In a *vitro* chromosome aberrations in Chinese Hamster Lung (CHL) cells and in an *in vivo* micronucleus test in mice indicated any genotoxic potential of Valtropin™. Appropriate positive controls included in all studies demonstrated the expected genotoxic responses and validity of the earlier studies.

Carcinogenicity:
No carcinogenicity studies have been performed with LBD-009.

Reproductive toxicology:

The rat fertility study with LBD-009 did not show any effect on mating or gestation rate or parameters related to implantations and fetuses. There was a slight increase in the number of dead fetuses (1, 2, 3 and 4% at 0, 1, 3 and 10 IU/kg/day, respectively). No teratogenic effects were observed in this study. In the rat embryo toxicity study, a slight increase in the number of dead fetuses (0.54, 3.88, 4.85 and 4.72% at 0, 1, 3 and 10 IU/kg/day, respectively) was observed. The rat embryo toxicity study included examination of fetuses delivered by Caesarean section on day 20. Some dams in each group were allowed to litter spontaneously and the development of the pups followed, which showed no definitive adverse findings.

Embryo toxicity investigations in the rabbit showed no effects. The peri/post-natal study in rats did not show any adverse reactions on either dams or pups. However, there was no systematic investigation of potential effects on development of F1 pups, weight gain being the only parameter reported. Mean body weights of pups from the high-dose group were slightly, but significantly, increased during the first two weeks of lactation, as were those of the mid-dose group during the second week.

Toxicokinetic study:

After subcutaneous injection of LB03002, hGH levels appeared to increase, with mean T_{max} values ranging from 4.50 to 10.0 hours on Day 1 and from 6.00 to 39.0 hours after multiple dosing. After reaching C_{max}, hGH concentrations slowly declined and levels were generally at or above the predose levels 72 hours postdose, especially during

Weeks 13 and 26.

There were no consistent gender differences in the mean C_{max} and AUC_{0-72} values in monkeys. Females had slightly higher mean C_{max} and AUC_{0-72} values compared to males at the 0.2 and 0.6 mg hGH/kg/week dose levels across the three collection days, but the opposite was true at the 2.0 mg hGH/kg/week dose level. There were no consistent changes in the mean AUC_{0-72} values after multiple dosing and due to the high variability of hGH levels among animals, these results should be interpreted with caution.
The increases in hGH mean C_{max} and AUC_{0-72} values were less than proportional to the increase in dose on all three collection days. For example, in males, mean C_{max} increased 1:2.5:5:8 fold and 1:1.9:5.7 fold on Day 1 and during Week 26, respectively.

Special toxicology:

Data regarding the local tolerance of s.c. LBD-009 come from the single and repeated-dose toxicity studies in mice and rats, particularly the single-dose studies where the doses administered were higher. The subcutaneous single-dose studies in mice and rats utilized a top dose of 80 IU/kg (ca. 32 mg/kg), administered as a concentration of 16 IU/ml. b(4)
A 14-day subchronic s.c. toxicity study with toxicokinetics was performed in rats — ——— IGS) at dose levels of 0, 0.2, and 2.0 IU/kg (0, 79, and 788 µg/kg) There were no signs of toxicity or deaths, but crust and hair loss was observed at the injection site. A specific study in rabbits has investigated the dermal irritant potential of LBD-009. No irritation was observed when 0.5 ml of LBD-009 solution (16 IU/ml, ca. 6.4 mg/ml) was applied to intact or abraded skin, followed by 24 h occlusion.

Antigenicity Study:

The potential antigenicity of LBD-009 has been specifically assessed in routine tests after sensitization of mice and guinea-pigs. No separate studies were conducted on LBD-009 to assess the potential effect on individual antibody production. Mice were sensitized either by repeated (3 times per week for 3 weeks) subcutaneous injections of 0.15 or 1.50 IU/kg (approx. 0.06, 0.6 mg/kg) of LBD-009 or intraperitoneal injections of 1.50 IU/kg mixed with aluminum hydroxide gel (alum) once every 3 weeks. Serum was harvested 6 days after the last sensitizing injection and was tested for the presence of immunoglobulin E (IgE) antibodies by 24-hour passive cutaneous anaphylaxis (PCA) reactions in the rat. No PCA reactions were observed with serum from mice sensitized with LBD-009 alone, whereas serum from LBD-009 plus alum sensitized animals did show a reaction with PCA titres of 40 to 160: serum from the positive control group sensitized with ovalbumin plus alum had PCA titres in the range 320 to 640.

Guinea-pigs were also sensitized to the same doses of LBD-009, using the same sensitization schedule, but with complete Freund's adjuvant (CFA) rather than alum as adjuvant in conjunction with the high (1.50 IU/kg, approx. 0.6 mg/kg) dose of LBD-009. Sensitization was measured either by active systemic anaphylaxis (ASA) after intravenous challenge with antigen or by PCA in guinea-pigs sensitized with serum harvested 12 days after the last sensitization. Systemic anaphylaxis was not observed in

any LBD-009 sensitized group; animals in the positive control group sensitized to ovalbumin plus CFA exhibited the expected anaphylactic shock. The PCA reactions with serum from animals sensitized in this way showed the presence of IgE antibodies in some animals sensitized with LBD-009 alone and all animals sensitized with LBD-009 plus CFA of ovalbumin plus CFA.

Antigenicity has also been evaluated in the repeated-dose toxicity studies with Valtropin™ SR in monkeys, both adult and juvenile. These studies included monitoring for antibody production, and none were detected except for one female, which showed a positive reaction on Week 26. Whilst the formulation and dosing regimen could influence the immunogenicity of the recombinant preparation, these results do provide reassurance on lack of antigenicity. Although the adverse events seen in early weeks of the mouse 90-day repeated-dose study were attributed by the authors to a reaction to foreign protein, no provision for measuring antibodies was included in this study, or in a similar study in the rat.

2.6.6.2 Single-dose toxicity
Most of single-dose toxicity studies in mice, rats, and monkeys were reviewed under Eutropin IND 62,376. Thus, the single acute toxicity studies are not reviewed again. The original reviews were attached.

2.6.6.3 Repeat-dose toxicity

4-Week Repeated Subcutaneous Dose Toxicity Study with hGH (Valtropin) in Rats
(This is a bridging toxicology study that compares valtropin to Humatrope.)

Key study findings:

Ten ———)IGS Br rats/sex/group were given valtropin or Eli Lilly humatrope subcutaneously at doses of 0, 0.2, 2.0 IU/kg/day for 4 weeks. Control animal had vehicle at a dose volume of 2 ml/kg. There were no deaths in all groups. There were no treatment effects on clinical observations, body weight, food consumption, hematology, blood chemistry or organ weight data. There were no gross lesions and histopathological findings as a result of the treatment. Increased bodyweight gain in the HD treated animals (group 3) in the first week. This study demonstrates that earlier batches are comparable to the current development processes. NOAEL=2 IU/kg/day.

b(4)

Study no.: S821
Conducting laboratory and location: Toxicology Center, LG Life Sciences R&D Park, Daejeon, Korea

Date of study initiation: 4/8/2004
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Lot#6RC36M

Methods

Doses: 0(vehicle), 0.2 and 2 IU/kg
Species/strain: Rat, [redacted]IGS BR
Number/sex/group or time point (main study): 10 rats/sex/group as shown below
Route, formulation, volume, and infusion rate: Subcutaneous, the injection volume was 2 ml/kg/day.
Satellite groups used for toxicokinetics or recovery: None
Age: 4 Weeks
Weight: Males 20-27 g; Females 17-22 g on arrival

b(4)

Group	Dose level (IU/kg/day)	Dose concentration (IU/ml)	No. of animals	
			Male	Female
1 (Vehicle control)	0	0	10	10
2 (Valtropin, standard dose)	0.2	0.1	10	10
3 (Valtropin, high dose)	2	1	10	10
4 (US Humatrope, standard dose)	0.2	0.1	10	10
5 (US Humatrope, high dose)	2	1	10	10

Observations and times:

Mortality: Twice a day
Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Ophthalmoscopy was done two times in all animals before treatment and after final administration.

EKG: NA
Hematology: Before autopsy, animals fasted overnight were ether anaesthetized. The sponsor took a blood sample from a posterior vein.
Clinical chemistry: From the posterior venous blood sample taken, the sponsor separated serum by centrifugation (3000 rpm, for 10 min) for the biochemical lab tests.
Urinalysis: In all animals which were going to be sacrificed, urinalysis was performed after the final administration. Specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen and nitrite in urine were examined within 3 hours of urination, in the last week of injection. Multistix (Ames) and CliniTek-10 (Ames) were used for the tests.

Gross pathology: For all animals on which autopsy was performed, the sponsor took the following internal organs and fixed them with 10 % neutral formalin solution (skin as well as testis and sternum were treated with Bouin's solution). In general, the samples were stained with hematoxylin-eosin before the gross pathological examination.

Organ weights (specify organs weighed if not in histopath table): Conventional methods were used.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Results

Mortality: No death in all groups.
Clinical Signs: There were no treatment related clinical signs except crust formation and local hair loss at the injection sites as shown below.

Table 2. Clinical signs (Group summary)

Clinical signs	Number of animals observed									
	Male (Days 1 to 29)					Female (Days 1 to 30)				
	1	2	3	4	5	1	2	3	4	5
	10	10	10	10	10	10	10	10	10	10
Normal	7	8	7	6	6	8	7	9	7	7
Crust at the injection area	3	2	3	3	1	2	2	1	2	3
Local hair loss at the injection area	2		1	4	4	2	1	1	2	2

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

Body Weight: Mean body weight gain in female group 5 were significantly increased on Weeks 1, 2, and 3 as shown below. There were no such changes in male groups.

Table 4. Bodyweights of females (Group summary)

Group	No. of animals	Group mean bodyweights (mean ± S.D., g)				
		Predose	Week 1	Week 2	Week 3	Week 4
1	10	140.6 ±8.3	165.0 ±8.3	188.2 ±15.5	211.5 ±15.9	224.9 ±16.8
2	10	140.4 ±7.9	171.3 ±10.3	197.7 ±16.0	222.2 ±15.4	233.6 ±18.5
3	10	139.6 ±7.4	173.7 ±10.4	197.9 ±14.4	218.8 ±18.0	230.6 ±18.8
4	10	140.3 ±6.7	170.0 ±8.8	193.0 ±13.2	215.0 ±13.0	229.9 ±18.5
5	10	141.0 ±6.6	179.8** ±12.4	208.0* ±13.2	233.0* ±17.4	243.8 ±19.6

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group ($p<0.05$, Dunnett's multiple comparison)
**: Significantly different compared to control group ($p<0.01$, Dunnett's multiple comparison)

Food consumption: There were significantly increases in the parameters in male group 3 and 5 on Week 3. In females, there was a significant increase in food consumption in group 5 on week 1.

Table 7. Food consumption of males (Group summary)

Group	No. of animals	Group mean food consumption (mean ±S.D., g/rat/day)			
		Week 1	Week 2	Week 3	Week 4
1	10	27.3 ±1.6	29.7 ±2.0	28.8 ±3.1	28.5 ±2.5
2	10	27.8 ±2.0	30.3 ±2.4	29.0 ±1.9	30.5 ±4.0
3	10	30.7** ±2.4	31.5 ±1.7	32.2* ±2.6	30.9 ±2.3
4	10	28.6 ±3.0	29.0 ±2.6	29.4 ±3.2	28.7 ±2.0
5	10	29.6 ±2.6	30.6 ±2.1	32.8** ±2.6	30.4 ±3.2

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group ($p<0.05$, Dunnett's multiple comparison)
**: Significantly different compared to control group ($p<0.01$, Dunnett's multiple comparison)

Table 8. Food consumption of females (Group summary)

Group	No. of animals	Group mean food consumption (mean ±S.D., g/rat/day)			
		Week 1	Week 2	Week 3	Week 4
1	10	19.0 ±1.9	20.7 ±2.8	22.4 ±2.5	22.2 ±2.0
2	10	20.3 ±2.0	21.8 ±3.5	23.3 ±2.6	22.3 ±3.3
3	10	21.0 ±2.9	23.3 ±3.1	23.0 ±3.9	23.4 ±1.7
4	10	20.4 ±2.0	22.4 ±3.6	21.8 ±2.0	23.3 ±4.3
5	10	21.5* ±1.8	23.5 ±3.8	25.0 ±2.4	24.2 ±2.7

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group ($p<0.05$, Dunnett's multiple comparison)

Ophthalmic exam: There were no abnormal findings during the study.
Hematology: In males, MCH and MCHC were increased significantly in group 3 rats with changes in WBC differential counts as shown below.

Table 10. Hematological values of males (Group summary)

Group	No. of animals	Hematological values (mean ±S.D.)							
		WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT (%)	PLT (10^3/mm^3)	MCV (μm^3)	MCH (pg)	MCHC (g/dl)
1	10	11.54 ±3.38	7.25 ±0.32	14.90 ±0.66	45.60 ±2.57	958.60 ±129.32	62.90 ±2.51	20.55 ±0.74	32.68 ±0.67
2	10	11.60 ±3.10	7.03 ±0.29	14.63 ±0.46	43.77 ±2.00	1034.40 ±179.31	62.40 ±2.22	20.87 ±0.91	33.47 ±0.94
3	10	11.87 ±2.35	7.19 ±0.26	15.34 ±0.45	45.75 ±1.93	1102.00 ±187.30	63.70 ±1.64	21.33* ±0.59	33.55* ±0.75
4	10	12.10 ±3.11	7.14 ±0.46	14.78 ±0.68	44.74 ±2.79	979.00 ±185.47	62.60 ±1.84	20.75 ±0.56	33.10 ±0.70
5	10	11.37 ±2.91	7.19 ±0.42	15.11 ±0.81	45.43 ±3.04	1007.70 ±126.59	63.10 ±1.52	21.03 ±0.51	33.28 ±0.66

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group ($p<0.05$, Dunnett's multiple comparison)

Table 10. (Continued) Hematological values of males (Group summary)

Group	No. of animals	Hematological values (mean ±S.D.)							
		WBC differential count (n / 100 WBCs)						PT† (sec)	APTT† (sec)
		Segs	Eos	Basos	Lymps	Monos	Bands		
1	10	13.20 ±3.65	0.90 ±0.74	0.00 ±0.00	85.60 ±3.84	0.30 ±0.48	0.00 ±0.00	15.89 ±0.56	21.24 ±2.40
2	10	15.80 ±2.30	1.20 ±0.63	0.00 ±0.00	82.90 ±2.51	0.10 ±0.32	0.00 ±0.00	16.28 ±0.77	20.85 ±1.49
3	10	14.60 ±4.58	0.40 ±0.70	0.00 ±0.00	85.00 ±4.35	0.00* ±0.00	0.00 ±0.00	16.47 ±0.63	20.76 ±1.56
4	10	15.60 ±2.88	0.80 ±0.92	0.00 ±0.00	83.70 ±2.83	0.00* ±0.00	0.10 ±0.32	16.72 ±0.70	21.44 ±2.41
5	10	21.20** ±4.08	0.90 ±0.88	0.00 ±0.00	77.80** ±4.76	0.00* ±0.00	0.10 ±0.32	16.54 ±0.83	21.44 ±2.46

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group ($p<0.05$, Dunnett's multiple comparison)
**: Significantly different compared to control group ($p<0.01$, Dunnett's multiple comparison)

†: N=9 in Groups 1 and 5

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Blood chemistry: In males, total cholesterol was increased in groups 3, 4, and 5 as shown below. It appears that there were no such changes in female rats.

Table 12. (Continued) Blood chemical values of males (Group summary)

Group	No. of animals	Blood chemical values (mean ±S.D.)						
		T-CHO (mg/dl)	GLU (mg/dl)	T-BIL (mg/dl)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	A/G ratio
1	10	68.90 ±9.95	130.70 ±21.46	0.07 ±0.03	146.40 ±1.58	4.74 ±0.21	105.00 ±1.83	0.69 ±0.06
2	10	83.50 ±13.18	124.00 ±15.94	0.06 ±0.01	146.20 ±1.32	4.81 ±0.37	105.10 ±2.42	0.67 ±0.05
3	10	95.00** ±12.74	118.50 ±16.01	0.07 ±0.01	146.10 ±1.66	4.67 ±0.33	104.00 ±1.76	0.70 ±0.00
4	10	89.10** ±18.38	114.20 ±10.12	0.06 ±0.02	146.10 ±1.29	4.77 ±0.44	105.40 ±1.71	0.67 ±0.05
5	10	91.40** ±14.25	118.40 ±20.29	0.07 ±0.05	146.50 ±1.84	4.67 ±0.44	105.10 ±1.79	0.67 ±0.05

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

**: Significantly different compared to control group (p<0.01, Dunnett's multiple comparison)

Urinalysis: No significant changes were noted.

Organ weights: In male rats, absolute adrenal weights in groups 3, 4, and 5 were increased. The absolute mean kidney weight in group 3 was also increased as shown below. There were no such changes in females.

Table 16. Organ weights of males (Group summary)

Group	No. of animals	Terminal bodyweight (g)	Absolute organ weight (mean ±S.D., g)								
			Brain	Thymus	Heart	Liver	Spleen	Adrenals	Kidneys	Testes	Epididymes
1	10	327.5 ±23.0	1.875 ±0.034	0.416 ±0.069	1.043 ±0.083	9.116 ±1.423	0.628 ±0.070	0.056 ±0.008	2.138 ±0.177	2.958 ±0.222	0.870 ±0.111
2	10	332.5 ±21.7	1.862 ±0.039	0.487 ±0.141	1.082 ±0.086	8.989 ±1.079	0.635 ±0.079	0.063 ±0.006	2.190 ±0.147	3.044 ±0.364	0.879 ±0.095
3	10	343.2 ±23.9	1.915 ±0.062	0.472 ±0.133	1.131 ±0.085	9.281 ±0.548	0.734 ±0.080	0.076** ±0.008	2.335* ±0.107	3.085 ±0.243	0.853 ±0.079
4	10	326.6 ±20.1	1.902 ±0.057	0.515 ±0.104	1.079 ±0.096	8.571 ±0.686	0.628 ±0.061	0.066* ±0.006	2.123 ±0.143	2.958 ±0.332	0.866 ±0.085
5	10	339.7 ±19.6	1.912 ±0.081	0.511 ±0.106	1.141 ±0.088	9.414 ±0.724	0.741 ±0.172	0.075** ±0.013	2.150 ±0.126	3.115 ±0.245	0.878 ±0.076

Group 1: Vehicle control (2 ml/kg); Group 2: Valtropin™ (0.2 IU/kg/day); Group 3: Valtropin™ (2 IU/kg/day); Group 4: US Humatrope (0.2 IU/kg/day); Group 5: US Humatrope (2 IU/kg/day)

*: Significantly different compared to control group (p<0.05, Dunnett's multiple comparison)
**: Significantly different compared to control group (p<0.01, Dunnett's multiple comparison)

Gross necropsy findings: An atrophy of testes was observed in the LD males and an enlarged spleen was seen in male group 5. In females, white reddish foci were observed in group 3 and 4, which were not appeared to be related to the test article. There were no test article dose-related changes except some incidences at injection sites as shown below.

Table 18. Gross necropsy findings (Group summary)

Sex	Male					Female				
Group	1	2	3	4	5	1	2	3	4	5
Dosage (IU/kg/day)	0	0.2	2	0.2	2	0	0.2	2	0.2	2
Number of animals examined at terminal sacrifice	10	10	10	10	10	10	10	10	10	10
External:										
No significant findings	10	10	10	10	10	10	10	10	10	10
Internal:										
No significant findings	2	3	1	1	2	5	5	5	6	2
Injection site:										
Scar	3	2	6	5	5	3	5	5	4	4
Subcutaneous hemorrhage	7	7	8	7	6	5	3	5	3	8
Testes:										
Atrophy		1								
Spleen:										
Enlarged					1					
Liver:										
White reddish foci								1	1	

Histopathological findings: Histopathological findings were limited to the injection sites, although there were some sporadic changes in a few organs, which appear not related to the treatment. Histology findings in males and females are summarized below (Tables 19 and 20).

Table 19. Histopathological findings of males (Group summary)

Group	1	2†	3	4†	5
Dosage (IU/kg/day)	0	0.2	2	0.2	2
Number of animals examined at terminal sacrifice	10	10	10	10	10
No significant findings	2	6	1	5	1
Skin at the injection site:					
Subcutaneous hemorrhage					
Minimal	4		5		2
Slight	3		2		3
Inflammatory cell infiltration					
Minimal	3		6		6
Slight	1		2		3
Adrenal glands:					
Cortical hypertrophy					
Minimal		4	4	5	5
Heart:					
Inflammatory cell infiltration, focal					
Minimal	1				
Thymus:					
Hemorrhage					
Minimal			1		
Epididymides:					
Sperm granuloma					
Slight			1		
Kidney:					
Inflammatory cell infiltration					
Minimal					1

†: Only adrenal glands of Groups 2 and 4 were examined microscopically.

Table 20. Histopathological findings of females (Group summary)

Group	1	2†	3	4†	5
Dosage (IU/kg/day)	0	0.2	2	0.2	2
Number of animals examined at terminal sacrifice	10	10	10	10	10
No significant findings	5	10	2	10	5
Skin at the injection site:					
Subcutaneous hemorrhage					
Minimal	1		2		
Slight	2		1		2
Inflammatory cell infiltration					
Minimal	3		5		4
Slight			2		1
Injected residual substance					
Minimal			1		
Kidney:					
Mineralization					
Minimal	2		1		1

†: Only adrenal glands of Groups 2 and 4 were examined microscopically.

Study title: A 90-Day Subcutaneous Repeated Toxicity Study of LBD-009 (recombinant human growth hormone without N-methionine) in Mice

Key study findings:
ICR mice were injected subcutaneously with LBD-009 continuously for up to 90 days. Decreased locomotor activity, decreased respiratory rate, difficulty in breathing and comatose state were observed during the 2nd and 3rd weeks after administration in female 10 IU/kg group. Since these clinical signs and symptoms disappeared spontaneously without specific intervention in the 4th week of administration. There were two deaths in the HD females, which may be due to be immune reactions to foreign protein in mice as the sponsor considered.

The high dose provided significant increase body weights with an increase in some organ weights, karyomegaly of liver cells seemed to be a result of facilitated protein synthesis. These changes were reversible based on the light microscopic examination, although there were no recovery observation groups in this test. Considering the two deaths during treatment and the observation of general clinical signs such as decreased activity, decreased respiratory rate, gasping and lethargy in the 2nd and 3rd weeks of administration in the female 10 IU/kg group, 10 IU/kg/day was considered to be the toxic dose in female animals. In male animals, the same dose was deemed to be a tolerated dose, considering that polyploidy of liver cells was observed.
Thus, the maximum tolerated dose is between 3 IU/kg/day for female mice, and may be 10 IU/kg/day for males. NOAEL = 3 IU/kg/day for male and female.

Study no.: Test No. S-234
Volume #, and page #: Toxicology 1-333
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 9/29/1991
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Lot#JI101

Methods

Doses: 0(vehicle), 1, 3, and 10 IU/kg
Species/strain: ICR mouse (SPF)
Number/sex/group or time point (main study): 15 mice/sex/group
Route, formulation, volume, and infusion rate: Subcutaneous, the injection volume was 5 ml/kg/day.
Satellite groups used for toxicokinetics or recovery: None
Age: 4 Weeks
Weight: Males 20-27 g; Females 17-22 g on arrival

Observations and times:

Mortality: Once a day
Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Ophthalmoscopy was done two times in all animals before treatment and after final administration.

EKG: NA
Hematology: Before autopsy, animals fasted overnight were ether anaesthetized. The sponsor took a blood sample from a posterior vein and treated the sampled blood with EDTA for anticoagulation and used it for the blood tests.
Clinical chemistry: From the posterior venous blood sample taken, the sponsor separated serum by centrifugation (3000 rpm, for 10 min) for the biochemical lab tests.
Urinalysis: In all animals which were going to be sacrificed, urinalysis was performed after the final administration. The sponsor examined specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen and nitrite in urine within 3 hours of urination, in the last week of injection. Multistix (Ames) and CliniTek-10 (Ames) were used for the tests.

Gross pathology: For all animals on which autopsy was performed, the sponsor took the following internal organs and fixed them with 10 % neutral formalin solution (skin as well as testis and sternum were treated with Bouin's solution). In general, the samples were stained with hematoxylin-eosin before the gross pathological examination.

Organ weights (specify organs weighed if not in histopath table): Conventional methods were used.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Results
Mortality: There was one death in the LD female group on Day 90 and two deaths in the HD female group on Days 14 and 21. The sponsor did not explain the exact causes of death, but appeared to be immunological reactions. It appears that the deaths are not related to the treatment duration and drug dose as shown below.

Table 2. Mortality of males and females (group summary)

GROUP SUMMARY OF MORTALITY

STUDY : S-234		DAYS ON TEST										
SEX	DOSE (IU/kg)	0	7	14	21	28	42	56	70	84	90	MORTALITY
MALE												
	0	0	0	0	0	0	0	0	0	0	0	0/15
	0	0	0	0	0	0	0	0	0	0	0	0/15
	1	0	0	0	0	0	0	0	0	0	0	0/15
	3	0	0	0	0	0	0	0	0	0	0	0/15
	10	0	0	0	0	0	0	0	0	0	0	0/15
FEMALE												
	0	0	0	0	0	0	0	0	0	0	0	0/15
	0	0	0	0	0	0	0	0	0	0	0	0/15
	1	0	0	0	0	0	0	0	0	0	1*	1/15
	3	0	0	0	0	0	0	0	0	0	0	0/15
	10	0	0	1	1	0	0	0	0	0	0	2/15

* Animal Found Dead

Clinical signs:

In the female 10 IU/kg group, there was decreased activity, piloerection and decreased respiratory rate in the 2nd week of administration, and in the 2nd and 3rd weeks there was crouching, gasping, lethargy and lying on the right side. These symptoms were present immediately after each injection, but they did not persist until the next administration. The degree and the frequency of symptoms decreased, and in the 4th week of administration, they were no longer observed. In the 3 IU/kg group, there was a decreased activity in the 2nd week and 3rd week of administration in addition to crouching and gasping at a low rate.

Body weights:

In the male 10 IU/kg group, there was an increase in body weights from the 3rd week of administration that persisted until the end of the test period. In the other treated groups, there were no dose-dependent body weight changes. In the female 10 IU/kg group, there was a significant increase in body weights from the 1st week of administration until the end of the test period. In the 3 IU/kg group, there was a significant increase in body weights in the 2nd week of administration, in the 3rd, 5th and 11th weeks of administration, body weights were decreased significantly compared to the negative control. These changes were not dose-dependent and only the HD may be effective dose in mice as shown below.

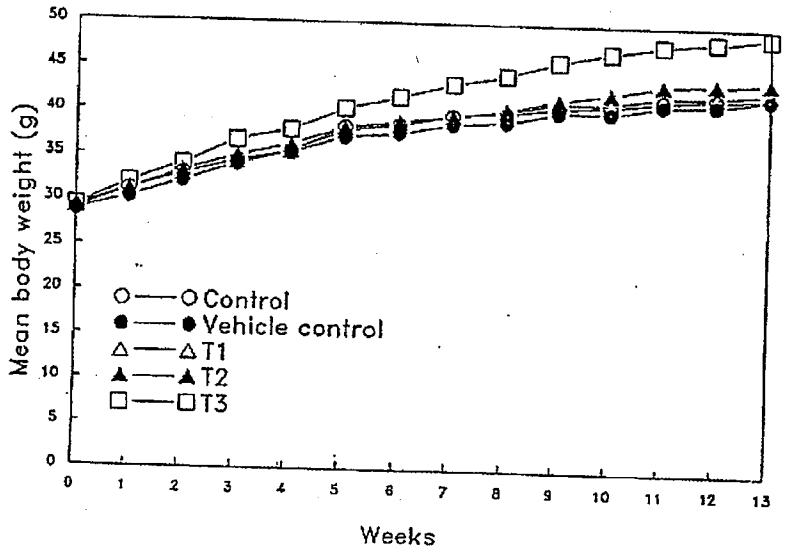

Fig. 1. Body weights of males

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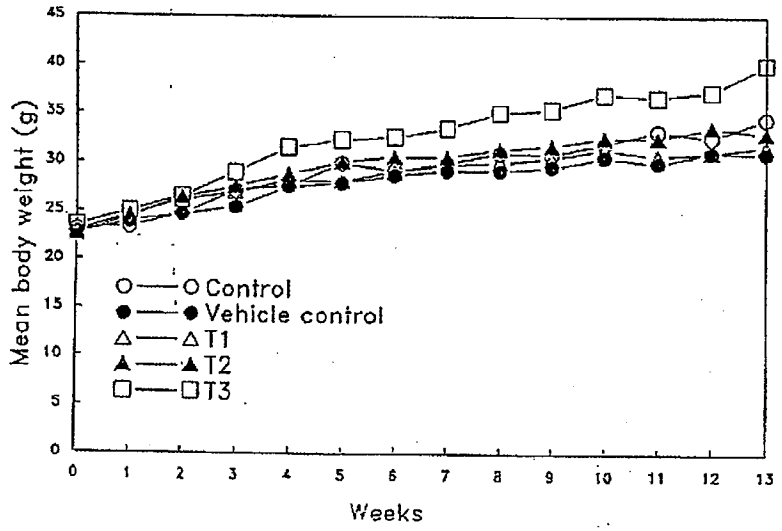

Fig. 2. Body weights of females

Food consumption:
There were no changes in food consumption in the male animals during the whole test period compared to the negative control group. In the female 10 IU/kg group, there was a significant increase of food consumption in the 6th week of administration. In the 1 and 3 IU/kg groups there was a decrease in food consumption in the 6th week of administration, which seemed to be unrelated to the injected amount of the test article. In the other treated groups, there were no changes in food consumption.

Ophthalmoscopy: In all treated groups of the 28-day group and 90-day main group, there were no abnormalities detected.

EKG: NA
Hematology:
In the male 10 IU/kg group of the 90-day main group, there was a significant increase in RBC, HGB and HCT. In the male 1 IU/kg group there was an increase of HGB and HCT. The sporadic changes appear not test article dose-dependent. No significant changes attributable to the test article were seen in the female animals of the treated groups.

Clinical chemistry:
In the male 10 IU/kg group there was a significant increase in glucose, albumin, TCHO, and total protein with a decrease in ALP in the 10 IU/kg group on Day 90. There were no

such increases in the LD or MD male groups. However, in females total cholesterol was significantly elevated in the HD group at Day 90. The level of glucose was elevated only in the LD group as shown below. Therefore, it is not clear the changes in several serum parameters are due to action of valtropin, although the changes appeared not related directly to the dose or treatment duration.

Table 9-3. Serum biochemical values of males examined at 90 days (group summary)

SUMMARY OF CLINICAL CHEMISTRY TESTS

STUDY : S-234 SEX : MALE

TESTS: / UNITS:	GOT IU/l	GPT IU/l	ALP IU/l	BUN mg/dl	CRN mg/dl	GLU mg/dl	TCHO mg/dl	TP g/dl
Group : CONTROL								
MEAN	124.17	55.92	153.58	22.83	0.30	165.58	131.04	8.24
S.D	59.805	21.889	38.986	4.125	0.045	38.541	21.193	0.579
N	10	10	10	10	10	10	10	10
Group : VEHICLE CONTROL								
MEAN	105.58	62.32	141.89	24.26	0.18	149.15	124.60	8.17
S.D	44.145	43.077	34.801	8.775	0.052	65.818	38.258	0.849
N	10	10	10	10	10	10	10	10
Group : T1								
MEAN	118.17	58.19	148.18	24.39	0.10	185.74	148.48	8.37
S.D	45.429	28.863	22.159	3.787	0.000	69.845	37.854	0.545
N	10	10	10	10	10	10	10	10
Group : T2								
MEAN	135.97	69.89	123.35	24.50	0.14	174.71	125.20	8.74
S.D	51.357	14.610	37.443	5.277	0.184	55.431	20.818	0.463
N	10	10	10	10	10	10	10	10
Group : T3								
MEAN	109.84	47.58	106.07*	24.71	0.12	257.83**	178.10*	7.45**
S.D	49.386	22.007	38.793	8.729	0.054	45.874	45.072	0.662
N	10	10	10	10	10	10	10	10

TESTS: / UNITS:	ALB g/dl	TBIL mg/dl	CL mEq/l	NA mEq/l	K mEq/l
Group : CONTROL					
MEAN	3.87	1.78	119.3	148.2	5.53
S.D	0.420	0.214	5.68	3.04	2.328
N	10	10	10	10	10
Group : VEHICLE CONTROL					
MEAN	3.60	1.88	120.7	152.8	6.53
S.D	0.383	0.152	5.60	5.80	2.771
N	10	10	10	10	10
Group : T1					
MEAN	4.02	1.84	117.8	149.3	7.56
S.D	0.353	0.148	6.54	5.61	1.162
N	10	10	10	10	10
Group : T2					
MEAN	4.18	1.90	118.1	149.6	6.89
S.D	0.302	0.295	6.11	8.02	2.430
N	10	10	10	10	10
Group : T3					
MEAN	4.54**	1.87	112.1*	143.1	7.65
S.D	0.429	0.168	2.75	9.15	2.735
N	10	10	10	10	10

Analysis of Variance using Dunnett's Procedure

* : Significantly different from control value at p<0.05
** : Significantly different from control value at p<0.01

Table 9-4. Serum biochemical values of females examined at 90 days (group summary)

SUMMARY OF CLINICAL CHEMISTRY TESTS

STUDY : S-234 SEX : FEMALE

TESTS: UNITS:	GOT IU/l	GPT IU/l	ALP IU/l	BUN mg/dl	CRN mg/dl	GLU mg/dl	TCHO mg/dl	TP g/dl
Group : CONTROL								
MEAN	76.08	29.27	225.74	20.14	0.34	152.92	87.05	6.70
S.D	18.640	18.808	48.112	10.565	0.338	21.691	22.779	0.769
N	10	10	10	10	10	10	10	10
Group : VEHICLE CONTROL								
MEAN	77.85	24.28	212.42	15.72	0.36	148.58	78.17	6.43
S.D	18.869	11.178	51.842	7.653	0.711	34.854	21.388	0.330
N	10	10	10	10	10	10	10	10
Group : T1								
MEAN	84.49	55.84	178.12	28.17	0.17	201.75**	92.33	6.01
S.D	15.054	65.630	42.407	8.491	0.183	41.155	18.276	0.849
N	9	9	9	9	9	9	9	9
Group : T2								
MEAN	78.65	24.11	188.50	18.69	0.69	138.12	80.27	6.92
S.D	11.445	7.071	15.113	4.533	0.903	43.043	19.600	0.628
N	10	10	10	10	10	10	10	10
Group : T3								
MEAN	73.55	24.64	172.40	13.18	0.58	165.08	135.05**	6.38
S.D	8.397	5.274	48.033	8.920	0.754	25.878	32.571	0.568
N	9	9	9	9	9	9	9	9

TESTS: UNITS:	ALB g/dl	TBIL mg/dl	CL mmol/l	NA mmol/l	K mmol/l
Group : CONTROL					
MEAN	3.56	1.59	115.5	140.2	4.66
S.D	0.534	0.212	6.94	5.42	0.837
N	10	10	10	10	10
Group : VEHICLE CONTROL					
MEAN	3.42	1.58	112.3	137.5	5.80
S.D	0.283	0.200	5.42	9.02	1.353
N	10	10	10	10	10
Group : T1					
MEAN	3.67	1.48	114.4	134.2	5.38
S.D	0.424	0.170	5.58	5.62	0.855
N	9	9	9	9	9
Group : T2					
MEAN	3.60	1.57	114.2	132.9	5.50
S.D	0.528	0.250	4.77	10.36	1.858
N	10	10	10	10	10
Group : T3					
MEAN	3.83	1.82	117.7	142.5	4.81
S.D	0.844	0.470	5.81	13.30	1.025
N	9	9	9	9	9

Analysis of Variance using Dunnett's Procedure

* : Significantly different from control value at p<0.05
** : Significantly different from control value at p<0.01

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Urinalysis: In all treated animals of the 28-day group and 90-day main group, there were no abnormalities.

Gross pathology: There was dark-red congestion of the duodenum, jejunum, ileum and cecum in animal no. 137 in the 10 IU/kg group, which died during treatment. In animal no. 143 there were milky-white spots on the adrenal glands and dark-red congestion of the duodenum and cecum.

Organ weights (specify organs weighed if not in histopath table):

In the 28-day observation group, there was an increase in the absolute weight of the left kidney in the male 10 IU/kg group, but in the other groups there were no changes in organ weights attributable to the treatment. In the female 10 IU/kg group, there was an increase in the absolute weight of the liver, kidney and right ovary and an increase in the relative weight of the liver. In the male 10 IU/kg group of the 90-day main group, there was a significant increase in body weight, an increase in the absolute weight of the liver, kidneys and spleen as well as an increase in the relative weight of the liver.

Furthermore, there was a decrease in the relative weight of the brain and testis. In the vehicle control group, there was a decrease in the absolute and relative weight of the spleen and testis, but in all other groups there were no such changes. In the female 10 IU/kg group, there was a significant increase in body weight as well as a significant increase in the absolute weight of the liver and heart and a significant increase in the relative weight of the liver. There was a significant decrease in the relative weight of the brain. In the vehicle control group, there was a significant decrease in the absolute weight of the right kidney, which was unrelated to the treatment as shown below.

Table 11-3. Absolute organ weights of males examined at 90 days (group summary)

ORGAN WEIGHT SUMMARY

STUDY: S-234 SEX : MALE

GROUP:	CONTROL	VEHICLE CONTROL	T1	T2	T3
DOSAGE: (MG/KG)	0	0	1	3	10
BODY WEIGHT(G)	38.4	38.6	38.2	39.9	44.8
SD	1.80	2.78	3.92	2.48	3.78**
NUMBER OF ANIMALS	10	10	10	10	10
LIVER(G)	1.514	1.501	1.558	1.651	2.008**
SD	0.1331	0.1400	0.2142	0.2251	0.3106
N	10	10	10	10	10
KIDNEY-LEFT(G) >	0.314	0.291	0.319	0.301	0.363*
SD	0.0458	0.0255	0.0416	0.0483	0.0480
N	10	10	10	10	10
KIDNEY-RIGHT(G) >	0.314	0.295	0.301	0.352	0.370*
SD	0.0378	0.0284	0.0462	0.0578	0.0517
N	10	10	10	10	10
KIDNEY TOTAL:	0.628	0.587	0.620	0.653	0.734*
SD	0.0823	0.0538	0.0855	0.1035	0.0991
N	10	10	10	10	10
SPLEEN(G)	0.103	0.0776	0.088	0.105	0.130*
SD	0.0219	0.0078	0.0107	0.0308	0.0352
N	10	10	10	10	10
HEART(G)	0.185	0.190	0.190	0.189	0.213
SD	0.0225	0.0225	0.0257	0.0282	0.0219
N	10	10	10	10	10
BRAIN(G)	0.490	0.505	0.519	0.507	0.517
SD	0.0238	0.0200	0.0203	0.0248	0.0298
N	10	10	10	10	10
LUNG(G)	0.211	0.192	0.202	0.231	0.224
SD	0.0165	0.0139	0.0317	0.0133	0.0167
N	10	10	10	10	10
ADRENAL-LEFT(G) >	0.00228	0.00241	0.00261	0.00268	0.00283
SD	.000622	.000505	.000642	.000719	.000510
N	10	10	10	10	10
ADRENAL-RIGHT(G) >	0.00214	0.00240	0.00263	0.00287	0.00256
SD	.000831	.000644	.000570	.000675	.000450
N	10	10	10	10	10
ADRENAL TOTAL:	0.00452	0.00481	0.00529	0.00555	0.00548
SD	.001339	.000442	.001050	.001551	.000941
N	10	10	10	10	10

Table 11-4. Absolute organ weights of females examined at 90 days (group summary)

ORGAN WEIGHT SUMMARY

STUDY: S-234 SEX : FEMALE

GROUP:	CONTROL	VEHICLE CONTROL	T1	T2	T3
DOSAGE: (μL/kg)	0	0	1	3	10
BODY WEIGHT(G)	30.2	27.7	28.2	30.1	35.0**
SD	2.13	1.71	2.50	1.65	2.37
NUMBER OF ANIMALS	10	10	9	10	9
LIVER(G)	1.237	1.129	1.231	1.273	1.618**
SD	0.2117	0.1328	0.2106	0.1814	0.1880
N	10	10	9	10	9
KIDNEY-LEFT(G) >	0.202	0.178	0.181	0.198	0.221
SD	0.0259	0.0220	0.0237	0.0200	0.0186
N	10	10	9	10	9
KIDNEY-RIGHT(G) >	0.210	0.185*	0.187	0.207	0.228
SD	0.0235	0.0149	0.0190	0.0198	0.0215
N	10	10	9	10	9
<LINK TOTAL:	0.412	0.362*	0.368	0.408	0.449
SD	0.0523	0.0365	0.0410	0.0371	0.0368
N	10	10	9	10	9
SPLEEN(G)	0.104	0.080	0.058	0.093	0.125
SD	0.0188	0.0170	0.0150	0.0255	0.0217
N	10	10	9	10	9
HEART(G)	0.145	0.136	0.145	0.141	0.169**
SD	0.0175	0.0117	0.0253	0.0135	0.0453
N	10	10	9	10	9
BRAIN(G)	0.513	0.491	0.500	0.508	0.520
SD	0.0374	0.0287	0.0192	0.0135	0.0132
N	10	10	9	10	9
[illegible](G)	0.191	0.224	0.252	0.190	0.280
SD	0.0158	0.1203	0.1817	0.0330	0.1259
N	10	10	9	10	9
ADRENAL-LEFT(G) >	0.00403	0.00444	0.00426	0.00443	0.00451
SD	.000547	.000854	.000871	.000510	.001096
N	10	10	9	10	9
ADRENAL-RIGHT(G) >	0.00418	0.00404	0.00432	0.00382	0.00402
SD	.001050	.000581	.000701	.001164	.000983
N	10	10	9	10	9
<LINK TOTAL:	0.00817	0.00848	0.00859	0.00825	0.00853
SD	.001693	.000944	.001395	.001460	.002228
N	10	10	9	10	9

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Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

In the male animals of the 28-day observation group, there were 1, 1, 3, 5 and 5 cases of karyomegaly and chromosome polyploidy manifested by binuclear cells, in the negative control group, vehicle control group, 1 IU/kg group, 3 IU/kg group and 10 IU/kg group, respectively. These changes were attributable to the test article. In the 10 IU/kg group, there were one case of an isolated cyst in each left and right kidney, one case of tubular basophilia in the left kidneys and one case of protein casts in the urinary bladder. But these changes happened at a very low rate and spontaneously, these were deemed to be unrelated to the test article. Furthermore, in other treated groups only spontaneous changes were observed. In the female animals of the 28-day observation group, there were 0, 0, 2, 4 and 5 cases of liver cell polyploidy in the negative control group, the vehicle control groups, 1 IU/kg group, 3 IU/kg group and 10 IU/kg group, respectively. Additionally, there was a case of vacuolation /reticularis and a case of congestion in left and right kidneys, which was not attributable to the test article.

In male animals of the 90-day group there were 6, 5, 8, 9 and 9 cases of liver cell polyploidy in the negative control group, the vehicle control group, 1 IU/kg group, 3 IU/kg group and 10 IU/kg group, respectively. In the 10 IU/kg group, there was one case of spindle cell proliferation in the adrenal gland and one case of hydronephrosis of the right kidney which was considered to be spontaneous. In the female animals of the negative control group, vehicle control group, 1 IU/kg group, 3 IU/kg group and 10 IU/kg group there were 5, 4, 4, 6 and 10 cases of liver cell polyploidy, respectively. In the 10 IU/kg group, there was one case of interstitial nephritis of the left kidney, two cases of isolated cyst in the right kidney, one case of a protein plug in the left and right kidneys and three cases of spindle cell proliferation in the adrenal gland and three cases of vacuolation, all of which happened at low rate and spontaneously and were deemed not to be attributable to the test article.

Toxicokinetics:
No data.

Study title: A 90-Day Subacute and Subcutaneous Toxicity Test of LBD-009 in Rats

Key study findings:

In the 90-day subacute hypodermic toxicity test in SD rats at doses of 1, 3, and 10 IU/kg/day, there was no death. No animals were found dead or moribund during the whole test period. The general clinical findings during the test period were hair loss, induration, ocular congestion, dark material around the eyes and the nose, wound limb and blood loss. There was no significant difference in the incidence of these clinical signs between the control groups and all treated groups, and the incidence rate was quite low. Thus, these signs and symptoms seemed to be unrelated with the injected dose. In the male 10 IU/kg group and in the female 3 IU/kg and 10 IU/kg groups there was a significant increase in body weights as the case in mice.

In the 90-day male main group of 10 IU/kg there were increases in the absolute weights of the adrenal gland, heart and spleen, as well as an increase in the relative spleen weight, and a decrease in the relative brain weight. In the 3 IU/kg group there was an increase in the absolute weight of the adrenal gland, as well as a decrease in the relative weight of the liver and an increase in the relative weight of the adrenal gland. In the 1 IU/kg group there was an increase in the absolute weight of the adrenal gland. In the 90-day female group of 10 IU/kg there was an increase in the absolute weights of the liver, kidney, spleen, ovary, thyroid gland, and lung, as well as a decrease in the relative heart weight and a decrease in the relative brain weight. In the 3 IU/kg group there was an increase in the absolute spleen weight and a decrease in the relative heart weight. The increases in organ weights seemed to be due to facilitation of tissue growth by the test article. The decrease in the relative brain weight observed in male and female animals did not seem to be due to the test article, since the brain weight was not changed while body weight was increased with treatment. Generally, the injection of growth hormone to animals was associated with increases of organ weights but not with changes of the brain weight. In this test, the maximum tolerated dose seemed to be more than 10 IU/kg/day and the NOAEL (no observed adverse effect level) to be greater than >3 IU/kg/day.

Study no.: Test No. S-235
Volume #, and page #: Toxicology 1-333
Conducting laboratory and location: [redacted]

b(4)

Date of study initiation: 10/4/1991
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Lot#JI1013/4, 100%
Methods

Doses: 0(vehicle), 1, 3, and 10 IU/kg/day
Species/strain: Rat/Sprague Dawley (SPF)
Number/sex/group or time point (main study): 15 rats/sex/group
Route, formulation, volume, and infusion rate: Subcutaneous, and injection volume was 5 ml/kg/day.
Satellite groups used for toxicokinetics or recovery: None
Age: 5 Weeks
Weight: Males 71-103 g; Females 67-96 g on arrival

Observations and times:

Mortality: Once a day
Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Ophthalmoscopy was done in all animals once before treatment and was repeated in the animals of the control groups and of the high dose group only at the last week of administration.

EKG: NA
Hematology: Before autopsy, animals fasted overnight were ether anaesthetized. The sponsor took a blood sample from a posterior vein, which was treated it with EDTA for anticoagulation before blood tests.

Clinical chemistry: The venous blood samples were separated serum by centrifugation (3000 rpm, for 10 min) for the biochemical lab tests.
Urinalysis: In all animals to be sacrificed, urinalysis was performed after the final administration. Specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen and nitrite in urine were examined within 3 hours of urination, in the last week of injection. Multistix(Ames) and CliniTek-10 (Ames) were used for the tests.

Gross pathology: All animals were subjected to autopsy. The following internal organs were collected and fixed them with 10 % neutral formalin solution (skin, testis, and sternum were treated with Bouin's solution). The sponsor stained the samples with hematoxylin-eosin before the gross pathological examination.
Organ weights (specify organs weighed if not in histopath table):
We measured the weights of the following organs: kidneys (left and right), liver, spleen, heart, lung, adrenal gland (left and right), thyroid, brain, testis (left and right) or ovary (left and right).

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )
For all animals on which autopsy was performed, the sponsor took the following internal

organs and fixed them with 10 % neutral formalin solution (sternum, testis, eyeball, epididymis and skin were treated with Bouin's solution).

Statistical Analysis:

The statistical analysis of data was done according to the method of multiple comparison-analysis. For body weight, food and water consumption, amount of urine, results of hematologic and blood chemistry tests, and the weight of internal organs, the level of significance to $\alpha = 0.05$ or 0.01 in one-way analysis of variance. If p-value was less than 0.05 or 0.01, the sponsor did a Dunnett's or Schaffer's multiple comparison analysis for differences between control and treatment groups. The result of urinalysis was analyzed by Kruskal-Wallis of non-parametric method using ranked data. If p-value was less than 0.05, Schaffer's test was used to detect the differences between control and treatment groups. Common clinical signs, findings in autopsy and gross pathological changes were presented as percentage.

Results

Mortality: There was no death during the study period.

Clinical signs:
In the 1 IU/kg group, in the 9th week, two cases of hair loss out of 10.
In the 3 IU/kg group, one case of induration out of 10 occurred in the 5th week. In the 10 IU/kg group, one case of congestion eyeball out of 15 in the first week, one case of dark material around the nose out of 10 in the 8th week, and one case of hair loss out of 15 in the 3rd week. In the female control animals, there was one case of a limb wound and blood loss out of 15 (first week of injection), and from the 9th week to 10th week there was one case of limb wound and blood loss out of 10.

Body weights:
In the male 10 IU/kg group, from the 8th week of injection (except 10th week) there was a significant increase in body weight ($p < 0.01$, $p < 0.05$). In the female 3 IU/kg ($p<0.05$, $p<0.01$) and 10 IU/kg ($p<0.01$, $p<0.05$) groups, there was a significant increase in body weight from the 2nd week of administration as shown below.

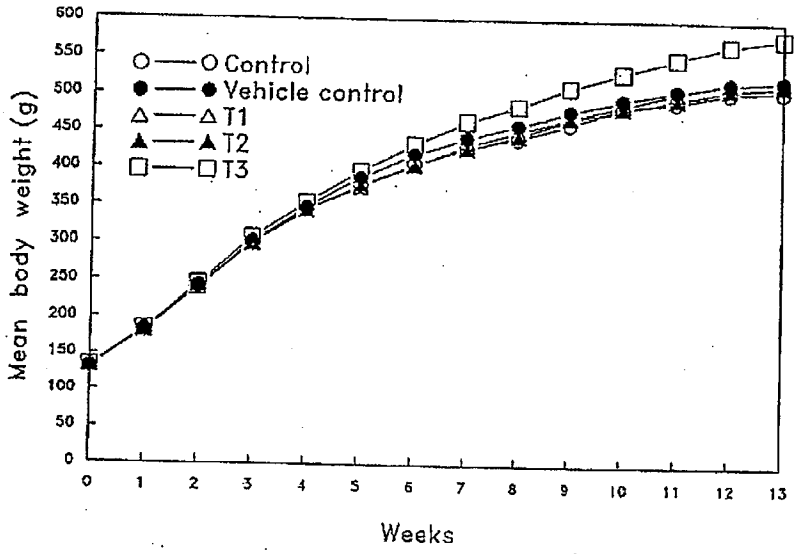

Fig. 1. Body weights of males

Appears This Way
On Original

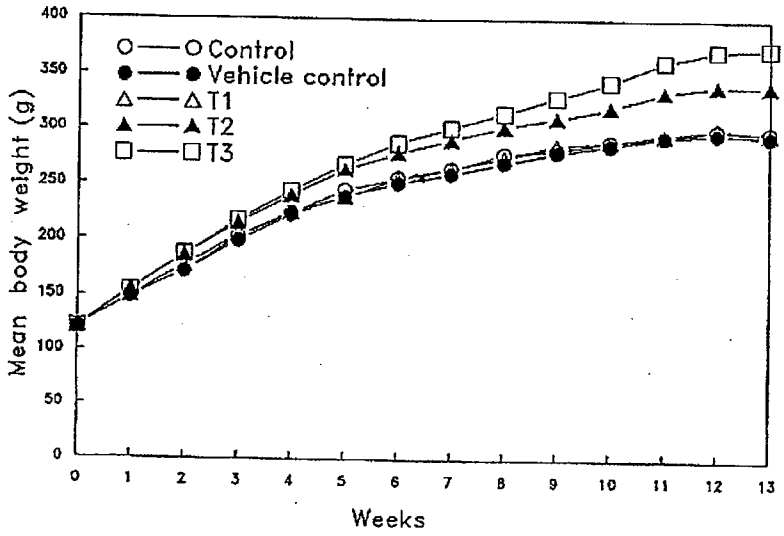

Fig. 2. Body weights of females

Food consumption:
In the male 10 IU/kg/day group, there was an increase in food consumption in the 11th week of injection ($p<0.01$) that normalized in the 12th week. In the female 10 IU/kg/day group, there was an increase of food consumption in the 10th week ($p<0.05$) and 12th week ($p<0.01$) that normalized in the 13th week.

Ophthalmoscopy:
In all treated groups of the 28-day group and 90-day main group, there were no abnormalities detected.
EKG: NA

Hematology:
In the 28-day female group of 1 IU/kg and 10 IU/kg groups, there was an increase in PLT (platelet) count ($p < 0.05$). This was not seen in the 28-day male animals and in the 90-day groups. In the 90-day male group of 1 IU/kg (main group) ($p < 0.05$) and 10 IU/kg groups ($p < 0.05$), there was a decrease of RBC count that was not seen in the male 3 IU/kg group. MCV value increased ($p < 0.01$) regardless of the injected amount in the male 1, 3 and 10 IU/kg groups. MCH value increased ($p < 0.01$) in the male 3 and 10 IU/kg groups. These changes were not seen in female animals.

Clinical chemistry:
In the 28-day female group of 1 IU/kg ($p < 0.01$) and 3 IU/kg ($p < 0.01$), there was a significant increase in the total amount of protein. This change was not seen in the 10 IU/kg group and in the 28-day male group and in the male and female main groups. In the 90-day male group of 10 IU/kg (main group), blood glucose decreased significantly ($p < 0.05$), and the total amount of bilirubin increased ($p < 0.01$). These changes were not observed in female animals, and only in the 3 IU/kg group, there was a significant increase in ALP ($p < 0.05$) as shown below.

Table 8-3. Serum biochemical values of males examined at 90 days (group summary)

SUMMARY OF CLINICAL CHEMISTRY TESTS

STUDY : 8-225 SEX : MALE

TESTS:	GOT	GPT	ALP	BUN	CRN	GLU	TCHO	TP
UNITS:	IU/l	IU/l	IU/l	mg/dl	mg/dl	mg/dl	mg/dl	g/dl
Group : CONTROL : 0 (IU/kg)								
MEAN	95.49	37.38	215.58	13.82	0.33	171.63	90.43	6.84
SD	11.519	8.565	32.858	1.382	0.033	27.182	13.997	0.289
N	10	10	10	10	10	10	10	10
Group : VEHICLE CONTROL : 0 (IU/kg)								
MEAN	98.43	56.74	223.24	14.08	0.37	158.88	80.19	6.90
SD	44.645	85.839	52.327	1.074	0.026	26.690	15.726	0.288
N	10	10	10	10	10	10	10	10
Group : T1 : 1 (IU/kg)								
MEAN	102.03	38.03	201.05	13.56	0.38	153.43	100.58	6.83
SD	30.606	12.850	58.263	2.576	0.048	28.037	18.399	0.479
N	10	10	10	10	10	10	10	10
Group : T2 : 3 (IU/kg)								
MEAN	70.22	28.88	203.98	13.35	0.35	146.55	102.38	6.80
SD	14.205	7.528	52.088	1.554	0.046	22.383	17.025	0.478
N	10	10	10	10	10	10	10	10
Group : T3 : 10 (IU/kg)								
MEAN	80.88	33.78	222.62	13.58	0.37	143.65*	101.29	7.01
SD	25.044	9.006	64.552	1.051	0.038	7.858	12.450	0.269
N	10	10	10	10	10	10	10	10

TESTS:	ALB	TBIL	CL	NA	K
UNITS:	g/dl	mg/dl	mmol/l	mmol/l	mmol/l
Group : CONTROL : 0 (IU/kg)					
MEAN	4.84	0.07	98.3	144.2	5.18
SD	0.258	0.122	3.67	0.22	1.008
N	10	10	10	10	10
Group : VEHICLE CONTROL : 0 (IU/kg)					
MEAN	5.01	0.09	97.6	141.4	5.12
SD	0.254	0.101	1.49	2.93	1.407
N	10	10	10	10	10
Group : T1 : 1 (IU/kg)					
MEAN	4.71	1.04	97.9	141.6	5.61
SD	0.297	0.168	2.33	4.02	1.368
N	10	10	10	10	10
Group : T2 : 3 (IU/kg)					
MEAN	4.94	1.09	97.9	140.7	5.85
SD	0.352	0.035	1.85	4.18	1.551
N	10	10	10	10	10
Group : T3 : 10 (IU/kg)					
MEAN	4.97	1.15**	97.7	141.6	4.87
SD	0.265	0.128	2.77	4.58	0.597
N	10	10	10	10	10

Analysis of variance using Dunnett's procedure

* : Significantly different from control group ($p<0.05$)
** : Significantly different from control group ($p<0.01$)

Table 9-4. Serum biochemical values of females examined at 90 days (group summary)

SUMMARY OF CLINICAL CHEMISTRY TESTS

STUDY : S-235 SEX : FEMALE

TESTS: UNITS:	GOT IU/l	GPT IU/l	ALP IU/l	BUN mg/dl	CRT mg/dl	GLU mg/dl	TCHO mg/dl	TP g/dl
Group : CONTROL : 0 (IU/kg)								
MEAN	38.47	32.24	108.42	15.99	0.49	182.80	76.12	7.45
SD	14.782	10.387	45.857	3.542	0.070	25.359	15.182	0.285
N	30	10	10	10	10	10	10	10
Group : VEHICLE CONTROL : 0 (IU/kg)								
MEAN	32.42	33.07	128.05	14.58	0.44	181.11	78.02	7.48
SD	24.967	12.929	28.287	1.538	0.047	57.303	18.647	0.238
N	30	10	10	10	10	10	10	10
Group : T1 : 1 (IU/kg)								
MEAN	32.43	41.24	98.75	15.07	0.42	156.10	85.08	7.49
SD	10.668	25.133	31.895	1.919	0.031	30.434	17.883	0.382
N	10	10	10	10	10	10	10	10
Group : T2 : 3 (IU/kg)								
MEAN	30.37	27.86	166.69*	15.33	0.39	142.89	80.58	7.11
SD	10.721	4.700	28.298	2.348	0.053	17.416	18.338	0.234
N	10	10	10	10	10	10	10	10
Group : T3 : 10 (IU/kg)								
MEAN	32.08	26.57	147.69	14.88	0.43	139.97	85.08	7.08
SD	10.202	3.533	50.726	2.104	0.064	20.934	14.378	0.522
N	10	10	10	10	10	10	10	10

TESTS: UNITS:	ALB g/dl	TBIL mg/dl	CL mEq/l	NA mEq/l	K mEq/l
Group : CONTROL : 0 (IU/kg)					
MEAN	5.77	1.03	101.5	137.3	4.24
SD	0.453	0.068	2.51	1.27	1.363
N	10	10	10	10	10
Group : VEHICLE CONTROL : 0 (IU/kg)					
MEAN	5.83	1.12	101.0	138.7	4.21
SD	0.406	0.100	3.75	2.38	1.022
N	10	10	10	10	10
Group : T1 : 1 (IU/kg)					
MEAN	5.87	1.00	99.8	137.8	4.58
SD	0.513	0.100	3.68	2.30	1.284
N	10	10	10	10	10
Group : T2 : 3 (IU/kg)					
MEAN	5.29	1.05	100.0	137.0	4.58
SD	0.287	0.127	4.00	1.69	1.033
N	10	10	10	10	10
Group : T3 : 10 (IU/kg)					
MEAN	5.23	1.14	98.2	137.7	4.25
SD	0.456	0.114	3.18	2.19	0.422
N	10	10	10	10	10

Analysis of variance using Dunnett's procedure

* : Significantly different from control group (p<0.05)
** : Significantly different from control group (p<0.01)

Urinalysis: In all treated animals of the 28-day group and 90-day main group, there were no abnormalities.

Gross pathology: In the 28-day male negative control group, there was one case (out of 5) of white or dark red lobus caudatus in the liver, which penetrated the diaphragm in the 4th week of administration. In the 1 IU/kg/day group, there was caliectasis of the right kidney. There was one case of fluid retention out of 5 and one case of distension of the thyroid gland out of 5. In the 3 IU/kg/day group, there was one case of shrinking of the left prostate gland out of 5. In the female animals, there was one case of a round-shaped white structure in the spleen in the 1 IU/kg group in the 4th week of injection (28-day group).

In the 90-day male group and in the 13th week, in negative control group there was one case of atrophy of the prostate gland out of 10, and in 1 IU/kg group there was one case of atrophy of the left and right epididymis out of 10 and one case of atrophy of the left and right testis. In the 3 IU/kg group, there was one case of generalized congestion left-side of the thorax midline, and in the 10 IU/kg/day group, there was one case of hypertrophy and discoloring in the mesentery. In the 90-day female animals, there was one case of mass type of lobus candatus in the liver, in one animal of the control group in the 13th week of administration. In the 1 IU/kg group there was one case of cystoma of the right ovary. There was also one case (out of 10) of dark red coloring of the lateral left lobe of the lung. It appears that these changes are not dose or time dependent.

Organ weights (specify organs weighed if not in histopath table):
In the male 10 IU/kg group after 90-day treatment, there was a significant increase in absolute weights of the adrenal gland, spleen and heart ($p<0.01$). In the 3 and 1 IU/kg groups, there was an increase in absolute weight of the adrenal gland ($p<0.05$). There was also a decrease in relative weight of the brain ($p<0.05$) in the 10 IU/kg group, and in the 3 IU/kg group there was a decrease in relative weights of the liver ($p<0.05$) and an increase in the adrenal gland ($p<0.05$). In the 1 IU/kg group, there was an increase in the relative weight of the adrenal gland ($p<0.05$) as shown below.

90-day female groups: In the 10 IU/kg/day group (main group), there was a significant increase in the absolute weights of the liver, kidney, spleen, ovary, lung, thyroid gland ($p<0.05$, $p<0.01$). In the 3 IU/kg group, there was an increase in absolute weight of the spleen ($p<0.05$). The absolute organ weights in females were not the same in regards to relative organ weights because there was a decrease in relative weight of the heart ($p<0.01$) and the brain ($p<0.01$) in the 10 IU/kg group and also found a decrease in relative weight of the heart ($p<0.05$) in the 3 IU/kg.

Table 11-3. Absolute organ weights of males examined at 90 days (group summary)

ORGAN WEIGHT SUMMARY

STUDY: S-235 SEX: MALE

GROUP:	CONTROL	VEHICLE CONTROL	T1	T2	T3
DOSE:	0	0	1	3	10
BODY WEIGHT(G)	486.46	498.58	500.52	491.54	552.99**
SD	48.008	35.606	37.735	29.982	42.168
N	10	10	10	10	10
LIVER(G)	12.726	12.873	12.084	11.785	13.692
SD	2.2214	0.9544	1.0817	1.5528	1.5389
N	10	10	10	10	10
KIDNEY-LEFT(G) >	1.398	1.485	1.457	1.439	1.542
SD	0.2285	0.1478	0.1140	0.1367	0.1677
N	10	10	10	10	10
KIDNEY-RIGHT(G) >	1.421	1.483	1.483	1.471	1.578
SD	0.2297	0.1528	0.1032	0.1279	0.1985
N	10	10	10	10	10
<LINK TOTAL:	2.820	2.968	2.941	2.910	3.118
SD	0.4549	0.2872	0.2137	0.2607	0.3517
N	10	10	10	10	10
SPLEEN(G)	0.715	0.687	0.774	0.787	0.928**
SD	0.1104	0.0711	0.1007	0.0814	0.1138
N	10	10	10	10	10
HEART(G)	1.374	1.443	1.425	1.398	1.557**
SD	0.1120	0.1017	0.1111	0.1029	0.1362
N	10	10	10	10	10
BRAIN(G)	2.096	2.159	2.103	2.182	2.154
SD	0.1092	0.0695	0.0821	0.0494	0.0862
N	10	10	10	10	10

Table 11-3. Absolute organ weights of males examined at 90 days (group summary)

ORGAN WEIGHT SUMMARY

STUDY: S-235 SEX: MALE

GROUP: / DOSE:	CONTROL 0	VEHICLE CONTROL 0	T1 1	T2 3	T3 10
ADRENAL GLAND-LEFT(G) >	0.032	0.031	0.038	0.035	0.039
SD	0.0051	0.0033	0.0045	0.0073	0.0033
N	10	10	10	10	10
ADRENAL GLAND-RIGHT(G) >	0.029	0.030	0.037*	0.033*	0.039**
SD	0.0049	0.0074	0.0059	0.0053	0.0081
N	10	10	10	10	10
<LINE TOTAL:	0.061	0.062	0.076*	0.068*	0.077**
SD	0.0083	0.0125	0.0075	0.0159	0.0074
N	10	10	10	10	10
TESTIS-LEFT(G) >	1.697	1.732	1.803	1.634	1.723
SD	0.1380	0.0763	0.1145	0.0847	0.1302
N	10	10	10	10	10
TESTIS-RIGHT(G) >	1.688	1.723	1.803	1.603	1.725
SD	0.1206	0.0978	0.1082	0.0508	0.1204
N	10	10	10	10	10
<LINE TOTAL:	3.384	3.455	3.204	3.638	3.448
SD	0.2494	0.1639	0.2187	0.1098	0.2550
N	10	10	10	10	10
LUNGS(G)	1.582	1.550	1.638	1.617	1.606
SD	0.1281	0.1755	0.1457	0.1556	0.1351
N	10	10	10	10	10
THYROID-LEFT(G) >	0.01188	0.01186	0.01075	0.01058	0.01218
SD	.002480	.004282	.001539	.002583	.002587
N	10	10	10	10	10
THYROID-RIGHT(G) >	0.01183	0.01105	0.01030	0.01170	0.01248
SD	.002485	.002344	.001963	.002335	.002980
N	10	10	10	10	10
<LINE TOTAL:	0.02329	0.02294	0.02106	0.02250	0.02402
SD	.004031	.006850	.002709	.004159	.004908
N	10	10	10	10	10

Analysis of variance using Dunnett's procedure

* Significantly different from control group ($p<0.05$)
** Significantly different from control group ($p<0.01$)

Table II-4. Absolute organ weights of females examined at 90 days (Group Summary)

ORGAN WEIGHT SUMMARY

STUDY: B-236 SEX: FEMALE

GROUP: / DOSE:	CONTROL 0	VEHICLE CONTROL 0	T1 1	T2 3	T3 10
BODY WEIGHT(G)	283.55	278.51	282.62	320.85	358.27**
SD	28.221	21.333	19.428	32.907	49.745
NUMBER OF ANIMALS	10	10	10	10	10
LIVER(G)	8.868	8.471	8.548	7.278	8.734**
SD	0.7032	0.8818	0.7286	1.0264	1.7488
N	10	10	10	10	10
KIDNEY-LEFT(G) >	0.834	0.838	0.822	0.929	1.008*
SD	0.1507	0.0405	0.0871	0.1084	0.1150
N	10	10	10	10	10
KIDNEY-RIGHT(G) >	0.803	0.852	0.853	0.851	1.018*
SD	0.1404	0.0838	0.0887	0.0973	0.1078
N	10	10	10	10	10
<LIVE TOTAL:	1.777	1.690	1.675	1.870	2.026*
SD	0.2670	0.1558	0.1853	0.1932	0.2774
N	10	10	10	10	10
SPLEEN(G)	0.455	0.430	0.481	0.541*	0.635**
SD	0.0880	0.0423	0.0788	0.0532	0.1095
N	10	10	10	10	10
HEART(G)	0.908	0.858	0.865	0.958	0.984
SD	0.0734	0.0462	0.0777	0.0893	0.1381
N	10	10	10	10	10
BRAIN(G)	1.925	1.870	1.863	1.970	2.018
SD	0.0671	0.0784	0.0773	0.0568	0.0849
N	10	10	10	10	10

Table 11-4 Absolute organ weights of females examined at 90 days (group summary)

ORGAN WEIGHT SUMMARY

STUDY: S-255

GROUP: / DOSE:	CONTROL 0	VEHICLE CONTROL 0	T1 1	T2 3	T3 10
ADRENAL GLAND-LEFT(G) >					
SD	0.032	0.034	0.015	0.038	0.035
N	0.0041	0.0081	0.0091	0.0042	0.0072
	10	10	10	10	10
ADRENAL GLAND-RIGHT(G) >					
SD	0.032	0.031	0.013	0.037	0.036
N	0.0069	0.0072	0.0050	0.0064	0.0077
	10	10	10	10	10
<LINE TOTAL:					
SD	0.063	0.065	0.083	0.075	0.070
N	0.0080	0.0120	0.0127	0.0137	0.0144
	10	10	10	10	10
OVARY-LEFT(G) >					
SD	0.040	0.049	0.051	0.041	0.058
N	0.0073	0.0043	0.0201	0.0074	0.0115
	10	10	10	10	10
OVARY-RIGHT(G) >					
SD	0.040	0.044	0.046	0.044	0.051
N	0.0082	0.0041	0.0192	0.0109	0.0082
	10	10	10	10	10
<LINE TOTAL:					
SD	0.080	0.093	0.099	0.085	0.102*
N	0.0088	0.0076	0.0340	0.0172	0.0158
	10	10	10	10	10
LUNG(G)					
SD	1.178	1.082	1.170	1.274	1.488*
N	0.1405	0.3281	0.2597	0.1883	0.3197
	10	10	10	10	10
THYROID-LEFT(G) >					
SD	0.00176	0.00122	0.00812	0.00842	0.00911
N	.0003218	.0001200	.0002126	.0003040	.0001928
	10	10	10	10	10
THYROID-RIGHT(G) >					
SD	0.00783	0.00769	0.00893	0.00820	0.01030*
N	.0019913	.0011477	.0021184	.0013209	.0025207
	10	10	10	10	10
<LINE TOTAL:					
SD	0.01571	0.01512	0.01726	0.01682	0.02201**
N	.0022417	.0022657	.0033190	.0035343	.0035062
	10	10	10	10	10

Analysis of variance using Dunnett's procedure

* Significantly different from control group ($p<0.05$)
** Significantly different from control group ($p<0.01$)

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

28-day male groups: In the negative control group, there was one case of fibrin proliferation and sinusoid extension in the liver and one case of congestion and hydronephrosis of the right kidney. One case of bladder blood loss was observed in vehicle control group and one case of protein cast in bladder was seen in the 10 IU/kg group. In other organs no pathological changes were observed. 28-day female groups: There was one case (out of five) of blood loss in the left and right kidneys in the control group. Otherwise there were no pathological changes.

90-day male groups: One case of protein cast in the bladder was observed in the negative control group, in the vehicle control group and in the 10 IU/kg/day group, respectively. In the 3 IU/kg group, there was one case of congestion in the thymus, and in the 10 IU/kg group, there was one case of protein cast in the right kidney and one case of fatty metamorphosis of the adrenal cortex. The other organs showed no definitive pathological changes.

90-day female groups: In the negative control group, there was one sample of hydronephrosis of the left kidney, and in the vehicle control group there were two cases of cytoplasmic vacuolization of the pancreas. In the 1 IU/kg group, there was one case of cystoma of the ovary, and in the 10 IU/kg group there were three cases of cytoplasmic vacuolization of the pancreas.

Toxicokinetics:
There was not TK study.

Other: None.

Study title: 26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002(Sr-rhGH) in Cynomolgus Monkeys with an 8-Week Recovery Period

Key study findings:

This study evaluated the toxicity and determined the toxicokinetics of LB03002 (Sr-hGH) when administered once weekly to cynomolgus monkeys via subcutaneous injection at dose levels of 0.2, 0.6, and 2.0 mg hGH/kg/week for at least 26 weeks. The study further assessed the reversibility, persistence, or delayed occurrence of any effects during an 8-week recovery.

hGH serum levels increased with the increase in the dose level from 0.2 to 2.0 mg hGH/kg/day after LB03002 treatment. The increases in hGH mean C_{max} and AUC_{0-72} values were less than proportional to the increase in dose on the three collection days. Concentrations of hGH generally declined slowly and were generally above the predose levels 72 hours postdose. In general, females had higher mean C_{max} and AUC_{0-72} values compared to males at the 0.2 and 0.6 mg hGH/kg/week dose levels, but the opposite was true at the 2.0 mg hGH/kg/week dose level. There were no consistent changes in the mean AUC_{0-72} values after multiple dosing. Results should be interpreted with caution due to the presence of variable baseline concentrations of growth hormone in these animals.

Assessment of toxicity was based on mortality, clinical observations, ophthalmic examinations, electrocardiograms, body weights, clinical pathology, anatomic pathology, and immunology evaluations. There were no LB03002 (Sr-hGH)-related ophthalmic, electrocardiographic, body weight, serum chemistry, urinalysis, urine chemistry, organ weight, or microscopic changes. LB03002 (Sr-hGH) was not immunogenic.

All monkeys survived until their scheduled sacrifice. LB03002 (Sr-hGH)-related clinical changes were limited to localized irritation (erythema, edema, atonia, desquamation and/or fissuring) at the injection site. These changes were primarily observed in 2.0 mg hGH/kg/week monkeys with only infrequent changes occurring in 0.2 or 0.6 mg hGH/kg/week animals. Elevated total leukocyte, neutrophil, and lymphocyte counts were observed primarily in 0.6 and 2.0 mg hGH/kg/week males at Weeks 14 and 27. LB03002 (Sr-hGH)-related macroscopic alterations were restricted to the injection site and consisted of thickened injection sites, dark areas, and a scab. NOAEL = 2.0 mg /kg/week.

Study no.: 7263-100
Volume #1 & 2, and page #: Toxicology 1-860
Conducting laboratory and location: b(4)

Date of study initiation: 9/13/2001
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: 01SH30-4, 96-97% purity

Methods

Doses: 0(vehicle=medium chain triglyceride), 0.2, 0.6 and 2.0 IU/kg/week
Species/strain: Monkey/Cynomolgus
Number/sex/group or time point (main study): 4-6 monkeys/sex/group
Route, formulation, volume, and infusion rate: Subcutaneous (See table below)
Satellite groups used for toxicokinetics or recovery: None
Age: 2 years
Weight: Males 1.7- 2.3 kg; Females 1.7-2.2 kg on arrival

	No. of Animals		Dose Levels		Dose Concentration
Group	Male	Female	(mg hGH/kg/week)	(mg powder/kg/dose)	mg powder/mL MCT
1 (Control)	6[a]	6[a]	0	0	0
2 (Low)	4	4	0.2	1.0	10
3 (Mid)	4	4	0.6	3.0	30
4 (High)	6[a]	6[a]	2.0	10.0	100

a The last two monkeys/sex in Groups 1 and 4 were designated as recovery monkeys and observed for at least 8 weeks posttreatment.

Observations and times:

Mortality: Twice a day
Clinical signs: Daily within 1 hour after daily injection
Body weights: Once prior to treatment, weekly thereafter, and at Weeks 27 and 32
Food consumption: Weekly

Ophthalmoscopy: Prior to treatment and during Weeks 26 and 34 on anesthetized monkeys using an indirect ophthalmoscope. Ketamine hydrochloride was used to anesthetize the animals for examination; Mydriacyl® was used for pupil dilation.
EKG: Once prior to initiation of treatment and during Weeks 26 and 34 on anesthetized monkeys; interpretation was done by a veterinarian. Ketamine hydrochloride was used to anesthetize the animals for examination.

Hematology, urinalysis, and clinical chemistry: Once prior to initiation of treatment, after at least 13 and 26 weeks of treatment, and within 3 days of scheduled sacrifice. Hematology samples were collected into 2 mL EDTA tubes; coagulation samples were collected into 1.8 mL sodium citrate tubes; serum chemistry samples were collected into 2.5 mL (no anticoagulant) tubes.

Gross pathology: During Week 27 (terminal sacrifice), necropsies were performed on the first four monkeys/sex/group by ascending animal number in Groups 1 and 4 and all monkeys in Groups 2 and 3. During Week 35 (recovery sacrifice), all remaining monkeys in Groups 1 and 4 were sacrificed. Prior to necropsy, all animals were immobilized with ketamine hydrochloride and anesthetized with sodium thiopental.

Organ weights (specify organs weighed if not in histopath table): Specified organs were weighed; paired organs were weighed together.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Specified tissues were preserved in 10% neutral-buffered formalin. Tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically from each monkey.

Toxicokinetics: Day 1: Blood was collected predose and approximately 6, 12, 24, 72, 120, and 168 hours postdose. First day of Weeks 13 and 26: Blood was collected predose and approximately 6, 12, 24, and 72 hours postdose. Approximately 1 mL of whole blood was collected into a 2 mL tube.

Antibody analysis:
The analysis was conducted once prior to initiation of treatment and during Weeks 13 and 26. Serum samples were assayed for the presence of antibodies to Sr-hGH using a method validated by ——— Approximately 1 mL of whole blood was collected into a 2 mL tube. b(4)

Statistics: Mean body weight, clinical pathology (except hemolysis and cellular morphology gradings and routine urinalysis data), terminal body weight, and organ weight data of the treated groups were compared statistically to the data from the same sex of the control group. Levene's test (Levene, 1960) was performed to test for variance homogeneity. In the case of heterogeneity of variance at $p \leq 0.05$, a rank transformation was used to stabilize the variance. If the transformation did not achieve variance homogeneity, the analyses were still performed on the rank-transformed data. One-way analysis of variance techniques were used to analyze the data. If the ANOVA was significant ($p \leq 0.05$), Dunnet's t-test was used for control versus treated group comparisons. Group comparisons (Groups 2 through 4 versus Group 1) were evaluated at the 5% two-tailed probability level. Statistical significance is designated throughout the text of this report by the term *significant.*

Results

Mortality: All monkeys survived until their scheduled terminal sacrifice.

Clinical signs: LB03002 (Sr-hGH)-related clinical changes were limited to localized irritation (erythema, edema, atonia, desquamation and fissuring) at the injection sites. These changes were primarily observed in 2.0 mg hGH/kg/week monkeys with only infrequent changes occurring in 0.2 or 0.6 mg rhGH/kg/week animals as shown below.

Table 3.1
Summary of Clinical Observations – Dosing Phase – All Animals

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

DAYS 1-184

NUMBER OF ANIMALS AFFECTED

CATEGORY / KEYWORD / QUALIFIER	SEX:	MALE				FEMALE			
	GROUP:	1	2	3	4	1	2	3	4
	DOSE:	0	0.2	0.6	2.0	0	0.2	0.6	2.0
	UNITS:	MG/KG/WK							
	NUMBER:	6	4	4	6	6	4	4	6
*** TOP OF LIST ***									
APPEARANCE									
SWOLLEN									
DORSAL-CERVICAL-LEFT		0	0	0	2	0	0	0	0
HAND-RIGHT		0	0	1	0	0	0	0	0
TAIL-DISTAL		0	0	0	0	0	1	0	0
SCAPULA LEFT		0	0	1	4	0	0	0	4
SCAPULA RIGHT		0	1	0	3	0	1	2	5
DISCHARGE									
VOMITUS									
CONTAINING FOOD		2	0	0	1	0	0	0	0
APPEARS TO BE MENSTRUATING		0	0	0	0	3	4	3	1
OTHER		0	0	0	2	0	0	0	0
DISCHARGE UNKNOWN SOURCE									
FOUND IN PAN									
RED IN COLOR		0	0	0	0	0	1	0	0
EXCRETION									
LIQUID FECES		0	0	0	0	0	0	0	1
NON-FORMED FECES		3	2	2	4	1	0	3	4
EYES									
OTHER		0	0	0	0	0	0	1	0

Appears This Way
On Original

Body weights:

There was no remarkable change in body weight during active treatment from Week 1 to 27 and during the recovery period from Week 28 to 31 both in males and females as shown below.

b(4)

TABLE 5.1
SUMMARY OF BODY WEIGHT DATA (KG) - DOSING PHASE - ALL ANIMALS

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

	SEX:	MALE				FEMALE			
	GROUP:	1	2	3	4	1	2	3	4
	DOSE:	0	0.2	0.6	2.0	0	0.2	0.6	2.0
WEEK	UNITS:	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK
25	N	6	4	4	6	6	4	4	6
	MEAN	2.8	2.9	2.8	2.4	2.5	2.4	2.3	2.5
	S.D.	0.47	0.47	0.26	0.27	0.21	0.26	0.29	0.20
26	N	6	4	4	6	6	4	4	6
	MEAN	2.9	2.8	2.8	2.5	2.5	2.4	2.3	2.5
	S.D.	0.46	0.47	0.27	0.23	0.21	0.22	0.29	0.20
27	N	6	4	4	6	6	4	4	6
	MEAN	2.8	2.8	2.8	2.5	2.5	2.4	2.3	2.5
	S.D.	0.46	0.47	0.26	0.26	0.19	0.22	0.23	0.18
1-27	N	6	4	4	6	6	4	4	6
CHNG	MEAN	0.8	0.9	0.9	0.6	0.6	0.5	0.5	0.6
	S.D.	0.29	0.41	0.19	0.18	0.10	0.10	0.15	0.08

TABLE 5.2
SUMMARY OF BODY WEIGHT DATA (KG) - RECOVERY ANIMALS

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

	SEX:	MALE				FEMALE			
	GROUP:	1	2	3	4	1	2	3	4
	DOSE:	0	0.2	0.6	2.0	0	0.2	0.6	2.0
WEEK	UNITS:	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK	MG/KG/WK
25	N	2	0	0	2	2	0	0	2
	MEAN	2.8			2.4	2.7			2.7
	S.D.	0.64			0.00	0.21			0.21
26	N	2	0	0	2	2	0	0	2
	MEAN	2.9			2.5	2.7			2.7
	S.D.	0.64			0.07	0.21			0.21
27	N	2	0	0	2	2	0	0	2
	MEAN	2.8			2.5	2.7			2.6
	S.D.	0.57			0.07	0.21			0.14
1-27	N	2	0	0	2	2	0	0	2
CHNG	MEAN	0.9			0.5	0.6			0.5
	S.D.	0.35			0.14	0.07			0.07
28	N	2	0	0	2	2	0	0	2
	MEAN	2.9			2.5	2.7			2.7
	S.D.	0.64			0.00	0.21			0.14
29	N	2	0	0	2	2	0	0	2
	MEAN	2.9			2.5	2.7			2.8
	S.D.	0.64			0.14	0.21			0.21
30	N	2	0	0	2	2	0	0	2
	MEAN	2.9			2.5	2.7			2.7
	S.D.	0.57			0.00	0.21			0.21
31	N	2	0	0	2	2	0	0	2
	MEAN	3.0			2.6	2.6			2.7
	S.D.	0.64			0.07	0.00			0.28

Food consumption:
There was no remarkable change in food consumption that can be attributable to the treatment.
Ophthalmoscopy: In all treated groups, there were no abnormalities detected.
EKG: There was no remarkable treatment-related effect on electrocardiographic examination.

Hematology:
The total leukocyte, neutrophils, and lymphocyte counts were elevated primarily in 0.6 and 2.0 mg hGH/kg/week males at Weeks 14 and 27. The elevations are consistent with inflammation and correlate with the swollen injection sites noted clinically for these groups. Similar alterations were not observed for the control or 0.2 mg hGH/kg/week males or any female group, despite the histologic evidence of inflammation observed for all groups. The relative and absolute reticulocyte counts decreased considerably in control monkeys from Week 27 to recovery Week 34, which may affect statistically the counts in the 2.0 mg hGH/kg/week monkeys. This finding is considered incidental to treatment because of the low magnitude of the differences and the lack of changes in erythrocyte count, hemoglobin, or hematocrit values at any interval. There were no other noteworthy differences in coagulation data and cellular morphology results. In males, WBC were increased at doses $\geq$ 0.6 IU/kg on Weeks 2 and 3, which was returned on Week 4. At the doses, lymphocytes were increased, although neutrophil counts were only increased at 0.6 IU/kg group. There were no such effects in females and the hematologic changes were not observed in other species.

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TABLE 6
SUMMARY OF CLINICAL HEMATOLOGY DATA

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

MALES

GROUP		PT - S WEEK -1	PT - S WEEK 14	PT - S WEEK 27	PT - S WEEK 34	APTT - S WEEK -1	APTT - S WEEK 14	APTT - S WEEK 27	APTT - S WEEK 34	WBC - TH/UL WEEK -1	WBC - TH/UL WEEK 14	WBC - TH/UL WEEK 27	WBC - TH/UL WEEK 34
1 (0 MG/KG/WK)	N	6	6	6	2	6	6	6	2	6	6	6	2
	MEAN	10.3	10.4	10.3	9.9	18.7	17.9	17.6	17.2	11.1	8.3	7.0	8.3
	S.D.	.37	.33	.21	.49	1.40	1.57	1.50	.71	4.23	2.18	1.22	2.83
2 (0.2 MG/KG/WK)	N	4	4	4		4	4	4		4	4	4	
	MEAN	10.3	10.6	10.2		18.9	18.2	17.9		10.3	9.6	9.5	
	S.D.	.13	.18	.08		1.17	1.07	1.25		2.85	1.10	1.10	
3 (0.6 MG/KG/WK)	N	4	4	4		4	4	4		4	4	4	
	MEAN	10.1	10.5	10.1		19.4	18.7	18.2		11.3	11.7*	13.1*	
	S.D.	.22	.18	.42		.89	.84	.42		3.32	1.38	3.22	
4 (2.0 MG/KG/WK)	N	6	6	6	2	6	6	6	2	6	6	6	2
	MEAN	10.5	10.7	10.3	10.6	17.5	17.3	16.6	17.2	10.8	12.1*	10.2*	10.0
	S.D.	.33	.50	.42	.14	1.89	1.62	1.38	.57	3.79	2.52	2.48	.14

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, P $\leq$ 0.05.

b(4)

TABLE 6
SUMMARY OF CLINICAL HEMATOLOGY DATA

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

MALES

GROUP		NEUT AB - TH/UL				LYMPH AB - TH/UL				MONO AB - TH/UL			
		WEEK				WEEK				WEEK			
		-1	14	27	34	-1	14	27	34	-1	14	27	34
1	(0 MG/KG/WK)												
	N	6	6	6	2	6	6	6	2	6	6	6	2
	MEAN	4.7	2.5	1.6	2.1	6.0	5.4	5.0	5.6	.3	.3	.3	.4
	S.D.	1.66	.98	.72	.28	3.32	1.20	.56	2.47	.12	.12	.08	.14
2	(0.2 MG/KG/WK)												
	N	4	4	4		4	4	4		4	4	4	
	MEAN	4.8	2.7	2.8		5.1	6.4	6.4		.2	.3	.3	
	S.D.	2.49	.66	1.86		.85	1.15	1.49		.08	.08	.14	
3	(0.6 MG/KG/WK)												
	N	4	4	4		4	4	4		4	4	4	
	MEAN	5.8	3.3	4.3*		5.2	7.8*	8.2*		.3	.4	.4	
	S.D.	3.25	.53	1.00		.67	1.12	2.66		.06	.08	.10	
4	(2.0 MG/KG/WK)												
	N	6	6	6	2	6	6	6	2	6	6	6	2
	MEAN	4.3	4.3	2.6	1.6	6.1	7.1*	7.0	7.5	.3	.5	.5	.6
	S.D.	1.96	2.63	1.22	.28	1.89	.74	1.67	.21	.16	.24	.20	.14

* - SIGNIFICANTLY DIFFERENT FROM CONTROL VALUE, P ≤ 0.05.

TABLE 6
SUMMARY OF CLINICAL HEMATOLOGY DATA

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

FEMALES

GROUP		EOSIN AB - TH/UL				BASO AB - TH/UL			
		WEEK				WEEK			
		-1	14	27	34	-1	14	27	34
1	(0 MG/KG/WK)								
	N	6	6	6	2	6	6	6	2
	MEAN	.1	.1	.1	.2	.0	.0	.0	.0
	S.D.	.08	.04	.06	.14	.04	.05	.04	.07
2	(0.2 MG/KG/WK)								
	N	4	4	4		4	4	4	
	MEAN	.1	.1	.0		.0	.0	.0	
	S.D.	.10	.10	.06		.00	.00	.00	
3	(0.6 MG/KG/WK)								
	N	4	4	4		4	4	4	
	MEAN	.0	.1	.1		.0	.0	.0	
	S.D.	.05	.00	.05		.06	.05	.00	
4	(2.0 MG/KG/WK)								
	N	6	6	6	2	6	6	6	2
	MEAN	.1	.1	.1	.1	.0	.0	.0	.1
	S.D.	.08	.08	.10	.07	.05	.05	.05	.00

Clinical chemistry:

Exposure to hGH generally increased as the dose level increased from 0.2 to 2.0 mg hGH/kg/week. Levels of hGH in serum were, in general, slightly higher after multiple dosing (Weeks 13 and 26) than on Day 1. Variability in the levels of hGH was high between animals dosed with hGH. The variability of baseline levels at the predose collection on Day 1 and in the control group on all three collection days was also very high. It appears that there were no remarkable differences in clinical chemistry data as a result of the treatment of Sr-hGH.

Urinalysis: There were no other noteworthy differences in urinalysis data that could be attributed to the administration of Sr-hGH. There were no clear abnormalities in urine analysis.

Gross pathology: The only meaningful gross and microscopic changes were observed in the injection site of both treated and control animals from the terminal sacrifice only. Macroscopic alterations observed in animals from 0.2, 0.6, and 2.0 mg hGH/kg/week included thickened injection sites, dark areas, and a scab as shown below. There were no other noteworthy differences in cellular morphology results that could be attributed to the administration of Sr-hGH.

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TABLE 8.1
INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED --							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:		4	4	4	4	4	4	4	4
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
TONGUE (TO)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
INJECTION SITE (IS)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	2	2	0	4	2	0	1
THICKENED		0	2	2	4	0	2	4	3
DARK AREA		0	0	1	0	0	0	0	1
SCAB		0	0	0	1	0	0	0	0
TESTIS (TE)	NUMBER EXAMINED:	4	4	4	4	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	4	4	4	4	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	4	4	4	4	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	0	0	0	0

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TABLE 8.1
INCIDENCE OF MACROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;SUBSET=ALL

ORGAN AND KEYWORD(S) OR PHRASE		-- NUMBER-OF-ANIMALS-AFFECTED -							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	4	4	4	4	4	4	4	4
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	4	4	4	4	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	3	4	4	4	3	4	4
WALL, THICKENED		0	1	0	0	0	1	0	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:	4	4	4	4	0	0	0	0
	NOT REMARKABLE:	4	4	4	4	0	0	0	0
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	2	3	4	4
CYST		0	0	0	0	1	1	0	0
UNEQUALLY SIZED		0	0	0	0	1	0	0	0
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	4	4	4	4
CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	4	4	4	4
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	4	4	4	4
	NOT REMARKABLE:	0	0	0	0	4	4	4	4

Organ weights (specify organs weighed if not in histopath table):
Organ-to-body weight changes were noted in the reproductive systems of the males, wherein the mean organ weights and organ-to-body weight ratios of the testis, epididymis, prostate, and seminal vesicle decreased at the high dose for both the terminal and recovery sacrifices. These tissues from all males in the study were classified as being immature in appearance and the changes were not statistically significant. No further microscopic changes were noted to account for these weight differences.

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TABLE 9.1
SUMMARY OF ORGAN WEIGHT DATA - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LA03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; WEEKS=1-35
DEATH=T; SUBSET=ALL

PROSTATE

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2025.0	0.52	0.018	0.008
		STANDARD DEV:	478.7	0.36	0.009	0.006
M	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2650.0	0.57	0.019	0.008
		STANDARD DEV:	465.5	0.31	0.007	0.004
M	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2750.0	0.63	0.022	0.009
		STANDARD DEV:	251.7	0.25	0.007	0.003
M	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2450.0	0.34	0.014	0.005
		STANDARD DEV:	341.6	0.14	0.005	0.002
F	1	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			
F	2	NUMBER IN GROUP:	4			
		MEAN:	2325.0			
		STANDARD DEV:	236.3			
F	3	NUMBER IN GROUP:	4			
		MEAN:	2250.0			
		STANDARD DEV:	288.7			
F	4	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			

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TABLE 9.1
SUMMARY OF ORGAN WEIGHT DATA - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;SUBSET=ALL

SEMINAL VESICLE

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2925.0	1.24	0.042	0.020
		STANDARD DEV:	478.7	0.75	0.017	0.013
M	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2850.0	1.64	0.052	0.023
		STANDARD DEV:	465.5	1.02	0.049	0.026
M	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2750.0	1.90	0.067	0.027
		STANDARD DEV:	251.7	0.96	0.031	0.013
M	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2450.0	0.83	0.031	0.012
		STANDARD DEV:	341.6	0.77	0.025	0.010
F	1	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			
F	2	NUMBER IN GROUP:	4			
		MEAN:	2325.0			
		STANDARD DEV:	236.3			
F	3	NUMBER IN GROUP:	4			
		MEAN:	2250.0			
		STANDARD DEV:	288.7			
F	4	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			

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TABLE 9.1
SUMMARY OF ORGAN WEIGHT DATA - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;SUBSET=ALL

EPIDIDYMIS

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2925.0	1.20	0.040	0.019
		STANDARD DEV:	478.7	0.86	0.021	0.015
M	2	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2850.0	1.15	0.039	0.016
		STANDARD DEV:	465.5	0.70	0.017	0.010
M	3	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2750.0	1.18	0.042	0.017
		STANDARD DEV:	251.7	0.39	0.012	0.006
M	4	NUMBER IN GROUP:	4	4	4	4
		MEAN:	2450.0	0.69	0.027	0.010
		STANDARD DEV:	341.6	0.44	0.013	0.006
F	1	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			
F	2	NUMBER IN GROUP:	4			
		MEAN:	2325.0			
		STANDARD DEV:	236.3			
F	3	NUMBER IN GROUP:	4			
		MEAN:	2250.0			
		STANDARD DEV:	288.7			
F	4	NUMBER IN GROUP:	4			
		MEAN:	2375.0			
		STANDARD DEV:	150.0			

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Microscopically, there were rather prominent inflammatory changes in animals from all treated and control groups. The change was classified as subacute inflammation and characterized, in many cases, by an infiltrate of mixed inflammatory cells, primarily involving the subcutaneous tissue. In some of the more severe cases, there was inflammatory cell infiltration into the dermis and, in a few cases, there was ulceration of the surface epithelium. Acanthosis, or thickening of the outer layer of the surface epithelium, was also occasionally present. In general, these changes were slightly more prominent in the 2.0 mg hGH/kg/week treatment group due primarily to the presence of surface ulceration; however, there were animals in the mid- and low-dose treatment groups and in the control females which had the most prominent degree of subacute inflammation (moderately severe). Therefore, it appears that both the test and control materials are capable of producing similar effects. These changes were not present in any recovery animals.

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Table 10.1
Incidence of Microscopic Observations - Terminal Sacrifice

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	4	4	4	4	4	4	4	4
*** TOP OF LIST ***									
BRAIN (BR)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
CORD, CERVICAL (CS)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
CORD, THORACIC (TC)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
CORD, LUMBAR (LC)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
PITUITARY (PI)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	3	4	4	4	2	4	4	3
--HEMORRHAGE, UNILATERAL		1	0	0	0	0	0	0	0
--NECROBIS, UNILATERAL		0	0	0	0	1	0	0	0
--MINERALIZATION, UNILATERAL		0	0	0	0	1	0	0	1
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=T;FIND=ALL;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	4	4	4	4	4	4	4	4
THYROID (TY)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
PARATHYROID (PT)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
LUNG (LU)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	1	0	0	0	0	0	0	0
--PIGMENT		3	4	4	4	4	4	4	4
--INFLAMMATION, INTERSTITIAL, FOCAL		0	1	2	0	0	1	0	0
--FIBROSIS, PLEURAL		0	0	0	0	0	1	0	0
SPLEEN (SP)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
LIVER (LI)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	2	2	4	3	2	3	2
--INFILTRATE, LYMPHOHISTIOCYTIC		0	2	1	0	0	1	1	1
--INFLAMMATION, SUBACUTE, FOCAL		0	0	1	0	0	0	0	0
--INFLAMMATION, CHRONIC, FOCAL		0	0	0	0	1	1	0	1
GALLBLADDER (GB)	NUMBER EXAMINED:	4	4	4	4	4	3	4	4
	NOT REMARKABLE:	4	4	4	4	4	3	4	4

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=T;FIND=ALL;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED --							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	4	4	4	4	4	4	4	4
HEART (HT)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	1	1	3	2	2	3	4	2
--INFLAMMATION, CHRONIC		3	3	1	2	2	1	0	2
KIDNEY (KD)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	2	2	0	1	0	0	1	1
--INFLAMMATION, CHRONIC		2	2	4	3	3	4	3	3
--REGENERATION, TUBULAR EPITHELIUM		0	0	1	0	0	0	0	0
--MINERALIZATION		0	0	0	0	1	1	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
DUODENUM (DU)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
JEJUNUM (JE)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
STOMACH, GL (ST)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	3	4	4	4	4	4
--CYST		0	0	1	0	0	0	0	0
ILEUM (IL)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED -							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	4	4	4	4	4	4	4	4
PANCREAS (PA)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	3	4
--INFLAMMATION, CHRONIC		0	0	0	0	0	0	1	0
CECUM (CE)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
COLON (CO)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
RECTUM (RE)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
LN, MESENTERIC (MS)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
SALIV GL, MANDIB (SG)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
THYMUS (TH)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
AORTA, THORACIC (AO)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFECTED -							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	4	4	4	4	4	4	4	4
LACRIMAL GL, INT (LG)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
EYE (EY)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
TONGUE (TO)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	3	4	4	4	3
--INFLAMMATION, SUBACUTE, FOCAL		0	0	0	1	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	0	0	0	0	1
INJECTION SITE (IS)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	2	0	0	0	1	1	1	0
--INFLAMMATION, SUBACUTE		1	4	4	4	3	3	3	4
--INFLAMMATION, ACUTE		0	0	0	1	0	0	0	0
--ACANTHOSIS		0	0	0	2	1	2	2	2
--BIREFRINGENT MATERIAL		1	0	0	0	0	0	0	0
--ULCERATION		0	0	0	2	0	0	0	1

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		SEX:	-------MALE-------				------FEMALE------			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	4	4	4	4	4	4	4	4
			-- NUMBER - OF - ANIMALS - AFFECTED -							
VAGINA (VA)	NUMBER EXAMINED:		0	0	0	0	4	4	4	4
	NOT REMARKABLE:		0	0	0	0	4	4	4	4
OVARY (OV)	NUMBER EXAMINED:		0	0	0	0	4	4	4	4
	NOT REMARKABLE:		0	0	0	0	3	2	2	3
--CYST			0	0	0	0	1	1	0	0
--MINERALIZATION			0	0	0	0	0	1	2	1
UTERUS (UT)	NUMBER EXAMINED:		0	0	0	0	4	4	4	4
	NOT REMARKABLE:		0	0	0	0	4	4	4	4
CERVIX (CV)	NUMBER EXAMINED:		0	0	0	0	4	4	4	4
	NOT REMARKABLE:		0	0	0	0	4	4	4	4
TESTIS (TE)	NUMBER EXAMINED:		4	4	4	4	0	0	0	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--IMMATURE			4	4	4	4	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:		4	4	4	4	0	0	0	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--IMMATURE			4	4	4	4	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:		4	4	4	4	0	0	0	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--IMMATURE			4	4	4	4	0	0	0	0

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TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		SEX:	-------MALE-------				------FEMALE------			
		GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
		NUMBER:	4	4	4	4	4	4	4	4
			-- NUMBER - OF - ANIMALS - AFFECTED							
SEMINAL VESICLE (SV)	NUMBER EXAMINED:		4	4	4	4	0	0	0	0
	NOT REMARKABLE:		0	0	0	0	0	0	0	0
--IMMATURE			4	4	4	4	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:		4	4	4	4	4	4	4	4
	NOT REMARKABLE:		4	3	4	4	4	3	4	4
--HYPERPLASIA, TRANSITIONAL CELL			0	1	0	0	0	0	0	0
--INFLAMMATION, CHRONIC			0	0	0	0	0	1	0	0
SKIN (SK)	NUMBER EXAMINED:		4	4	4	4	4	4	4	4
	NOT REMARKABLE:		4	3	3	3	2	4	4	3
--ACANTHOSIS			0	1	0	1	1	0	0	0
--HEMORRHAGE, FOCAL			0	0	1	0	0	0	0	0
--INFLAMMATION, CHRONIC			0	1	0	0	1	0	0	1
--HAIR FOLLICLES DECREASED			0	0	0	0	1	0	0	0
MAMMARY, MALE (MM)	NUMBER EXAMINED:		4	4	4	4	0	0	0	0
	NOT REMARKABLE:		4	4	4	4	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:		0	0	0	0	4	4	4	4
	NOT REMARKABLE:		0	0	0	0	4	4	4	4
TRACHEA (TR)	NUMBER EXAMINED:		4	4	4	4	4	4	4	4
	NOT REMARKABLE:		4	4	4	4	4	4	4	4

TABLE 10.1
INCIDENCE OF MICROSCOPIC OBSERVATIONS - TERMINAL SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DRATE=T;FIND=ALL;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AFFE							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	4	4	4	4	4	4	4	4
BONE, STERNUM (SB)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
MARROW, STERNUM (SE)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
BONE, FEMUR (FE)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
MARROW, FEMUR (FM)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
BONE, RIB (RI)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
^DEATH COMMENT (DC)	NUMBER EXAMINED:	4	4	4	4	4	4	4	4
	NOT REMARKABLE:	4	4	4	4	4	4	4	4
SKIN, OTHER (SS)	NUMBER EXAMINED:	0	0	0	0	0	1	0	0
	NOT REMARKABLE:	0	0	0	0	0	1	0	0

*** END OF LIST ***

Table 10.2
Incidence of Microscopic Observations – Recovery Sacrifice

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=U;FIND=ALL;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	0	0	2	2	0	0	2
*** TOP OF LIST ***									
BRAIN (BR)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
CORD, CERVICAL (CS)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
CORD, THORACIC (TC)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
CORD, LUMBAR (LC)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
PITUITARY (PI)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	1	0	0	1
--MINERALIZATION, UNILATERAL		0	0	0	0	1	0	0	1
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
THYROID (TY)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2

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TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=1-35 DEATH=U;FIND=ALL;SUBSET=ALL		-- NUMBER-OF-ANIMALS-AFFECTED-							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	0	0	2	2	0	0	2
PARATHYROID (PT)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
LUNG (LU)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--PIGMENT		2	0	0	2	2	0	0	2
--INFLAMMATION, INTERSTITIAL, FOCAL		0	0	0	1	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
LIVER (LI)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	1	0	0	1	0	0	0	0
--INFILTRATE, LYMPHOHISTIOCYTIC		1	0	0	0	1	0	0	1
--INFLAMMATION, CHRONIC, FOCAL		0	0	0	1	0	0	0	1
--VACUOLATION, HEPATOCELLULAR		0	0	0	0	1	0	0	0
GALLBLADDER (GB)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
HEART (HT)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	1	0	0	0	0	0	0	2
--INFLAMMATION, CHRONIC		1	0	0	2	2	0	0	0

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LE03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

		-- N U M B E R - O F - A N I M A L S - A F F E							
TABLE INCLUDES: SEX=ALL; GROUP=ALL; WEEKS=1-35 DEATH=U; FIND=ALL; SUBSET=ALL	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	0	0	2	2	0	0	2
KIDNEY (KD)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	0	0	0	0	0
--INFLAMMATION, CHRONIC		0	0	0	2	2	0	0	2
--MINERALIZATION		0	0	0	0	1	0	0	0
ESOPHAGUS (ES)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
DUODENUM (DU)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
JEJUNUM (JE)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
STOMACH, GL (ST)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
ILEUM (IL)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
PANCREAS (PA)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	1	0	0	2	2	0	0	2
--INFLAMMATION, CHRONIC		1	0	0	0	0	0	0	0

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; WEEKS=1-35
DEATH=U; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER OF ANIMALS AFFE							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	2	0	0	2	2	0	0	2
CECUM (CE)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
COLON (CO)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
RECTUM (RE)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
LN, MESENTERIC (MS)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
SALIV GL, MANDIB (SG)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
THYMUS (TH)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
AORTA, THORACIC (AO)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
LACRIMAL GL, INT (LG)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS MONKEYS WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; WEEKS=1-35
DEATH=U; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER OF ANIMALS AFFE							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	2	0	0	2	2	0	0	2
EYE (EY)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
TONGUE (TO)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	1
NERVE, SCIATIC (SN)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
MUSCLE, SKELETAL (SM)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
INJECTION SITE (IS)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
VAGINA (VA)	NUMBER EXAMINED:	0	0	0	0	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	2	0	0	2
OVARY (OV)	NUMBER EXAMINED:	0	0	0	0	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	1	0	0	1
--MINERALIZATION		0	0	0	0	1	0	0	1
UTERUS (UT)	NUMBER EXAMINED:	0	0	0	0	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	2	0	0	2

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LE03002 IN CYNOMOLGUS MON WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL; GROUP=ALL; WEEKS=1-35
DEATH=U; FIND=ALL; SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		-- NUMBER-OF-ANIMALS-AI							
SEX:		--------MALE--------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
NUMBER:		2	0	0	2	2	0	0	2
CERVIX (CV)	NUMBER EXAMINED:	0	0	0	0	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	2	0	0	2
TESTIS (TE)	NUMBER EXAMINED:	2	0	0	2	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--IMMATURE		2	0	0	2	0	0	0	0
EPIDIDYMIS (EP)	NUMBER EXAMINED:	2	0	0	2	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--IMMATURE		2	0	0	2	0	0	0	0
PROSTATE (PR)	NUMBER EXAMINED:	2	0	0	2	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--IMMATURE		2	0	0	2	0	0	0	0
SEMINAL VESICLE (SV)	NUMBER EXAMINED:	2	0	0	2	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0
--IMMATURE		2	0	0	2	0	0	0	0
URINARY BLADDER (UB)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
SKIN (SK)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS M
WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=U;FIND=ALL;SUBSET=ALL

		-- N U M B E R - O F - A N I M A L S -							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	0	0	2	2	0	0	2
MAMMARY, MALE (MM)	NUMBER EXAMINED:	2	0	0	2	0	0	0	0
	NOT REMARKABLE:	2	0	0	2	0	0	0	0
MAMMARY, FEMALE (MF)	NUMBER EXAMINED:	0	0	0	0	2	0	0	2
	NOT REMARKABLE:	0	0	0	0	2	0	0	2
TRACHEA (TR)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
BONE, STERNUM (SB)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
MARROW, STERNUM (SE)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
BONE, FEMUR (FE)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
MARROW, FEMUR (FM)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
BONE, RIB (RI)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2

TABLE 10.2
INCIDENCE OF MICROSCOPIC OBSERVATIONS - RECOVERY SACRIFICE

26-WEEK SUBCUTANEOUS INJECTION CHRONIC TOXICITY AND TOXICOKINETIC STUDY WITH LB03002 IN CYNOMOLGUS
WITH AN 8-WEEK RECOVERY PERIOD

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-35
DEATH=U;FIND=ALL;SUBSET=ALL

		-- N U M B E R - O F - A N I M A L S -							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	2	0	0	2	2	0	0	2
^DEATH COMMENT (DC)	NUMBER EXAMINED:	2	0	0	2	2	0	0	2
	NOT REMARKABLE:	2	0	0	2	2	0	0	2
SKIN, OTHER (SS)	NUMBER EXAMINED:	0	0	0	0	0	0	0	0
	NOT REMARKABLE:	0	0	0	0	0	0	0	0

*** END OF LIST ***

Toxicokinetics:

After subcutaneous injection of LB03002, hGH levels appeared to increase, with mean T_{max} values ranging from 4.50 to 10.0 hours on Day 1 and from 6.00 to 39.0 hours after multiple dosing. After reaching C_{max}, hGH concentrations slowly declined and levels were generally at or above the predose levels 72 hours postdose, especially during Weeks 13 and 26.

There were no consistent gender differences in the mean C_{max} and AUC_{0-72} values. Females had slightly higher mean C_{max} and AUC_{0-72} values compared to males at the 0.2 and 0.6 mg hGH/kg/week dose levels across the three collection days, but the opposite was true at the 2.0 mg hGH/kg/week dose level. There were no consistent changes in the mean AUC_{0-72} values after multiple dosing and due to the high variability of hGH levels among animals, these results should be interpreted with caution. The increases in hGH mean C_{max} and AUC_{0-72} values were less than proportional to the increase in dose on all three collection days.

For example, in males, mean C_{max} increased 1:2.5:5.8 fold and 1:1.9:5.7 fold on Day 1 and during Week 26, respectively, for a 1:3:10-fold increase in the dose level. In females, mean C_{max} increased 1:2.0:3.5 fold and 1:1.4:1.8 fold on Days 1 and during Week 26, respectively, for a 1:3:10-fold increase in the dose level. Similarly, the mean AUC_{0-72} in males increased 1:2.6:7.9 fold and 1:1.3:5.2 fold on Days 1 and during Week 26, respectively, for a 1:3:10-fold increase in the dose level. In females, mean AUC_{0-72} increased 1:2.5:5.8 fold and 1:1.3:1.7 fold on Day 1 and during Week 26, respectively, for a 1:3:10-fold increase in the dose level.

While some effects were observed at all dose levels of LB03002 (Sr-hGH) adminstered, none are considered adverse. The NOAEL of LB03002 (Sr-hGH) for monkeys after at least 26 weekly subcutaneous injections is greater than 2.0 mg hGH/kg/week.

Summary of Toxicokinetic Parameters for hGH in Monkey Serum: Day 1

Dose Level (mg hGH/kg/week)	Group	Sex		C_{max} (ng/mL)	T_{max} (Hours)	AUC_{0-72} (ng-hr/mL)	AUC_{0-t} (ng-hr/mL)
0.2	2	M	Mean	42.5	4.50	746	1551
			SD	22.0	3.00	630	1381
			N	4	4	4	4
		F	Mean	64.5	6.00	865	2436
			SD	27.9	0	304	1795
			N	4	4	4	4
0.6	3	M	Mean	108	7.50	1942	3411
			SD	16	3.00	215	924
			N	4	4	4	4
		F	Mean	130	6.00	2180	3543
			SD	12	0	542	1048
			N	4	4	4	4
2.0	4	M	Mean	248	10.0	5882	7152
			SD	113	7.27	1153	1539
			N	6	6	6	6
		F	Mean	225	8.00	5014	6037
			SD	83	3.10	1228	1289
			N	6	6	6	6

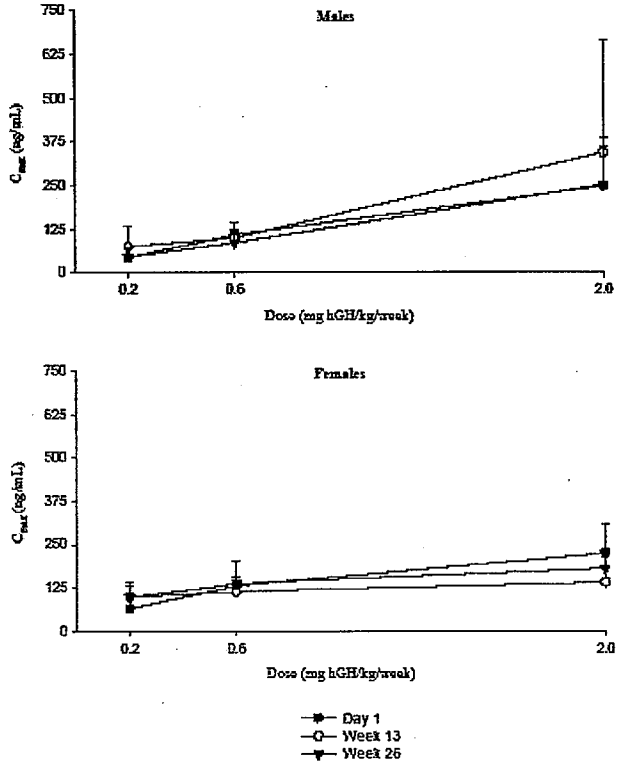
Summary of Toxicokinetic Parameters for hGH in Monkey Serum: Weeks 13 and 26

Dose Level (mg hGH/kg/week)	Group	Sex		C_{max} (ng/mL)	T_{max} (Hours)	AUC_{0-72} (ng·hr/mL)
			Week 13			
0.2	2	M	Mean	74.1	22.5	2425
			SD	60.7	33.0	2128
			N	4	4	4
		F	Mean	97.9	39.0	4305
			SD	40.2	38.1	1977
			N	4	4	4
0.6	3	M	Mean	99.1	6.00	2597
			SD	42.1	0	826
			N	4	4	4
		F	Mean	113	6.00	3215
			SD	41	0	1145
			N	4	4	4
2.0	4	M	Mean	344	9.00	8103
			SD	323	3.29	7631
			N	6	6	6
		F	Mean	140	7.00	4005
			SD	48	2.45	1354
			N	6	6	6
			Week 26			
0.2	2	M	Mean	44.5	22.5	1679
			SD	26.9	33.0	1248
			N	4	4	4
		F	Mean	97.8	27.0	3497
			SD	33.8	31.6	2499
			N	4	4	4
0.6	3	M	Mean	84.2	7.50	2175
			SD	24.9	3.00	866
			N	4	4	4
		F	Mean	136	6.00	4704
			SD	65	0	1247
			N	4	4	4
2.0	4	M	Mean	252	10.0	8723
			SD	133	3.1	7069
			N	6	6	6
		F	Mean	181	10.0	5885
			SD	55	3.1	1724
			N	6	6	6

Note: AUC_{0-72} is equivalent to AUC_{0-t} for Week 13 and Week 26.

Figure 5
hGH C_{max} Dose Relationships

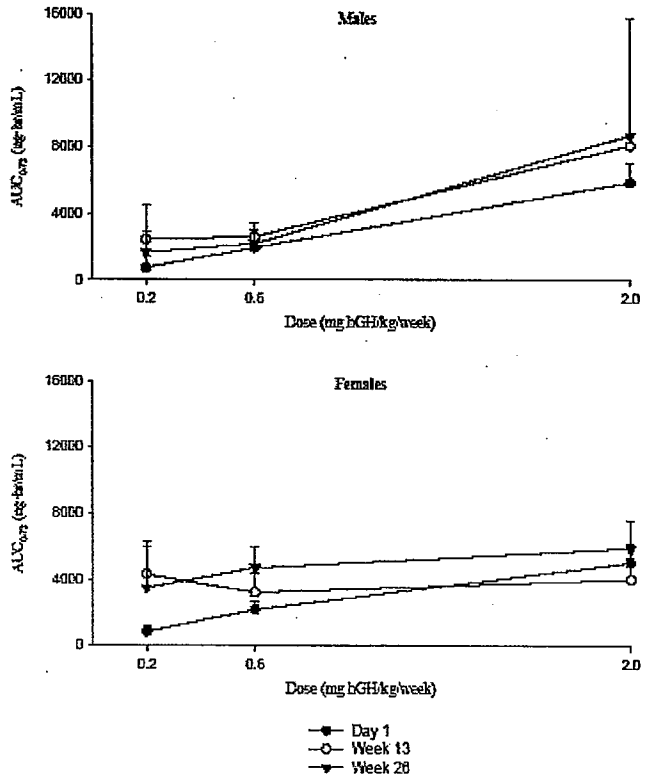
26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002 in Cynomolgus Monkeys with an 8-Week Recovery Period



Note: Error bars represent standard deviations.

Figure 6
hGH AUC_{0-72} Dose Relationships

26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002 in Cynomolgus Monkeys with an 8-Week Recovery Period



Note: Error bars represent standard deviations.

After subcutaneous injection of LB03002 in monkeys, hGH serum levels increased with the increase in the dose level from 0.2 to 2.0 mg hGH/kg/day but variability between individual animals was large. The increases in hGH mean C_{max} and AUC_{0-72} values were less than proportional to the increase in dose on the three collection days. Concentrations of hGH generally declined slowly and were generally above the predose levels 72 hours postdose. In general, females had higher mean C_{max} and AUC_{0-72} values compared to males at the 0.2 and 0.6 mg hGH/kg/week dose levels except at the 2.0 mg hGH/kg/week dose level. There were no consistent changes in the mean AUC_{0-72} values after multiple dosing. Results should be interpreted with caution due to the presence of variable baseline concentrations of growth hormone in these animals. AUC ratio was estimated from the monkey study as shown below. However, AUC values were not available in other species such as mice and rats.

Calculation of AUC Ratio on Day 1 and in Week 26 in Monkeys*

Dose (mg/kg)	Sex	TK Parameters on Day 1		TK Parameters in Week 26	
		AUC_{0-24}	AUC ratio	AUC_{0-24}	AUC ratio
0.2	M	1551	5.2	1679	5.6
	F	2436	8.1	3479	11.6
0.6	M	3411	11.4	3543	11.8
	F	2175	7.3	4704	15.7
2.0	M	7152	23.8	6037	20.1
	F	8723	29.0	5885	19.6

*AUC ratios were calculated based on human AUC_{0-24} (300.1 ng.h/ml) after Valtropin administration in healthy volunteer at dose of 7.3 mg. The unit of monkey AUC was ng.h/ml on both time periods. The proposed human dose is 0.06 mg/kg (0.15 IU/kg).

Antibody analysis:

The sponsor did not summarize antibody data in this NDA submission. However, it is clear that no animals had positive antibody reactions on Days 1, 86 and 177 as shown below (Appendix 7).

Appendix 7
Individual Antibody Data

26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002 in Cynomolgus Monkeys with an 8-Week Recovery Period

Animal Number	Day	1	86	177
Group: Female 1 - 0 mg/kg/wk				
I52852		Negative	Negative	Negative
I52853		Negative	Negative	Negative
I52854		Negative	Negative	Negative
I52855		Negative	Negative	Negative
I52856		Negative	Negative	Negative
I52857		Negative	Negative	Negative
Group: Female 2 - 0.2 mg/kg/wk				
I52858		Negative	Negative	Negative
I52859		Negative	Negative	Negative
I52860		Negative	Negative	Negative
I52861		Negative	Negative	Negative
Group: Female 3 - 0.6 mg/kg/wk				
I52862		Negative	Negative	Negative
I52863		Negative	Negative	Positive[a]
I52864		Negative	Negative	Negative
I52865		Negative	Negative	Negative
Group: Female 4 - 2.0 mg/kg/wk				
I52866		Negative	Negative	Negative
I52867		Negative	Negative	Negative
I52868		Negative	Negative	Negative
I52869		Negative	Negative	Negative
I52870		Negative	Negative	Negative
I52871		Negative	Negative	Negative

a Titer >1/50, <1/100 in Assay 008BR (see Appendix 13).

Appendix 7
Individual Antibody Data

26-Week Subcutaneous Injection Chronic Toxicity and Toxicokinetic Study with LB03002 in Cynomolgus Monkeys with an 8-Week Recovery Period

Animal Number	Day	1	86	177
Group: Female 1 - 0 mg/kg/wk				
I52852		Negative	Negative	Negative
I52853		Negative	Negative	Negative
I52854		Negative	Negative	Negative
I52855		Negative	Negative	Negative
I52856		Negative	Negative	Negative
I52857		Negative	Negative	Negative
Group: Female 2 - 0.2 mg/kg/wk				
I52858		Negative	Negative	Negative
I52859		Negative	Negative	Negative
I52860		Negative	Negative	Negative
I52861		Negative	Negative	Negative
Group: Female 3 - 0.6 mg/kg/wk				
I52862		Negative	Negative	Negative
I52863		Negative	Negative	Positive[a]
I52864		Negative	Negative	Negative
I52865		Negative	Negative	Negative
Group: Female 4 - 2.0 mg/kg/wk				
I52866		Negative	Negative	Negative
I52867		Negative	Negative	Negative
I52868		Negative	Negative	Negative
I52869		Negative	Negative	Negative
I52870		Negative	Negative	Negative
I52871		Negative	Negative	Negative

a Titer >1/50, <1/100 in Assay 008BR (see Appendix 13).

Other:

Title: 4 Week Comparative Toxicokinetic and Toxicity Study with LB03002 (SR-hGH) and hGH in Juvenile Rhesus Monkeys

Key study findings:
Juvenile male rhesus monkeys (3/group) received daily injections of Genotropin® at 0.086 and 1.0 mg hGH/kg/dose (Groups 1 and 2). Groups 3 and 4 received weekly injections of LB03002 at 0.6 and 7.0 mg hGH/kg/dose at dose volumes of 0.03 and 0.35 mL/kg, respectively. Assessment of toxicity was based on mortality, clinical observations, ophthalmic examinations, clinical pathology, toxicokinetics, IGF-1 and anti-GH antibody analyses, and anatomic pathology evaluations.

All monkeys survived to scheduled sacrifice on Day 30. The only dose-related clinical signs were episodes of swollen dose site, observed in all three of the monkeys given LB03002 equivalent to 7.0 mg hGH/kg/dose. These became apparent the day after each injection and persisted for 1 to 3 days. The sustained release product, LB03002 did not induce antibodies against hGH in response to administration of either Genotropin® or LB03002. LB03002 administration at 0.6 mg hGH/kg/dose was comparable to daily injection of Genotropin® at 0.086 mg hGH/kg/dose. No remarkable adverse systemic effects were observed. It appears that LB03002 produced comparable effect on IGF-1 to once daily dosed Genotropin®. Although LBD-009 has not been evaluated in juvenile animals, valtropin SR has been tested in juvenile and adult monkeys. It appears that the two products had similar effects.

Study no.: Covance 7263-130
Volume #, and page #: Toxicology report#4.2.3.2.4 (1-270 pages)
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 2/7/2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: Lot#MCT301

Methods:

Doses: Control(genotropin 0.086 and 1 mg hGH/kg/dose) and LB03002 at doses of 0.6 and 7 mg hGH/kg/dose

Species/strain: Male rhesus monkeys/Macaca mulatta

Number/sex/group or time point (main study): 3 males/group as shown below.

Route, formulation, volume, and infusion rate: Subcutaneous

Satellite groups used for toxicokinetics or recovery: None

Age: NA

Weight: Males NA; Females NA

Group Designation and Dose Levels

Group	Test Material	No. of Animals Male	Female	Dose Level (mg hGH/kg/dose) hGH	Test Material Concentration mg hGH/mL	Dose Volume mL/kg	Animal Numbers
1[a]	Genotropin®	3	-	0.086	5	0.0172	I55005-I55007
2[a]	Genotropin®	3	-	1.000	5	0.2	I55008-I55010
3[b]	LB03002	3	-	0.600	20	0.03	I55011-I55013
4[b]	LB03002	3	-	7.000	20	0.35	I55014-I55016

a Dosed with Soluble hGH once daily.
b Dosed with LB03002 once a week.

Observations and times:

Mortality: Once a day
Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Ophthalmoscopy was done two times in all animals before treatment and after final administration.

EKG: NA
Hematology: Before autopsy, animals fasted overnight were ether anaesthetized. The sponsor took a blood sample from a posterior vein and treated the sampled blood with EDTA for anticoagulation and used it for the blood tests.
Clinical chemistry: From the posterior venous blood sample taken, the sponsor separated serum by centrifugation for the biochemical lab tests.
Urinalysis: In all animals which were going to be sacrificed, urinalysis was performed after the final administration. The sponsor examined specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen and nitrite in urine within 3 hours of urination, in the last week of injection. Autistics (Ames) and CliniTek-10 (Ames) were used for the tests.

Gross pathology: For all animals on which autopsy was performed, the sponsor took the following internal organs and fixed them with 10 % neutral formalin solution (skin as well as testis and sternum were treated with Bouin's solution). In general, the samples were stained with hematoxylin-eosin before the gross pathological examination.

Organ weights (specify organs weighed if not in histopath table): Conventional methods were used.

Histopathology: Adequate Battery: yes (x), no ( )—explain
Peer review: yes (x), no ( )

Results
Mortality: All monkeys survived to the end of the scheduled sacrifice on Day 30.

Clinical signs: Incidences of swollen tissues at injection sites were observed in all animals. The maximum duration of the observed swelling was 2-4 days after injection, which was resolved within 2 days. A few monkeys also had discharges of foamy vomitus, excretion and alopecia as shown below.

Table 2
Summary of Clinical Observations – Groups 1 and 2

DAYS 1-30	NUMBER OF ANIMALS AFFECTED	
SEX:	----MALE----	
GROUP:	1	2
CATEGORY DOSE:	0.086	1.000
KEYWORD UNITS:	MG hGH/KG/DOSE	
QUALIFIER NUMBER:	3	3
*** TOP OF LIST ***		
DISCHARGE		
VOMITUS		
FOAMY	0	1
EXCRETION		
NON-FORMED FECES	1	2
SKIN & PELAGE		
ALOPECIA		
LIMB-HIND-RIGHT	1	0
LIMBS-HIND	2	1
DOSE SITE		
SUBCUTANEOUS		
LEFT SCAPULAR REGION	3	3
RIGHT SCAPULAR REGION	3	3
QUALITATIVE FOOD CONSUMPTION		
LOW	1	1
*** END OF LIST ***		

Body weights: There were no dose-related changes on the parameter.
Food consumption: No remarkable treatment effects on the parameter.
Ophthamic exam: There were no abnormal findings.
Hematology: There were no remarkable treatment effects on the parameter.

Organ weight: Minor differences in mean organ weights of heart, thymus, and thyroid/parathyroid were observed. Mean weights of heart and of thymus, absolute and relative to body and to brain, tended to be slightly higher in monkeys given LB03002 than those given Genotropin® as shown below. In monkeys given LB03002 equivalent to 7.0 mg hGH/kg/dose the mean weight of thyroid/parathyroid, absolute and relative to body and to brain, was lower than in other groups. It appears that the observations were not related to the dose or treatment duration. Thus, it may not be treatment effects because there were no clear histomorphologic correlates.

TABLE 11
SUMMARY OF ORGAN WEIGHT DATA

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-5
DEATH=ALL;SUBSET=ALL

HEART

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2066.7	10.5	0.51	0.11
		STANDARD DEV:	208.2	0.4	0.04	0.01
M	2					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2133.3	10.4	0.49	0.11
		STANDARD DEV:	251.7	0.9	0.06	0.01
M	3					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2033.3	11.1	0.55	0.12
		STANDARD DEV:	351.2	2.0	0.02	0.01
M	4					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2100.0	12.2	0.58	0.13
		STANDARD DEV:	300.0	1.2	0.04	0.01

TABLE 11
SUMMARY OF ORGAN WEIGHT DATA

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-5
DEATH=ALL;SUBSET=ALL

THYMUS

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2066.7	2.74	0.133	0.030
		STANDARD DEV:	208.2	0.36	0.010	0.007
M	2					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2133.3	3.02	0.146	0.033
		STANDARD DEV:	251.7	1.58	0.092	0.015
M	3					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2033.3	3.28	0.156	0.034
		STANDARD DEV:	351.2	1.95	0.088	0.019
M	4					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2100.0	3.40	0.161	0.036
		STANDARD DEV:	300.0	0.78	0.015	0.009

TABLE 11
SUMMARY OF ORGAN WEIGHT DATA

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=1-5
DEATH=ALL;SUBSET=ALL

THYROID/PARATHYROID

SEX	DOSE GROUP		TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
M	1					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2066.7	0.33	0.016	0.004
		STANDARD DEV:	208.2	0.06	0.003	0.001
M	2					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2133.3	0.37	0.017	0.004
		STANDARD DEV:	251.7	0.21	0.008	0.002
M	3					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2033.3	0.32	0.016	0.003
		STANDARD DEV:	351.2	0.08	0.001	0.000
M	4					
		NUMBER IN GROUP:	3	3	3	3
		MEAN:	2100.0	0.22	0.010	0.002
		STANDARD DEV:	300.0	0.04	0.000	0.000

Gross pathology: Unremarkable.
Histopathology: Microscopic observations in brain, heart, and adrenal gland were comparable in all four groups. However, it appears that the incidences of inflammation, vacuoles formation and hemorrhage were high in group 4 animals, which may not be treatment related because the chronic inflammation was not detectable in the group (Please see Table 12).

Table 12
Incidence of Microscopic Observations

TABLE INCLUDES, SEX=ALL;GROUP=ALL;WEEKS=1-5 DEATH=ALL;FIND=ALL;SUBSET=ALL		-- NUMBER OF ANIMALS			
	SEX:	-------MALE-------			
	GROUP:	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	3	3	3	3
*** TOP OF LIST ***		-=-	-=-	-=-	-=-
INJECTION SITE (IS)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	1	0	1	1
--INFLAMMATION, CHRONIC		2	3	2	0
--INFLAMMATION, GRANULOMATOUS		0	0	0	2
--VACUOLES, SUBCUTANEOUS TISSUE		0	0	0	2
--HEMORRHAGE		0	0	0	1
BRAIN (BR)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	3	3	3	3
HEART (HT)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	1	3	3	3
--INFLAMMATION, CHRONIC, FOCAL		2	0	0	0
PITUITARY (PI)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	3	3	3	3
ADRENAL, CORTEX (AC)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	2	2	2	2
--MINERALIZATION, FOCAL		1	1	1	1
ADRENAL, MEDULLA (AM)	NUMBER EXAMINED:	3	3	3	3
	NOT REMARKABLE:	3	3	3	3

Toxicokinetic study:

Cmax and AUC_{0-t} values on Day 22 were similar or lower than those observed on Day 1. To compare the exposure of Genotropin® and LB03002, an assumption was made that daily exposure of Genotropin® will remain similar after seven consecutive days of dosing. On Day 1, the mean AUC_{0-t} values after administration of LB03002 were 11.7 fold and 6.5 fold higher when comparing Groups 1 and 3 or 2 and 4, respectively, versus an anticipated difference of 7 fold in the values if the two doses were similar. At steady state (Day 22), the close proximity of the two different types of doses was more apparent, with 7.8 fold or 5.0 fold differences at the two different doses, based on mean AUC_{0-t} values. The overall mean difference between the two dosing regimens was approximately 7.8 fold. Using this assumption and based on the AUC_{0-t} values on Day 1 and AUC_{0-t} values on Day 22, cumulative exposure is expected to be similar if Genotropin® was given daily for 7 days compared to LB03002 given once a week. The sponsor did not provide summary tables for individual animal TK data on genotropin and LB03002.

2.6.6.4 Genetic toxicology
Reviewed under IND62,376.

2.6.6.5 Carcinogenicity
No carcinogenicity study was performed.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Fertility study of LBD-009 in rats

Key study findings:

Sprague-Dawley rats, 80 female and 40 male, were divided into 4 groups: a control (vehicle), a low-dose (1 IU/kg), a medium-dose (3 IU/kg), and a high-dose (10 IU/kg) of LBD-009 treated groups. LBD-009 was administered to female rats from 14 days prior to mating until 7 days after delivery. Male rats were administered from 60 days prior to mating until day 7. Neither the LBD-009 treated groups nor the negative control group showed any anomalies in mating rate, gestation rate, number of corpus luteum, implantations, and fetus when animals were necropsied at the end of pregnancy. The sponsor failed to provide mortality data of dams, their body weights, food and consumption. However, the reviewers would like to believe what the sponsor indicated in this submission because several commercial rh-GH preparations are known to safe and effective. It is also quite clear that LBD-009 has little or no detrimental effect on pregnancy and gestation under tested conditions.

Study no.: SNUV92-001
Volume #1, and page #1-20
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 12/22/1992
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: JI108, no statement on purity

Methods

Doses: 0, 1, 3, and 10 IU/kg
Species/strain: Rat/Sprague Dawley
Number/sex/group: 20 females and 10 males per group as shown below
Route, formulation, volume, and infusion rate: Subcutaneous
Satellite groups used for toxicokinetics: None.
Study design:

Rats were divided into 4 groups, including a negative control group. To each group, at least 30 pregnant rats were assigned and the animals were allowed to adjust to the environment of the animal study room for 1 week before the administration of testing article. Animals were allowed to mate (1 pair) during the night, and the females were examined in the morning using vaginal smear. When spermatozoids were identified by vaginal smear examination, the animal was considered pregnant, and that day was counted as day 0 of gestation. These animals were divided into groups and were given administration daily from day 7 through 17 of gestation via subcutaneous injection. The

study complies with the Guidelines for Toxicity Studies by the Ministry of Health and Welfare (October 29, 1988)

Parameters and endpoints evaluated: Please see item under results below.

Results:

Mortality:
The sponsor did not provide information on mortality of dams.

Clinical signs:
The sponsor indicated that there were no unusual clinical signs without providing actual data. They also stated that there was no significant difference between the treatment groups and the control group.

Body weight:
The sponsor did not provide relevant data on body weight of mother animals.

Food consumption:
The sponsor did not provide information on this parameter.

Toxicokinetics: N/A

Necropsy:

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):
The number of animals that had successful mating were comparable in all group so that mating rate (%) were also comparable, although the control and the HD group had 94%, while the LD and MD groups had 84%. The number of pregnant animals in all group being 16 to 18, were also comparable in all groups as shown below.

The numbers of implantation were slightly lower in the treated groups compared to the control as shown in Table 2 below. It appears that number of dead fetuses increases with the dose, although dead fetuses rate (%) was not really different. Per cent of implantation rate

Table 1. Mating and pregnancy rate of rats treated with LSD-009

Groups / Dose	Low Dose (1IU/kg)	Middle Dose (3IU/kg)	High Dose (10 IU/kg)	Control
No. of Animals	20	19	18	20
No. of Mating Animals	17	16	17	19
No. of Pregnancy Animal	17	16	16	18
Pregnancy rate(%)[a]	100	100	94.1	94.7
Mating rate(%)[b]	85	84	94.4	95

[a] No. of Pregnancy Animal / No. of Mating Animals×100
[b] No. of Mating Animals / No. of Animals×100

Table 2. Some Aspects of Rats treated with LBD-009

Groups / Dose	Low Dose (1 IU/kg)	Middle Dose (3 IU/kg)	High Dose (10 IU/kg)	Control
No. of CL*	336	325	320	365
Rt	10.65±3.16	10.75±3.02	9.29±2.66	10.00±2.99
Lt	9.12±3.06	9.56±2.65	9.53±2.33	9.21±3.04
No. of Implantation	292	289	286	319
Rt	9.62±2.16	9.00±1.23	8.12±0.21	8.68±1.12
Lt	7.00±1.12	8.44±3.12	8.06±1.26	7.89±1.24
No. of Dead fetuses	6	10	11	4
Rt	3	4	4	2
Lt	3	6	7	2
No. of Live fetuses	286	279	275	315
Dead fetuses rate(%)a)	2	3	4	1
Implantation rate(%)b)	87	89	89	87

* : Corpus Luteum
a): No. of Dead Fetuses/No. of Implantation×100
b): No. of Implantation/No. of Corpus luteum×100

Embryofetal development

Study title: Teratogenicity study of LBD-009 in rats

Key study findings:
Sprague Dawley rats, 120 female and 75 male, were divided into 3 dose-groups for LBD-009: a low-dose group (1 IU/kg), a medium-dose group (3 IU/kg), and a high-dose group (10 IU/kg). LBD-009 was administered to female rats for 11 days from day 7 through day 17 of gestation. Twenty animals from each group were necropsied on day 21 of gestation, and examined for the presence of anomalies in mother animals and fetuses was examined. Ten remaining animals in each group were allowed to give natural birth to examine the first generation dams after delivery. Neither the LBD-009 treated groups nor the negative control group showed changes in the body weights of mother animals nor fetuses.

No significant changes in duration of pregnancy, weights of fetus and placenta, sex ratio, absorbed fetus or dead fetus in the negative control and the 3 LBD-009 treatment groups. Although a slight increase in the number of dead fetuses was observed in the LBD-009 treatment groups compared to the control groups, the same can be expected even in untreated animals. There were no anomalies in fetuses. Examinations of the internal organs and skeletons likewise showed no significant anomalies. Therefore, it is safe to say that LBD-009 has no effect on fetuses in rats during pregnancy, especially during the period when the organs are formed.

Study no.: SNUV-002
Volume #, and page #: 21-40
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 1/14/1992
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI108

Methods

Doses: 0, 1, 3, and 10 IU/kg
Species/strain: Rat/Sprague Dawley (SD)
Number/sex/group: 30 female rats/group
Route, formulation, volume, and infusion rate: Subcutaneous
Satellite groups used for toxicokinetics: none
Study design:

Rats were divided into 4 groups, including a negative control group. Animals were allowed to mate (1 pair) during the night, and the females were examined in the morning using vaginal smear. When spermatozoids were identified by vaginal smear

examination, the animal was considered pregnant, and that day was counted as day 0 of gestation. These animals were divided into groups and were given administration daily from day 7 through 17 of gestation via the same administration route as the one to be used in the clinic (subcutaneous injection).

Parameters and endpoints evaluated: Please see the individual sections.

Results

Mortality (dams):

The sponsor did not provide the relevant data on animal deaths.

Clinical signs (dams):

The sponsor indicated that no effects or changes in mother animals were observed in any of the treatment groups without providing actual data.

Body weight (dams):

Increases in the body weight of mother animals were seen in the high dose group, although the differences were not statistically significant, compared to the control group as shown (Table 3). Organ weights that were measured at necropsy of the dams were not different from the control group as demonstrated in several tissues (Table 2).

Table 3. Body Weight of Maternal Rats during Lactation Periods.

Days	Low	Middle	High	Negative Control
0	257.67 ±20.70	257.71 ±19.25	262.00 ±28.28	256.71 ±15.45
7	263.17 ±16.94	263.50 ±12.18	284.00 ±14.14	266.50 ±14.80
14	270.50 ±14.71	284.75 ±17.75	298.50 ± 6.36	268.80 ±25.17
21	282.23 ±15.32	296.26 ±19.25	300.20 ±12.29	279.75 ±18.19

Table 2. Relative Organ Weights(%) of Rats treated with LSD-009 on autopsy

		Low	Middle	High	Negative Control
Liver (g/100g B.W)		4.28 ±1.16	4.28 ±0.56	4.60 ±0.89	4.21 ±0.47
Kidneys (g/100g B.W)	LT[a)]	0.39 ±0.06	0.56 ±0.11	0.40 ±0.05	0.41 ±0.05
	RT[b)]	0.37 ±0.06	0.58 ±0.05	0.41 ±0.07	0.38 ±0.03
Spleen (g/100g B.W)		0.48 ±0.31	0.27 ±0.17	0.32 ±0.13	0.22 ±0.04
Ovaries (mg/100g B.W)	LT	32.71 ±29.02	28.73 ±21.14	27.42 ±18.32	28.71 ±17.07
	RT	26.12 ±19.01	27.54 ±31.06	25.84 ±24.11	25.87 ±16.23

a) : Left, b) : Right

Food consumption (dams):
The sponsor did not provide the data.
Toxicokinetics: None.
Embryonic development of F1 generation:
The number of corpus lutea in the treated group was not significantly different from the control group. In the MD and HD groups, number of implantations is appeared to be slightly less, compared to the control and LD groups. The numbers of dead fetuses and the rate of dead fetuses were slight low, compared to the control. Sex ratio, body weight and weight of placenta were comparable in all treated and control group (Table 1).

Table 1. Influence of LSD-009 in embryonic development(F1) during pregnancy

Groups	Low	Middle	High	Negative Control
No. of dams	20	20	20	20
Mean B.W of maternal rats	319.35 ±37.35	295.28 ±31.48	305.88 ±39.13	325.67 ±41.71
No. of corpus lutea	245	223	195	291
mean	16.33	14.80	15.08	14.50
S.D	±3.58	±3.47	±2.10	±2.46
No. of implantations	208	165	169	186
mean	13.73	11.00	13.00	11.60
S.D	±2.66	±5.84	±2.36	±4.04
Implantation rate(%)(a)	84.07	74.32	86.22	80.62
No. of undeveloped embryos	17	21	13	10
Undevelopment rate(%)(b)	8.25	12.73	7.69	5.38
No. of dead fetuses	8	8	8	1
Dead fetuses rate(%)(c)	3.88	4.85	4.73	0.54
No. of live fetuses	181	135	148	175
mean	12.07	10.78	12.33	10.71
S.D	±4.18	±8.68	±4.16	±4.75
Live fetuses rate(%)(d)	87.86	82.42	87.57	94.09
Sex ratio(male/female)	0.94	0.95	0.93	0.90
F.W of fetuses: mean	4.81	3.83	3.71	4.44
S.D	±0.84	±1.03	±0.80	±1.41
Weight of placenta				
mean	0.60	0.56	0.59	0.58
S.D	±0.10	±0.18	±0.11	±0.10
No. of external anomalies	0	0	0	0
malformed head	0	0	0	0
hydrocephalic head				
malformed extremities	0	0	0	0
Ext. anomaly rate(%)(e)	0	0	0	0

(a) : (No. of implantations / No. of corpus lutea)×100
(b) : (No. of undeveloped embryos / No. of implantations)×100
(c) : (No. of dead fetuses / No. of implatations)×100
(d) : (No. of live fetuses / No. of implatations)×100
(e) : (No. of fetuses showing external anomalies / No. of live fetuses)×100
** :Significantly different from negative control($P < 0.01$)
*** :Significantly different from negative control($P < 0.001$)

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Body weight of offerspring:
During lactating period, the body weight of F1 generation increased as a function of LBD-009 dose and its treatment duration (Table 4). However, the growth hormone did not altered developmental physiological parameters such as separation of eyelids, eruption of teeth and opening of ear (Table 5).

Table 4. Body weight change on young rats during lactation periods

Days	Low	Middle	High	Negative Control
0 day	5.89 ±0.94	5.92 ±0.88	5.95 ±0.96	5.81 ±0.63
7 day	14.68 ±2.06	15.78 ±1.80	17.18 ±1.46	14.12 ±1.93
14 day	27.35 ±1.70	30.75 ±1.60	33.52 ±1.58	25.19 ±2.04
21 day	49.25 ±3.25	51.25 ±2.68	54.68 ±8.92	48.23 ±5.78

Table 5. Physiological some aspects on young rats during lactation periods

	Low	Middle	High	Negative Control
Separation of eyelids (days)	12.82 ±0.64	13.06 ±0.72	12.92 ±0.49	13.22 ±0.74
Eruption of lower teeth(days)	10.31 ±0.60	10.56 ±0.51	10.64 ±0.50	10.68 ±0.48
Opening of ear (days)	13.13 ±0.34	13.44 ±0.50	13.15 ±0.38	13.43 ±0.61
Vaginal Opening (days)	ND*	ND	ND	ND
Descending of Testis(days)	ND	ND	ND	ND

ND* : No detection

Offspring (malformations, variations, etc.): There were no remarkable abnormalities.

Skeletal development of Fetuses (F1): Degree of ossification in cervical, thoracic, lumbar, and sacral vertebra; rib, sternum, metacarpus, metatarsus and forepaw was the same in all treated and control groups without exception (Table 6).

Table 6. Influence of LEB-009 on Skeletal Development of Fetuses(F1)

		Low	Middle	High	Negative Control
No.of fetuses observed		50	50	50	50
Degree of ossification					
Skull					
Extra sutural bone		0	0	0	0
Large open fontanelle		0	0	0	0
Cervical vertebra		7.0±0.0	7.0±0.0	7.0±0.0	7.0±0.0
Thoracic vertebra		13.0±0.0	13.0±0.0	13.0±0.0	13.0±0.0
Lumber vertebra		6.0±0.0	6.0±0.0	6.0±0.0	6.1±0.3
Sacral vertebra		4.0±0.0	3.8±0.4	3.7±0.5	3.9±0.3
Caudal vertebra		24.1±0.1	23.2±1.2	23.5±2.3	24.5±0.2
Rib		13.0±0.0	13.0±0.0	13.0±0.0	13.0±0.0
Sternebra		6.0±0.0	6.0±0.0	5.7±0.8	5.9±0.3
Metacarpus	Lt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
	Rt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
Prox.phal of	Lt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
forepaw	Rt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
Dis.phal of	Lt	4.0±0.0	4.0±0.0	4.0±0.0	4.0±0.0
forepaw	Rt	4.0±0.0	4.0±0.0	4.0±0.0	4.0±0.0
Metatarsus	Lt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
	Rt	5.0±0.0	5.0±0.0	5.0±0.0	5.0±0.0
Prox.phal of	Lt	4.0±0.0	4.1±0.2	4.3±0.3	4.1±0.1
hindpaw	Rt	4.0±0.0	4.2±0.3	4.0±0.0	4.0±0.0
Dis.phal of	Lt	4.1±0.0	4.0±0.0	4.0±0.0	4.0±0.0
hindpaw	Rt	4.3±0.0	4.1±0.3	4.0±0.0	4.0±0.0
Fission of thoracic vertebral center		ND*	ND	ND	ND
Lumbar rib		ND	ND	ND	ND
Cleft sternum		ND	ND	ND	ND
No.of fetuses showing variations		0	0	0	0
Variation rate(%)(a)		0	0	0	0

(a)(No.of fetuses showing variations/No.of fetuses observed)×100
*: Not detected

Visceral Tissues of Fetuses:

Visceral tissues of F1 generation were examined. Renal pelvis dilatation, ventricular septal defect, and renal displacement were observed in the control as well as the treated groups. Visceral anomaly rate was higher in the control, compared to the treated groups as presented below (Table 70).

Table 7. Influence of LGD-009 on Fetal Viscera & Soft Tissue(F1)

	Low	Middle	High	Negative Control
No. fetuses observed	50	50	50	50
Dilatation of renal-pelvis	1	3	3	4
Ventricular septal defect	0	1	0	1
Renal displacement	2	2	3	5
Hydrocephalus	0	0	0	0
No. of fetuses showing anomaly	3	6	6	10
Anomaly rate(%)(a)	6	12	12	20

(a)(No. of fetuses showing anomaly/ No. of fetuses observed) × 100
*** :Significantly different from negative control($P < 0.001$)

Study title: Teratogenicity Study of LBD-009 in Rabbits

Key study findings: New Zealand white female rabbits were divided into 4 groups; 1 vehicle control and 3 treatment groups for LBD-009 [a low-dose (1 IU/kg), a medium-dose (3 IU/kg), and a high-dose (10 IU/kg)]. LBD-009 was administered to 20 pregnant rabbits/group from day 6 through day 18 of gestation, for a total of 13 days.
All rabbits from each group were necropsied one day before the delivery, day 22 of gestation, and presence of anomalies in mother animals and fetuses was examined. Neither the LBD-009 treated groups nor the negative control group showed significant changes in the body weights of mother animals and fetuses or any anomalies in fetuses. Examinations of the internal organs and skeletons likewise showed no significant changes. No significant changes in duration of pregnancy, weights of fetus and placenta, sex ratio, absorbed fetus or dead fetus in the negative control and any of the 3 LBD-009 treatment groups. No anomalies were found in examination of internal organs. Also, no significant changes in the skeletal and visceral tissue development were observed in any of the treatment groups. Base on the above findings, LBD-009 does not induce toxicity or deformity in fetuses.

Study no.: SNUV-003
Volume #, and page #: 41-66
Conducting laboratory and location:

b(4)

Date of study initiation: 1/14/1992
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI108

Methods

Doses: 0, 1, 3, and 10 IU/kg
Species/strain: Rabbit/New Zealand White
Number/sex/group: 12 female rabbits/group
Route, formulation, volume, and infusion rate: Subcutaneous
Satellite groups used for toxicokinetics: None.
Study design:

Twelve pregnant rabbits/group were assigned a control and three treated (LD, MD and HD) group. The animals were allowed to adjust to the environment of study rooms for a week before the treatment. Animals were given LBD-009 injection subcutaneously from day 6 through day 18 of gestation. The study complies with the Guidelines for Toxicity Studies by the Ministry of Health and Welfare (October 29, 1988).

Parameters and endpoints evaluated: Please see relevant section below.

Results:

Mortality (dams):
The sponsor did not provide mortality data of the dams.
Clinical signs (dams): The sponsor stated that there were no significant clinical signs without data.
Body weight (dams): There was slight increase in bodyweight in the HD group, which is not significant as shown below(Table 1).

Table 1, Effect of LBD-009 on Maternal Body weights treated subcutaneously from day 6 to day 18 of pregnancy

Pregnancy day	Control	Low	Middle	High
day 0	3352±132	3340±124	3345±114	3334±143
day 7	3436±165	3413±185	3394±162	3421±196
day 14	3493±254	3438±248	3488±116	3509±204
day 21	3638±296	3519±251	3644±262	3624±112
day 29	3803±165	3814±133	3793±139	3821±157

* Data were presented as Mean±S.D

Food consumption (dams):
The sponsor did not provide information on food consumption of the dams.
Toxicokinetics: None.
Effects of LBD-009 on Fetuses:
Number of corpus luteum and implantations and implantation rates: No significant differences in the number of corpus luteum, number of implantations, or in the gestation rate were seen between the LBD-009 treatment groups and the vehicle control group as shown below (Table 2). Number and death rates of fetuses observed upon caesarean section immediately before delivery were comparable in all groups including the treated groups (Table 2). No dead fetus was found in any of the tested groups. Although absorbed fetuses were observed (2 in the LD group, one each in the control, HD and MD groups), no evidence of dose-dependency or treatment effect was seen (Table 2). Body weight, placenta weight and sex ratio observed upon caesarean section immediately before delivery were also comparable in all groups (Table 2).

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

Table 2. Effect of LBD-009 on fetuses(F_1) from female rabbits(P) treated subcutaneously from day 6 to day 18 of pregnancy

Group	Control	Low	Middle	High
No. of dams sacrificed	20	20	20	20
Mean B.W of maternal rabbits(g)	3803 ±165	3814 ±133	3793 ±139	3821 ±157
No. of corpora lutea	186	182	189	184
mean	9.30	9.10	9.45	9.20
S.D	±1.25	±1.14	±1.40	±1.17
No. of implantations	172	168	170	174
mean	8.60	8.40	8.50	8.70
S.D	±2.61	±1.73	±2.44	±2.18
Implantation rate(%)(a)	92.47	92.30	89.94	94.57
No. of undeveloped embryos	1	2	1	1
Undevelopment rate(%)(b)	0.58	1.19	0.59	0.57
No. of dead fetuses	0	0	0	0
No. of live fetuses	163	159	160	164
mean	8.15	7.95	8.25	8.20
S.D	±1.13	±2.17	±1.83	±1.51
Live fetuses rate(%)(c)	94.77	94.64	94.70	94.25
Sex ratio(d)	0.57 ±0.14	0.53 ±0.12	0.58 ±0.11	0.64 ±0.19
B.W of fetuses: mean	41.47	40.31	41.53	41.69
S.D	±6.58	±2.13	±5.14	±5.29
Weight of placenta				
mean	6.02	6.08	6.34	6.03
S.D	±1.34	±1.14	±1.57	±1.28

(a) : (No. of implantations / No. of corpora lutea) × 100
(b) : (No. of undeveloped embryos / No. of implantations) × 100
(c) : (No. of live fetuses / No. of implantations) × 100

External Anomalies:
External anomalies of the fetuses were examined upon caesarean section immediately before delivery. No external anomalies were seen in the control group and any of the LBD-009 treatment groups (Table 3).

Table 3. External examination in fetuses(F_1) from female rabbits(P) treated subcutaneously with LBD-009 from day 6 to day 18 of pregnancy

Group	Control	Low	Middle	High
No. fetuses examined	168	159	160	164
No. of fetus with external malformation	0	0	0	0
Ext. malformation rate(%)(c)	0	0	0	0

Anomalies of the internal organs:
Anomalies of the internal organs in fetuses were examined upon caesarean section immediately before delivery. No significant changes were observed in any of the treatment groups, compared to the control (Table 4).

Table 4. Visceral examinations in fetuses(F_1) from female rabbits(P) treated subcutaneously with LBD-009 from day 6 to day 18 of pregnancy

Group	Control	Low	Middle	High
No. fetuses examined	100	100	100	100
No. of fetuses with abnormality(%)	5(5.00)	5(5.00)	6(6.00)	4(4.00)
Ventricular septal defect	0	0	1	0
Dilatation of renal pelvis	2	1	2	2
Renal displacement	3	4	3	2

Ossification and Skeletal Anomalies in Fetuses:

Ossification and skeletal anomalies in fetuses were examined upon caesarean section immediately before delivery. There were variations in ribs, lumber vertebra, and lumbar in all groups (Table 5, 6). However, there was no difference in the incidence between the control and the treated three groups. Thus, it appears that the changes may not be significant.

Table 5. Skeletal examination for abnormality and variation in fetuses(F_1) from female rabbits(F) treated subcutaneously with LED-009 from day 6 to day 18 of pregnancy

Group	Control	Low	Middle	High
No. of fetuses examined	50	50	50	50
Skeletal abnormality				
No. of fetuses with skeletal abnormalities(%)	0(0.00)	1(2.00)	0(0.00)	0(0.00)
Skeletal variation				
No. of fetuses with skeletal variation(%)	22(44.0)	25(44.0)	21(42.0)	21(42.0)
Thirteen ribs	10	13	11	9
Eight lumbar vertebra	12	11	10	11
Lumbarization of the 1st sacral vertebra	0	1	0	0
Spilting of sternebra	0	0	0	1

Table 8. Skeletal examination for ossification in fetuses(F_1) from female rabbits(P) treated subcutaneously with L88-009 from day 6 to day 18 of pregnancy

Group	Control	Low	Middle	High
No. of fetuses examined	50	50	50	50
No. of ossification centers				
Phalanges of forepaw				
Distal	10.0±0.00	10.0±0.00	10.0±0.00	10.0±0.00
Middle	8.0±0.01	8.0±0.04	8.0±0.00	8.0±0.00
Proximal	10.0±0.00	10.0±0.00	10.0±0.00	10.0±0.00
Metacarpal	10.0±0.00	10.0±0.00	10.0±0.00	10.0±0.00
Palanges of hindpaw				
Distal	8.0±0.00	8.0±0.00	8.0±0.00	8.0±0.00
Middle	8.0±0.00	8.0±0.00	8.0±0.00	8.0±0.00
Proximal	8.0±0.00	8.0±0.00	8.0±0.00	8.0±0.00
Metatarsal	8.0±0.00	8.0±0.00	8.0±0.00	8.0±0.00
Cervical vertebral body	7.0±0.00	7.0±0.00	7.0±0.00	7.0±0.00
Sacral and coccygeal vertebrae	19.9±0.24	19.9±0.47	19.9±0.22	19.9±0.07
Sternbrae	6.0±0.07	6.0±0.11	6.0±0.24	6.0±0.08
No. of fetuses with pooly ossified hyoid bone (%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
No. of fetuses with pooly ossified sternbrae (%)	0 (0.00)	1 (2.00)	0 (0.00)	0 (0.00)

* Data were presented as Mean±S.D

Prenatal and postnatal development

Study title: Peri and postnatal toxicity study of LBD-009 in rats

Key study findings:

Twenty Sprague Dawley female rats/group were given LBD-009 at dose of 1, 3, or 10 IU/kg subcutaneously for 11 days from day 7 through day 17. The animals from each group were necropsied on day 21 of gestation, and examined for the presence of anomalies in mother animals and fetuses. To examine the first generation dams after the delivery, ten remaining animals in each group were allowed to give natural birth. Neither the LBD-009 treated groups nor the negative control group showed changes in the body weights of mother animals and fetuses or any anomalies in fetuses. Examinations of the internal organs and skeletons likewise showed no significant changes. There was no statement or data on the physical development, behavioral evaluation, F1 reproduction and F1 findings in this NDA submission. However, the sponsor concluded that LBD-009 had no effect on fetuses in rats during pre- and postnatal development period.

Study no.: SNUV92-004
Volume # 1, and page #: 68-88
Conducting laboratory and location: _____ b(4)

Date of study initiation: 1/14/1992
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI108
Methods

Doses: 0, 1, 3, and 10 IU/kg
Species/strain: Rat/Sprague Dawley (SD)
Number/sex/group: 20 female rats/group
Route, formulation, volume, and infusion rate: Subcutaneous
Satellite groups used for toxicokinetics: None
Study design:

Twenty Sprague Dawley female rats/group were given LBD-009 at dose of 1, 3, or 10 IU/kg subcutaneously for 11 days from day 7 through day 17. When spermatozoids were identified by vaginal smear examination, the animal was considered pregnant, and that day was counted as day 0 of gestation. The animals from each group were necropsied on day 21 of gestation, and examined for the presence of anomalies in mother animals and fetuses. To examine the first generation dams after the delivery, ten remaining animals in each group were allowed to give natural birth. The study complies with the Guidelines for Toxicity Studies by the Ministry of Health and Welfare (October 29, 1988).

Results:

F_0 in-life:
Mortality and clinical signs:
There was no death in dams in this study. There were no remarkable clinical signs in the control as well as the treated groups as shown (Table 4).

Table 4. Mortality and cilinical sign of maternal rats given to LBD-009

Group	Clinical sign								Mortality
	P0[a]	P1	P2	P3	L0[b]	L1	L2	L3	
Control	NCS*	NCS	NCS	NCS	NCS	NCS	NCS	NCS	0/20
Low	NCS	NCS	NCS	NCS	NCS	NCS	NCS	NCS	0/20
Middle	NCS	NCS	NCS	NCS	NCS	NCS	NCS	NCS	0/20
High	NCS	NCS	NCS	NCS	NCS	NCS	NCS	NCS	0/20

P0[a], pregnacy week; L0[b], Lactating week
NO* : No clinical sign

Food and water consumption in Fo rat after parturition:

There were no differences between the control animals and animals that were treated with the testing substance in food and water consumption in Fo rat after parturition as shown below (Table 3).

Table 3. Feed and water consumption of maternal rats treated with LED-009 after parturition

Week\Groups	Low	Middle	High	Negative Control
Feed Consumption(unit: g/rat/day)				
1	62.23 ±29.80	73.43 ±19.74	71.20 ±26.42	69.21 ±24.21
2	73.69 ±22.89	80.75 ±36.55	82.33 ±13.01	82.69 ±26.22
3	95.65 ±32.48	96.25 ±42.47	99.20 ±31.24	95.24 ±29.15
Water Consumption(unit: ml/rat/day)				
1	134.44 ±58.93	138.57 ±37.75	135.81 ±37.74	134.09 ±37.00
2	180.36 ±43.52	176.55 ±69.91	177.50 ±45.16	179.62 ±51.98
3	202.61 ±40.26	199.39 ±26.38	203.54 ±33.25	200.20 ±32.56

Body weight of fetuses during lactation period:

Mean body weights of fetuses during lactation period increased in the HD group in the first and second week. In the MD group, there was a significant increase in the parameter in the second week of lactation (Table 2).

Table 2, Mean body weight of fetal sprague-dawley rats during lactation periods

Week\Groups	Low	Middle	High	Negative Control
0	6.35 ±0.79	6.44 ± 0.84	6.58 ±0.62	6.48 ±0.59
1	16.82 ±2.14	16.30 ±2.69	17.69* ±3.60	16.48 ±1.90
2	27.63 ±4.48	30.07* ±4.33	31.15* ±5.52	27.78 ±4.32
3	35.76 ±5.42	36.56 ±8.44	36.56 ±9.36	36.22 ±7.34

* : Significantly different from control group(p<0.05)

F1 mortality and external anomaly:

Number of live fetuses was comparable in all treated groups including the control. Dead fetuses in the control, in the LD, MD and HD groups were 6, 8, 9 and 5, respectively. Thus, per cent mortality in the HD group was low, compared to the control or other two treated groups as shown (Table 5). There was no external abnormality in the fetuses.

Table 5. Pregnancy periods of maternal rats, and mortality and external abnormalities of fetuses.

Groups	Low	Middle	High	Control
Dams				
Pregnancy periods	23.00 ±0.00	22.85 ±1.22	22.38 ±1.02	22.18 ±1.01
Fetuses	229	236	229	231
Live fetuses	220	229	224	225
Dead fetuses	8	9	5	6
Mortality(%)[a]	3.50	3.78	2.18	2.69
External Abnormalities	NA[b]	NA	NA	NA

[a]: dead fetuses/fetus No. X 100
[b]: No Abnormality

Comment and Conclusion:

The sponsor indicated that neither the LBD-009 treated groups nor the negative control group showed changes in the body weights of mother animals and fetuses or any anomalies in fetuses. Examinations of the internal organs and skeletons likewise showed no significant changes. However, there is no statement or data on the physical development, behavioral evaluation, F1 reproduction and F1 findings in this NDA submission. Thus, the reviewer considers the pre/postnatal toxicology study is incomplete. However, the reviewer also agrees that LBD-009 had no remarkable adverse effect on fetuses in rats during pre- and post-natal development period, based on extensive published documents on commercial available GH products.

2.6.6.7 Local tolerance

Study title: Valtropin Effect on Skin Irritation in Rabbits

Key study findings:
A skin irritation test on LBD-009 (Growth hormone without N-terminal) has been conducted 72 hours after application, using 6 New Zealand White male rabbits. There were no clinical signs or changes in body weight of the animals, which might be caused by the treatment throughout the test period. There was no observation of irritation (erythema, escher or edema) at the injection sites. The Primary Irritation Index (PII) according to the Draize method was scored as 0. The sponsor concluded that no skin irritation was produced by LBD-009 in New Zealand White Rabbits, which is in agreement with the reviewer.

Study no.: S-256
Volume # 1, and page #: 1-30
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 11/30/1991
GLP compliance: Yes
The above test has been conducted in compliance with 'Toxicity Test Standards for Medicines etc.' issued by the National Institute of Safety Research (NISR), Korea (October 29, 1988) and the 'Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies' issued by the Ministry of Health and Social Affairs, Korea (October 29, 1987. KGLP).

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI104
Methods:
The hair was removed 24 hours before the application of test article. The test-article was applied subcutaneously to the back of the rabbits, dividing the control and treated area as shown below. For each animal, 0.5 ml/site of the test article was applied once to each area. Vehicle without any treatment was applied to a control area. The applied area was covered by cotton gauze, fixed with non-toxic adhesive tape, and left for 24 hours. Examination of affected area was took place 24 and 72 hours after application for appearance of edema, eschar, erythema, or other potential local damage. Skin reaction is evaluated based on 'Toxicity Test Standards for Medicines'; no irritation, mild, moderate, and severe irritation, respectively.

Results:
Clinical Findings: There was no death and there were no clinical signs in the control and the treated animals.
Changes in Body Weight: When body weight was measured 24 hours after application, 4 samples out of 6 showed a temporary decrease, but all reverted to normal in 72 hours, showing an increase in body weight.

A common body-weight decrease was due to stress from the tape affixed on the body. Individual body weights of the six rabbits are attached below (Table 2).

Table 2. Body weight changes

(unit : g)

Sex	Animal No.	Day after administration			Weight Gains
		0 day	24 hrs	72 hrs	
Male	1	2717.8	2784.3	2732.5	+ 14.7
	2	2570.2	2503.8	2581.8	+ 11.6
	3	2736.0	2732.9	2739.4	+ 3.4
	4	2772.6	2723.0	2810.6	+ 38.0
	5	2808.4	2915.8	2911.1	+102.7
	6	2722.7	2674.5	2770.4	+ 47.7
	Mean	2721.3	2722.4	2757.6	36.4
	S.D.	81.6	135.2	108.1	36.6
	N	6	6	6	6

Observation of Applied Area:
When the observation was made at 24 hours and 72 hours after application, there was no edema, eschar, erythema in all control and treated animals (Table 3).

Table 3. Results of skin reaction

Sites		Control site				Test site			
Change		Erythema & Eschar		Edema		Erythema & Eschar		Edema	
		Intact	Abraded	Intact	Abraded	Intact	Abraded	Intact	Abraded
Phasea) (hrs.)		24 72	24 72	24 72	24 72	24 72	24 72	24 72	24 72
Ani. No.	Sex								
1	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
2	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
3	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
4	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
5	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
6	♂	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Total Score		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Mean Score		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
P.I.I.b)		0				0			

a) : Time after topical application
b) : P.I.I. : Primary Irritation Index = ΣMean Score / 4

Reviewer's Comment and Conclusion:
It appears that the local irritation study was conducted under valid condition. The volume of LBD-009 (0.5 ml/site) was adequate for transdermal injection. There were no significant clinical signs and mortality in both the control and treated groups. Obviously there were no significant changes in body weight of the rabbits after local injections. It is quite clear that there was no remarkable skin irritation such as edema, eschar or erythema after the drug application. Thus, the reviewer is in agreement with the sponsor's conclusion that the test article, LBD-009 did not produce local irritation in New Zealand White rabbits.

2.6.6.8 Special toxicology studies: Antigenicity study

Study title: Valtropin Effect on Antigenicity in Mice and Rats

Key study findings:
This is one of the LBD-009 antigenicity tests to examine the reaction of passive cutaneous anaphylaxis (PCA) using mice and rats. There was a low-dose group (0.15 IU/kg, the estimated clinical dose), a high-dose group (1.5 IU/kg), a high-dose + alum (aluminum hydroxide gel) group, a positive-control group (OVA [ovalbumin] + alum) and a vehicle control group. Except for the OVA + alum group (positive control) and the high-dose + alum group, there was no IgE antibody in all other groups. After dilution of the antigen from 10 times to 640 times (OVA + alum group) and from 10 times to 160 times (high-dose + alum group), respectively, IgE was detected due to the increase of the permeability of the post-capillary venules. In conclusion, LBD-009 (in the amount of 0.15 IU/kg, the estimated clinical dose) had no antigenicity in this PCA-reaction test using mice and rats, in comparison to the ovalbumin (positive control) group.

Study no.: S-244
Volume # 1, and page #: 1-54
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 3/31/1992
GLP compliance: Yes
The above test has been conducted in compliance with 'Toxicity Test Standards for Medicines etc.' issued by the National Institute of Safety Research (NISR), Korea (October 29, 1988) and the 'Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies' issued by the Ministry of Health and Social Affairs, Korea (October 29, 1987. KGLP).

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI104

Methods:
Eight week old male mice (BALB/c) were used for sensitization test. Eight week old male Sprague Dawley (SD) rats were used for passive cutaneous anaphylaxis test. The body weights of mouse and rat were 22.0 - 32 g and 266 - 363 g, respectively. The methods, group composition and dose selection for mouse sensitization test and rat PCA test are described below. In brief, subcutaneous injections were administered into the BALB/c mice abdomen 3 times a week (9 times in total) in the low- and high-dose groups. In the high-dose + alum group, the OVA + alum group and the vehicle group, intraperitoneal injections were given to the animals once every three weeks (3 times in total). On the 6th day after sensitization, blood samples were obtained the from retro-orbital venous plexus. The blood sera were diluted from 10 to 5120 times and the PCA-reaction was tested by injecting the antiserum (50 μl) intradermally into the abdomen of rats. After 24 hours, each was challenged with LBD-009 mixed with 1 %-Evans blue in

the same amount. Solution was injected into a vein, and after 30 minutes of challenge the rats were exsanguinated, and leakage of the dye at the serum injected site was examined to determine the PCA titer. The end point was set at a diameter of 5 mm or more.

Group	Antigen-Sensitisation	Sex	Number of Animals Used	Animal No.	Amount of Antigen-Sensitisation IU/kg	Applied Amount ml/kg	Application Route
I	LBD-009 (Low Dose)	Male	5	1 - 5	0.15	10	s.c.
II	LBD-009 (High-Dose)	Male	5	6 - 10	1.5	10	s.c.
III	LBD-009 + Alum	Male	5	11 - 15	1.5	10	i.p.
IV	OVA + Alum	Male	5	16 - 20	330 µg/kg	10	i.p.
V	Vehicle	Male	5	21 - 25	0	10	i.p.

(b) PCA Challenge of Rats

Group	Applied-Group	Sex	Number of Animals Used	Animal No.	Injection Route (serum)	Challenging Antigen	Amount of Challenging Antigen IU/kg	Injected Amount ml/kg	Injection Route
A	I (50 µl)	Male	10	26 - 35	i.d.	LBD-009	0.15	1	i.v.
B	II (50 µl)	Male	10	36 - 45	i.d.	LBD-009	0.15	1	i.v.
C	III (50 µl)	Male	10	46 - 55	i.d.	LBD-009	0.15	1	i.v.
D	IV (50 µl)	Male	10	56 - 65	i.d.	OVA	2860 µg/kg	1	i.v.
E	V (50 µl)	Male	10	66 - 75	i.d.	LBD-009	0.15	1	i.v.

Results:

Mortality: All mice and rats in the control as well as treated groups survived for the entire study period. There was no single animal death for any causes.

Clinical Findings: There were no abnormalities in all treated groups including the control group as shown below (Appendix 1-1/2).

Appendix 1-1. Fate and clinical findings of male mice

INDIVIDUAL OBSERVATIONS

STUDY: S-244 GROUP : I
0 DAY-25 DAY DOSE : LBD-009(0.15 IU/kg)

ANIMAL #	OBSERVATIONS	TIME OCCURRED
1	Normal	0 DAY-25 DAY
2	Normal	0 DAY-25 DAY
3	Normal	0 DAY-25 DAY
4	Normal	0 DAY-25 DAY
5	Normal	0 DAY-25 DAY

STUDY: S-244 GROUP : II
0 DAY-25 DAY DOSE : LBD-009(1.5 IU/kg)

ANIMAL #	OBSERVATIONS	TIME OCCURRED
6	Normal	0 DAY-25 DAY
7	Normal	0 DAY-25 DAY
8	Normal	0 DAY-25 DAY
9	Normal	0 DAY-25 DAY
10	Normal	0 DAY-25 DAY

(REPORT CONTINUED)

Appendix I-2. Fate and clinical findings of male mice

INDIVIDUAL OBSERVATIONS

STUDY: S-244 GROUP : III
0 DAY-49 DAY DOSE : LBD-009(1.5 IU/kg) + Alum

ANIMAL #	OBSERVATIONS	TIME OCCURRED
11	Normal	0 DAY-49 DAY
12	Normal	0 DAY-49 DAY
13	Normal	0 DAY-49 DAY
14	Normal	0 DAY-49 DAY
15	Normal	0 DAY-49 DAY

STUDY: S-244 GROUP : IV
0 DAY-49 DAY DOSE : OVA(330μg/kg) + Alum

ANIMAL #	OBSERVATIONS	TIME OCCURRED
16	Normal	0 DAY-49 DAY
17	Normal	0 DAY-49 DAY
18	Normal	0 DAY-49 DAY
19	Normal	0 DAY-49 DAY
20	Normal	0 DAY-49 DAY

Measurement of Body Weight:
There were no differences in body weight between the control and the treated groups (Table 3).

Table 3. Body weights of male mice

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: S-244

PERIOD	GROUP:	I	II	III	IV	V
0 DAY	MEAN	29.09	29.31	28.55	28.32	28.95
	S.D.	3.09	3.06	2.34	2.47	2.12
	N	5	5	5	5	5
1 WEEK	MEAN	29.81	30.10	29.00	28.21	29.51
	S.D.	3.12	3.05	2.60	2.30	2.23
	N	5	5	5	5	5
2 WEEK	MEAN	30.86	30.48	29.65	29.06	29.80
	S.D.	3.35	3.18	2.58	2.03	2.52
	N	5	5	5	5	5
3 WEEK	MEAN	31.09	30.82	30.94	29.53	30.73
	S.D.	3.33	3.26	2.77	2.45	2.42
	N	5	5	5	5	5
4 WEEK	MEAN	31.12	30.97	30.39	29.68	31.11
	S.D.	3.08	2.97	2.75	1.96	2.11
	N	5	5	5	5	5
5 WEEK	MEAN	—	—	30.84	29.73	31.08
	S.D.	—	—	2.69	2.07	2.08
	N	—	—	5	5	5
6 WEEK	MEAN	—	—	31.03	30.18	31.16
	S.D.	—	—	2.41	2.37	2.10
	N	—	—	5	5	5
7 WEEK	MEAN	—	—	32.05	30.99	31.95
	S.D.	—	—	3.01	2.59	2.11
	N	—	—	5	5	5

PCA-reaction:

There was an antigen reaction when the high-dose + alum group was diluted from 10 times to 160 times and the OVA + alum group from 10 times to 640 times (Table 4). There were no antigen reactions in the control group and the low and high doses groups without addition of aluminum. Antigen reactions in individual rats after mouse serum challenge are also attached below as Appendix 3-2.

Table 4. 24-hour heterologous passive cutaneous anaphylaxis test in rats with sera of sensitized mice

Sensitizing antigen	Challenging[a] antigen	PCA [b] titer	Positive ratio
LBD-009 (0.15 IU/kg)	LBD-009 (0.15 IU/kg)	—[c]	0/10
LBD-009 (1.5 IU/kg)	LBD-009 (0.15 IU/kg)	—	0/10
LBD-009+alum (1.5 IU/kg)	LBD-009 (0.15 IU/kg)	x40 ~ x160	9/10
OVA + alum (330 μg/kg)	OVA (2.86 mg/kg)	x320 ~ x640	9/10
Vehicle (10 ml/kg)	LBD-009 (0.15 IU/kg)	—	0/10

[a] Challenging antigen was intravenously injected 24 hours after sensitization of rats with sera.
[b] PCA titer represents the maximum dilution factor of original serum which gives positive reaction.
[c] Specific antibodies were not detected in 10-fold dilution of original sera.

Appendix 3-1. 24-hour heterologous passive cutaneous anaphylaxis test in rats with sera of sensitized mice

Sensitized Antigen	Challenged Antigen	Animal No.		Dilution of antiserum in sensitized mice										
		Mouse	Rat	x10	x20	x40	x80	x160	x320	x640	x1280	x2560	x5120	Saline
LED-009 (0.15 IU/kg)	LED-009 (0.15 IU/kg)	1	26	—	—	—	—	—	—	—	—	—	—	—
			27	—	—	—	—	—	—	—	—	—	—	—
		2	28	—	—	—	—	—	—	—	—	—	—	—
			29	—	—	—	—	—	—	—	—	—	—	—
		3	30	—	—	—	—	—	—	—	—	—	—	—
			31	—	—	—	—	—	—	—	—	—	—	—
		4	32	—	—	—	—	—	—	—	—	—	—	—
			33	—	—	—	—	—	—	—	—	—	—	—
		5	34	—	—	—	—	—	—	—	—	—	—	—
			35	—	—	—	—	—	—	—	—	—	—	—
LED-009 (1.5 IU/kg)	LED-009 (0.15 IU/kg)	6	36	—	—	—	—	—	—	—	—	—	—	—
			37	—	—	—	—	—	—	—	—	—	—	—
		7	38	—	—	—	—	—	—	—	—	—	—	—
			39	—	—	—	—	—	—	—	—	—	—	—
		8	40	—	—	—	—	—	—	—	—	—	—	—
			41	—	—	—	—	—	—	—	—	—	—	—
		9	42	—	—	—	—	—	—	—	—	—	—	—
			43	—	—	—	—	—	—	—	—	—	—	—
		10	44	—	—	—	—	—	—	—	—	—	—	—
			45	—	—	—	—	—	—	—	—	—	—	—
LED-009 (1.5 IU/kg) + Alum	LED-009 (0.15 IU/kg)	11	46	+	+	+	+	—	—	—	—	—	—	—
			47	+	+	+	+	+	—	—	—	—	—	—
		12	48	+	+	+	—	—	—	—	—	—	—	—
			49	+	±	+	±	—	—	—	—	—	—	—
		13	50	+	+	+	+	+	—	—	—	—	—	—
			51	+	+	+	+	+	—	—	—	—	—	—
		14	52	+	+	+	+	+	—	—	—	—	—	—
			53	+	+	+	+	+	—	—	—	—	—	—
		15	54	+	+	+	—	—	—	—	—	—	—	—
			55	—	—	—	—	—	—	—	—	—	—	—

Appendix 3-2. 24-hour heterologous passive cutaneous anaphylaxis test in rats with sera of sensitized mice

Sensitized Antigen	Challenged Antigen	Animal No.		Dilution of antiserum in sensitized mice										
		Mouse	Rat	x10	x20	x40	x80	x160	x320	x640	x1280	x2560	x5120	Saline
OVA (330 μg/kg) + Alum	OVA (2.8Smg/kg)	16	56	+	+	+	+	+	+	+	—	—	—	—
			57	+	+	+	+	+	+	+	—	—	—	—
		17	58	+	+	+	+	+	+	+	—	—	—	—
			59	+	+	+	+	—	+	+	—	—	—	—
		18	60	+	+	+	+	+	+	+	—	—	—	—
			61	—	—	—	—	—	—	—	—	—	—	—
		19	62	+	+	+	+	+	+	—	—	—	—	—
			63	+	+	+	+	+	+	—	—	—	—	—
		20	64	+	+	+	+	+	+	+	—	—	—	—
			65	+	+	+	+	+	+	—	—	—	—	—
Vehicle (10ml/kg)	LED-009 (0.15 IU/kg)	21	66	—	—	—	—	—	—	—	—	—	—	—
			67	—	—	—	—	—	—	—	—	—	—	—
		22	68	—	—	—	—	—	—	—	—	—	—	—
			69	—	—	—	—	—	—	—	—	—	—	—
		23	70	—	—	—	—	—	—	—	—	—	—	—
			71	—	—	—	—	—	—	—	—	—	—	—
		24	72	—	—	—	—	—	—	—	—	—	—	—
			73	—	—	—	—	—	—	—	—	—	—	—
		25	74	—	—	—	—	—	—	—	+	—	—	—
			75	—	—	—	—	—	—	—	—	—	—	—

All animals was injected intradermally on the clipped back of each recipient rat. 24 hours later 50μl of the challenged antigen mentioned above was injected intravenously 30 mins later, their back skins were removed for measuring the sizes of the blue spot caused by extravasation of the dye.

[—] : less than 5 mm of PCA titer
[±] : approximatly equal 5 mm of PCA titer
[+] : more than 5 mm of PCA titer

Discussion and Conclusion:

PCA (passive cutaneous anaphylaxis) reaction was induced by injection of an antiserum intradermally into the animal, passively sensitizing its basophils and mast cells. Afterwards, antigen and dye were i.v injected to cause an antigen-antibody reaction. This was assessed by the degree of colouring following the increase of permeability of the post-capillary venules, which is caused by the extrication of chemical mediator of the cell. In this study, the PCA-reaction was tested using mice and rats with LBD-009.

There was no mortality, changes in body weight or abnormal clinical signs during the period of sensitization. As a result of the PCA-reaction, there was 160 times IgE-antibody in the high-dose + alum group, where high antibody formation was occurred using aluminum hydroxide gel, and 640 times in an OVA + alum group. But there was no IgE-antibody in one sample out of 10, which might be due to variation between samples. Nine other samples were positive, which means it had no effect on the test. In the other groups there were no antibodies. Thus, it is safe to say that the final antibody sensitized by the estimated clinical dose (0.15 IU/kg) was not antigenic.

Study title: Valtropin Effect on Antigenicity in Guinea pigs

Key study findings:
A low-dose group (0.15 IU/kg, the estimated clinical dose), a high dose group (1.5 IU/kg, 10 times the clinical dose), a high-dose plus complete Freund's adjuvant (CFA) group, a OVA (ovalbumin) plus CFA group and a control group were used in the study. In the case of OVA + CFA groups, antibodies of IgG type due to the increase of permeability of the post-capillary venules were detected when the 640 to 2560X diluted serum was injected. Also, in the case of the low-dose group (0.15 IU/kg) when 10 to 160X diluted serum was injected, 4/10 samples showed IgG type (an antibody with cell-affinity). In the high-dose group (1.5 IU/kg), when 10 to 40X serum dilution was injected, 5 samples showed the IgG type, and in the high-dose + CFA group, when 20 to 640X serum dilution was injected, all samples showed the type of reaction. It appears that LBD-009 has antigenicity in the homologous PCA test in guinea pigs.

Study no.: S-246
Volume # 1, and page #: 1-46
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 3/9/1992
GLP compliance: Yes
The above test has been conducted in compliance with 'Toxicity Test Standards for Medicines etc.' issued by the National Institute of Safety Research (NISR), Korea (October 29, 1988) and the 'Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies' issued by the Ministry of Health and Social Affairs, Korea (October 29, 1987. KGLP).

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI104

Methods:
Ten male Hartley guinea pigs/group were administered Valtropin subcutaneously 3 times a week (9 times in total) at doses of 0.15 or 1.5 IU/kg. There were five groups as shown in table below. The high dose plus completed Freund adjuvant (CFA) group and ovalbumin (OVA) + CFA group (positive control), subcutaneous injections were administered into the animals to sensitize once in three weeks (3 times in total for 6 weeks). In the reference group, injections were given once every three weeks and three times per week concurrently, and they were sensitized 11 times in total for 6 weeks. On the 12th day, after final sensitization, a guinea pig's blood was sampled from the retro-orbital venous plexus and the serum was diluted in a range of 10X to 5120X. Serum (50 μl) was injected into the abdominal skin intradermally, and then after 4 hours, a 1:1 mixture of LBD 009 or OVA solution and 1% solution of Evans blue were injected into the leg vein. Thirty minutes after the final inoculation, the guinea pigs were exsanguinated and leakage of the dye at the serum injected site was examined to determine the PCA titer. The end point was set at a diameter of 5 mm or more.

(a) Guinea Pig Sensitisation

Group	Antigen-Injection	Sex	Number of Animals Used	Animal No.	Amount of sensitizing antigen (IU/kg)	Applied Amount (ml/kg)	Application Route
I	LBD-009 (Low Dose)	Male	5	1-5	0.15	1	SC (subcutaneously)
II	LBD-009 (High-Dose)	Male	5	6-10	1.5	1	SC
III	LBD-009 + CFA	Male	5	11-15	1.5	1	SC
IV	OVA + CFA	Male	5	16-20	2.5 mg/kg	1	SC
V	Vehicle	Male	5	21-25	0	1	SC

Mortality: No animals were found dead during the whole test period (Table 1).

Table 1. Mortality of male guinea pigs

MORTALITY SUMMARY REPORT

STUDY: S-246

	WEEKS AFTER DOSING							
GROUP	1	2	3	4	5	6	7	8
I	0/5a)	0/5	0/5	0/5	0/5			
II	0/5	0/5	0/5	0/5	0/5			
III	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
IV	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
V	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5

a) : No. of dead animal/No. of dosed animal

Clinical Signs: No abnormal clinical signs were observed in the positive-control group and all other groups as shown below (Appendix 1).

Appendix I-1. Fate and clinical findings of male guinea pigs

INDIVIDUAL OBSERVATIONS

STUDY: S-246 GROUP : I
0 DAY-33 DAY DOSE : LBD-009(0.15 IU/kg)

ANIMAL #	OBSERVATIONS	TIME OCCURRED
1	Normal	0 DAY-33 DAY
2	Normal	0 DAY-33 DAY
3	Normal	0 DAY-33 DAY
4	Normal	0 DAY-33 DAY
5	Normal	0 DAY-33 DAY

STUDY: S-246 GROUP : II
0 DAY-33 DAY DOSE : LBD-009(1.5 IU/kg)

ANIMAL #	OBSERVATIONS	TIME OCCURRED
6	Normal	0 DAY-33 DAY
7	Normal	0 DAY-33 DAY
8	Normal	0 DAY-33 DAY
9	Normal	0 DAY-33 DAY
10	Normal	0 DAY-33 DAY

Appendix 1-2. Fate and clinical findings of male guinea pigs

INDIVIDUAL OBSERVATIONS

STUDY: S-246 GROUP : III
0 DAY-56 DAY DOSE : LBD-009(1.5 IU/kg) + CFA

ANIMAL #	OBSERVATIONS	TIME OCCURRED
11	Normal	0 DAY-56 DAY
12	Normal	0 DAY-56 DAY
13	Normal	0 DAY-56 DAY
14	Normal	0 DAY-56 DAY
15	Normal	0 DAY-56 DAY

STUDY: S-246 GROUP : IV
0 DAY-56 DAY DOSE : OVA(2.5 mg/kg) + CFA

ANIMAL #	OBSERVATIONS	TIME OCCURRED
16	Normal	0 DAY-56 DAY
17	Normal	0 DAY-56 DAY
18	Normal	0 DAY-56 DAY
19	Normal	0 DAY-56 DAY
20	Normal	0 DAY-56 DAY

Measurement of Body Weight: There were no significant differences between the control group and treated groups in body weight (Table 3).

Table 3. Body weights of male guinea pigs

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: S-246

PERIOD	GROUP:	I	II	III	IV	V
0 DAY	MEAN	432.2	435.8	427.1	432.8	432.6
	S.D.	29.48	36.22	18.13	23.34	18.30
	N	5	5	5	5	5
1 WEEK	MEAN	454.1	462.9	484.2	460.7	453.4
	S.D.	39.77	40.20	18.43	23.89	15.91
	N	5	5	5	5	5
2 WEEK	MEAN	492.4	494.4	519.2	473.6	502.6
	S.D.	41.76	45.23	30.79	28.08	20.47
	N	5	5	5	5	5
3 WEEK	MEAN	512.5	497.1	527.2	471.8	506.8
	S.D.	78.65	60.02	34.08	38.44	27.88
	N	5	5	5	5	5
4 WEEK	MEAN	542.0	586.5	594.5	532.6	565.1
	S.D.	87.03	73.18	40.15	33.41	23.86
	N	5	5	5	5	5
5 WEEK	MEAN	546.8	564.5	646.7	559.1	607.1
	S.D.	77.81	80.21	52.55	31.11	33.02
	N	5	5	5	5	5
6 WEEK	MEAN	—	—	685.5	573.8	648.1
	S.D.	—	—	59.65	28.82	44.49
	N	—	—	5	5	5
7 WEEK	MEAN	—	—	683.5	647.8	679.1
	S.D.	—	—	69.72	24.48	49.83
	N	—	—	5	5	5
8 WEEK	MEAN	—	—	713.5	634.0	644.8
	S.D.	—	—	81.81	24.93	57.54
	N	—	—	5	5	5

— = Data Unavailable

Evaluation of PCA-Reaction:

In the low-dose (0.15 IU/kg) group, when sera was diluted from 10 fold to 160 fold, 4 out of 10 samples of antigen were detected. 5 samples out of 10 samples in the high dose (1.5 IU/kg) were positive for antigen when the sera were diluted from 10 fold to 40 fold dilution. The high-dose plus CFA group (from 20 fold to 640 fold dilution), 10 out of 10 were detected. In the positive-control group, when sera were diluted from 640 fold to 2560 fold, all antigen samples were detected as presented (Table 4) below. The control (vehicle) group was negative.

Table 4. Four-hour homologous passive cutaneous anaphylaxis test in guinea pigs with sera of sensitized guinea pigs

Sensitizing antigen	Challenging[a] antigen	PCA [b] titer	Positive ratio
LBD-009 (0.15 IU/kg)	LBD-009 (0.15 IU/kg)	x 10 ~ x160	4/10
LBD-009 (1.5 IU/kg)	LBD-009 (0.15 IU/kg)	x 10 ~ x 40	5/10
LBD-009+CFA (1.5 IU/kg)	LBD-009 (0.15 IU/kg)	x 20 ~ x640	10/10
OVA + CFA (2.5 mg/kg)	OVA (1.67 mg/kg)	x640 ~ x2560	10/10
Vehicle (1 ml/kg)	LBD-009 (0.15 IU/kg)	— [c]	0/10

[a] Challenging antigen was intravenously injected 4 hours after sensitization of guinea pig with sera.
[b] PCA titer represents the maximum dilution factor of original serum which gives positive reaction.
[c] Specific antibodies were not detected in 10-fold dilution of original sera.

Comments and Conclusion:

Antisera were injected intradermally in animal skin to induce passive sensitization of basophils and mast cells. Furthermore, antigen and dye were i.v. injected to induce antigen-antibody reaction. This can assess the degree of colouring depending on the permeability increase of the post capillary venules, which is caused by the extraction of a chemical mediator of the cell. In this test, the homologous PCA-reaction was examined to the high-polymer drug LBD-009 in guinea pigs. There were no changes in general clinical signs, mortality and body weight caused by the test substance. However, the PCA-reaction in 4 out of 10 samples in the low dose group (0.15 IU/kg) showed the antigen with cell affinity (IgG type) with diluted sera (10-160 fold). In the high-dose group (1.5 IU/kg) 5 samples of antigen type from 10 fold to 40 fold dilution were detected, and in the high-dose plus CFA group (dilution from 20 fold to 640 fold) there was IgG type reactions in all samples.

Also, in the positive-control group, when sera were diluted from 640 to 2560 fold, there was a cell-affinity antibody caused by increase of permeability of the post-capillary venules in all samples. Thus, it is clear that sensitization of guinea pigs with clinically relevant dose (0.15 IU/kg) at the value of final antigenicity of LBD-009 was 160 fold. In the homologous PCA-reaction test using guinea pigs, there was immunity at more than 10 fold antisera dilution after sensitization with LBD-009 (0.15 or 1.5 IU/kg) or the mixture of Adjuvant (CFA) and LBD-009 (1.5 IU/kg). Comparing with ovalbumin (positive control), this test substance showed antigenicity in the homologue PCA-reaction test in guinea pigs.

Study title: Valtropin Effect on Antigenicity in Guinea pigs (Anaphylactic Shock)

Key study findings:
A low-dose group (0.15 IU/kg, the estimated clinical dose), a high dose group (1.5 IU/kg), a high-dose plus complete Freund's adjuvant (CFA) group, an OVA (ovalbumin) plus CFA group and a control group were used in the study. Three animals out of 5 in the low-dose group, 2/5 in the high-dose group, 1/5 in the high dose + CFA group and 2/5 in the control group had mild symptoms of urination and evacuation. One out of 5 animals in the low dose group (0.15 IU/kg) showed hydropericardium and 2/5 animals in the high dose group (1.5 IU/kg group) showed petechiae in the lungs.

The positive control group (OVA + CFA) showed clear anaphylactic symptoms and shock before death. They were urination, evacuation, sneezing, piloerection, saliva, rhinorrhea, epiphora, coughing, convulsions, breathing abnormalities, dysbasia, bronchi, cyanosis, decumbence, and depravation. Two out of 5 animals in the positive control group experienced anaphylactic shock and died. Whole body symptoms caused by anaphylactic shock for 30 minutes were also observed and an autopsy was performed for by visual observation. As a result, 4/5 in OVA + CFA group (positive control) showed

bronchial mucosa congestion and bleeding, bleeding as well as tache blanche in the heart and bleeding in the diaphragm. Thus, it appears that LBD-009 did caused antigenicity in the anaphylactic shock in guinea pigs.

Study no.: S-245
Volume # 1, and page #: 1-55
Conducting laboratory and location: [redacted] b(4)

Date of study initiation: 1/10/1992
GLP compliance: Yes
The above test has been conducted in compliance with 'Toxicity Test Standards for Medicines etc.' issued by the National Institute of Safety Research (NISR), Korea (October 29, 1988) and the 'Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies' issued by the Ministry of Health and Social Affairs, Korea (October 29, 1987. KGLP).

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Lot# JI104
Animal/species: Guinea Pig/Hartley
Animal number: 5 male guinea pigs/group as shown below
Age and sex: 5 weeks old male
Body weights: 313-416 g
Methods:
This LBD-009 (recombinant human growth hormone without N-terminal methionine) antigenicity test examined the reaction of anaphylactic shock in a low-dose group (0.15 IU/kg), a high-dose group (1.5 IU/kg), a high-dose plus CFA (Complete Freund's Adjuvant) group, a OVA (ovalbumin) + CFA group(a positive control group), and a control group (vehicle) as shown below. Subcutaneous injections were made into the abdomen of Hartley guinea pigs 3 times a week (9 times in total) for the low-dose and high-dose groups. In the high dose plus CFA and the OVA + CFA groups, animals were sensitized once every three weeks (3 times in total). In the control group, the vehicle was injected once every three weeks and three times a week at the same time (11 times in total). On the 14th day of final sensitization, the challenging antigen solution was injected into a leg vein of the guinea pigs, and for 30 minutes systemic symptoms such as urination, evacuation, coughing, sneezing, piloerection, saliva, epiphora, rhinorrhea, convulsions, cyanosis, breathing abnormalities, dysbasia, decumbence, depravation, and death were examined.

The following grading systems were used to characterize the anaphylactic shock:
[-] : Asymptomatic: No symptoms
[+/-] : Mild: Urination and evacuation
[+] : Moderate: Coughing and sneeze
[++] : Severe: Piloerection, saliva, rhinorrhea, epiphora, convulsions, breathing abnormalities, dysbasia, cyanosis, decumbence, depravation, etc.
[+++] : Death: Death

Group	Antigen-Injection	Sex	Number of Animals Used	Animal No.	Amount of Antigen-Injection (IU/kg)	Applied Amount (ml/kg)	Application Route
I	LBD-009 (Low Dose)	Male	5	1-5	0.15	1	SC
II	LBD-009 (High-Dose)	Male	5	6-10	1.5	1	SC
III	LBD-009 + CFA	Male	5	11-15	1.5	1	SC
IV	OVA + CFA	Male	5	16-20	2.5 mg/kg	1	SC
V	Vehicle	Male	5	21-25	0	1	SC

Results:

Mortality: There were no deaths in all groups from the initiation of sensitization until the start of challenge as shown below.

Table 1. Mortality of male guinea pigs

MORTALITY SUMMARY REPORT

STUDY: S-245

GROUP	WEEKS AFTER DOSING							
	1	2	3	4	5	6	7	8
I	0/5[a)]	0/5	0/5	0/5	0/5			
II	0/5	0/5	0/5	0/5	0/5			
III	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
IV	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5
V	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5

a) : No. of dead animal/No. of dosed animal

Clinical signs: There were no remarkable clinical signs in all groups from the initiation of sensitization until the start of challenge.
Change in body weight: There were no significant differences between the control and all other four groups from the initiation of sensitization until the start of challenge as shown below.

Table 3. Body weights of male guinea pigs

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: S-245

PERIOD	GROUP:	I	II	III	IV	V
0 DAY	MEAN	432.2	435.8	427.1	432.8	432.6
	S.D.	29.48	38.22	16.13	23.34	18.30
	N	5	5	5	5	5
1 WEEK	MEAN	454.1	462.9	484.2	460.7	453.4
	S.D.	39.77	40.20	18.43	23.89	15.91
	N	5	5	5	5	5
2 WEEK	MEAN	492.4	494.4	519.2	473.8	502.6
	S.D.	41.76	45.23	30.79	28.08	20.47
	N	5	5	5	5	5
3 WEEK	MEAN	512.5	497.1	527.2	471.6	508.8
	S.D.	76.65	60.02	34.08	38.44	27.86
	N	5	5	5	5	5
4 WEEK	MEAN	542.0	506.5	594.5	532.6	565.1
	S.D.	87.03	73.18	40.15	33.41	23.86
	N	5	5	5	5	5
5 WEEK	MEAN	546.8	564.5	646.7	559.1	607.1
	S.D.	77.81	80.21	52.55	31.11	33.02
	N	5	5	5	5	5
6 WEEK	MEAN	—	—	665.5	573.8	648.1
	S.D.	—	—	59.85	28.82	44.49
	N	—	—	5	5	5
7 WEEK	MEAN	—	—	683.5	647.8	679.1
	S.D.	—	—	69.72	24.48	49.83
	N	—	—	5	5	5
8 WEEK	MEAN	—	—	713.5	634.0	644.8
	S.D.	—	—	81.81	24.93	57.54
	N	—	—	5	5	5

— = Data Unavailable

Anaphylactic shock:
Three animals in the low-dose group, 2 animals in the high-dose group, one animal in the high dose plus CFA group and 2 animals in the control group showed mild symptoms such as urination and evacuation. Three animals in the ovalbumin plus CFA group has severe symptoms like near death such as coughing, sneezing, convulsions, breathing abnormalities, piloerection, saliva, rhinorrhea, epophora, cyanosis, decumbence and depravation. Two out of 5 animals in that group died from anaphylactic shock due to ovalbumin challenge as shown (Table 4).

Table 4. Active systemic anaphylaxis in guinea pigs

Sensitizing antigen	Challenging antigen	No. of animals	Severity of anaphylaxis a)				
			[-]	[±]	[+]	[++]	[+++]
LBD-009 (0.15IU/kg)	LBD-009 (0.15IU/kg)	5	2	3			
LBD-009 (1.5IU/kg)	LBD-009 (0.15IU/kg)	5	3	2			
LBD-009 + CFA (1.5IU/kg)	LBD-009 (0.15IU/kg)	5	4	1			
OVA + CFA (2.5 mg/kg)	OVA (1.67 mg/kg)	5				3	2
Vehicle (1 ml/kg)	LBD-009 (0.15IU/kg)	5	3	2			

a) Severity of anaphylaxis was expressed as follows
[-] : Asymptomatic
[±] : Mild : urination, evacuation
[+] : Moderate : above, coughing, sneezing
[++] : Severe : above, piloerection, salivation, nostril discharge, lacrimation, convulsion, dyspnea, staggering gait, rhonchus, cyanosis, side position, flattening
[+++] : Death

Autopsy: In the OVA plus CFA group, 4 animals out of 5 showed congestion and bleeding in bronchial mucosa, and tache blanche and bleeding in the heart. One sample in the low-dose group showed hydropericardium as shown (Table 5). Two animals out of 5 in the high-dose group showed petechiae in the lung. There were no remarkable abnormalities in the control group animals.

Table 5. Necropsy findings of active systemic anaphylaxis test animals

Group	Sensitization		Animal	Challenge		Organs				
	antigen	route	No.	antigen	route	Trachea[a]	Lung[b]	Heart[c]	Thorax	Diaphragm[d]
I	LBD-009 (0.15IU/kg)	S.C	1	LBD-009 (0.15IU/kg)	i.v.	—	—	—	—	—
			2			—	—	+	—	—
			3			—	—	—	—	—
			4			—	—	—	—	—
			5			—	—	—	—	—
II	LBD-009 (1.5IU/kg)	S.C	6	LBD-009 (0.15IU/kg)	i.v.	—	—	—	—	—
			7			—	—	—	—	—
			8			—	+	—	—	—
			9			—	+	—	—	—
			10			—	—	—	—	—
III	LBD-009 (1.5IU/kg) + CFA	S.C	11	LBD-009 (0.15IU/kg)	i.v.	—	—	—	—	—
			12			—	—	—	—	—
			13			—	—	—	—	—
			14			—	—	—	—	—
			15			—	—	—	—	—
IV	OVA (2.5 mg/kg) + CFA	S.C	16	OVA (1.87 mg/kg)	i.v.	+	—	—	—	+
			17			+	—	+	—	—
			18			+	—	+	—	+
			19			—	—	—	—	—
			20			+	—	—	—	—
V	Vehicle (1 ml/kg)	S.C	21	LBD-009 (0.15IU/kg)	i.v.	—	—	—	—	—
			22			—	—	—	—	—
			23			—	—	—	—	—
			24			—	—	—	—	—
			25			—	—	—	—	—

a) congestion or hemorrhage
b) hemorrhagic petechea
c) hemorrhage or white nodule
d) hemorrhage

Discussion and Conclusion:

To evaluate the potential of anaphylactic shock of Valtropin, an antigen was injected into 5 male guinea pigs/group as described under method. There were no remarkable differences between the control and treated groups in body weight, clinical signs and anaphylactic symptoms until the challenge of antigens. Mild symptoms such as urination and evacuation in the high-dose (1.5 IU/kg), the low-dose (0.15 IU/kg), the high-dose plus CFA, and the control group (vehicle only) were observed when the animals were rechallenged. The numbers of animals that had such mild symptoms were not significantly different from the control and treated groups. Autopsy indicated that one animal from the low-dose group (0.15 IU/kg) showed hydropericardium. Two animals in the high-dose group (1.5 IU/kg) showed petechiae in the lung.

However, the animals in the positive group (OVA + CFA treated group) had severe anaphylatic symptoms such as urination, evacuation, coughing, sneezing, piloerection, saliva, rhinorrhea, epiphora, convulsions, breathing abnormalities, dysbasia, cyanosis, decumbence, depravation, shock and death. Two out of 5 animals died from anaphylactic shock in the group. An autopsy was performed to examine bronchial mucosa, lung, heart, thoracic cavity and diaphragm with the naked eye 30 minutes after the shock. 4 animals out of 5 in the OVA + CFA group showed bronchial mucosal congestion and bleeding, bleeding and tache blanche in the heart, bleeding in the diaphragm. It is safe to conclude that LBD-009 will not likely produce anaphylactic shock reaction because the incidences in the control were the same to the treated groups.

Study title: Biological Activity of Valtropin: Rat weight gain assay

Key study findings:
The potency of Valtropin™ drug product was determined against the NIBSC 98/574 standard, through injection into the hypophysectomized rats and parallel-line analysis of body weight gain. The test procedure was based on the information in USP somatropin monograph. The procedure in the USP was adopted to have 3 dose levels (2, 4 and 8 μg per day) per standard and each test material for parallel analysis. In addition, the schedule prior to treatment was slightly modified for adaptation of the test animals due to their air delivery.

Validity of the result and relative potency of Valtropin™ drug product were evaluated for experimental data. The statistical analyses were performed by using the completely randomized design analysis of parallel-line assay (Current European Pharmacopoeia) against the body weight gain of each rat during 10-day treatment. The relative potencies and confidence intervals of Valtropin™ drug product against NIBSC98/574 are summarized (Table) below. The determined potency for Valtropin™ drug product was from 2.97 to 3.56 IU/mg. Therefore it can be concluded that the potency of Valtropin™ drug product is consistent with that of international reference standard and comparable between lots by considering high variability of the animal experiment.

The potency of human growth hormone can be estimated by comparing its effects of increasing the width of the proximal epiphysis of the tibia in immature hypophysectomized rats with the international standard of human growth hormone. In this tibia assay, rats used in weight gain assay of Valtropin™ from Study #2 were used for the tibia assay. The rats were killed 24 hours after the last injections and the two tibiae of those were cut out. The rat tibia assay was performed once in order to confirm that the body weight gain is correlated with tibia bone growth. All regular biological assays have been performed with the rat weight gain assay.

The tibiae were fixed in 10% neutral-buffered formalin for 2 days, decalcified in 10% aqueous formic acid for 3 days and dehydrated in ethanol and embedded in paraffin. Sagittal sections of knee were cut with the plane of section oriented parallel to the longitudinal axis of the bone. Sections of 5 am thick were cut with a microtome and stained with hematoxylin and eosin (H&E). The length of the epiphysis was measured for the whole growth plate, proliferating zone and hypertrophic zone, respectively, at ten different sites using a microscope with an ocular micrometer and averaged. The statistical analyses were performed by the same method as weight gain assay. Figures below show the representative micrograph of epiphysis after indicated doses of Vatropin. The potencies of Valtropin™ drug product MGH006 were from 2.22 to 2.91 depending on the epiphyseal site where the measurement were made. It appears that the potencies at tibia assay were lower than weight gain assay. However, it is clear that the rat weight gain assay as a typical method of biological activity is well correlated with the tibia bone growth.

Table 3.2.S.3.1-43: Potency and confidence interval of Valtropin™ drug product by weight gain assay

	NIBSC 98/574	Valtropin™ MGH006	Valtropin™ MGH005	Valtropin™ MGH006	Valtropin™ MGH007	Valtropin™ MGH008
Relative Potency	100.0%	99.1%	109.31%	118.75%	105.13%	110.34%
Lower Limit	N/A	83.2%	89.38%	97.12%	85.94%	90.22%
Upper Limit	N/A	118.1%	133.91%	145.64%	128.72%	135.18%
Stated Potency (IU/mg)	3.00	N/A	N/A	N/A	N/A	N/A
Estimated Potency (IU/mg)	N/A	2.97	3.28	3.56	3.15	3.31
Low Estimated	N/A	2.50	2.68	2.91	2.58	2.71
High Estimated	N/A	3.54	4.02	4.37	3.86	4.06
Reference		Study #2	Study #5			

Table 3.2.S.3.1-44: Potency and confidence interval of Valtropin™ drug product in tibia assay

	NIBSC 98/574	Valtropin™ MGH006		
		Whole growth plate	Proliferating zone	Hypertrophic zone
Relative Potency	100.00%	80.95%	73.86%	96.90%
Lower Limit	N/A	67.51%	60.96%	75.97%
Upper Limit	N/A	96.57%	88.77%	123.41%
Stated Potency (IU/mg)	3.00	N/A	N/A	N/A
Estimated Potency (IU/mg)	N/A	2.43	2.22	2.91
Low Estimated	N/A	2.03	1.83	2.28
High Estimated	N/A	2.90	2.66	3.70
Reference	Study #2			

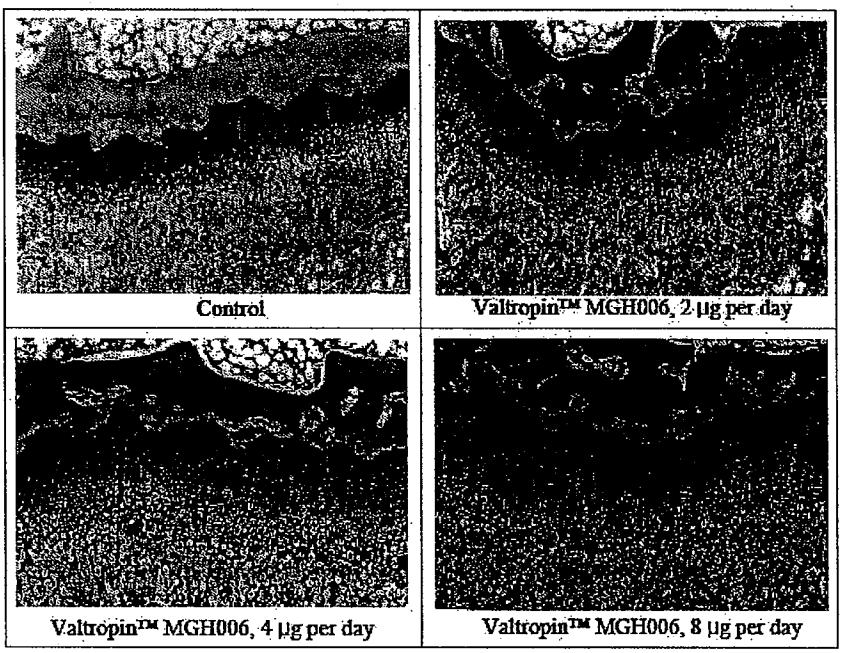

Figure 3.2.S.3.1-78: Micrograph (magnification 100) of epiphysis of control and Valtropin™ drug product (Study #2)

2.6.6.9 Discussion and Conclusions:

Pharmacology and safety studies for Valtropin were conducted in mice and rats support its clinical use. General toxicity, genetic and reproductive toxicity studies indicate that Valtropin has no remarkable toxicological risk in human. The findings in antigenicity in mice, rats and guinea pigs indicate that the product would not likely induce immunotoxicity in human. The reviewers can safely conclude that the preclinical data support the NDA.

2.6.6.10 Tables and Figures
None

2.6.7 TOXICOLOGY TABULATED SUMMARY
None.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There are no preclinical pharmacology and toxicology issues with this Valtropin NDA.

Unresolved toxicology issues (if any): None.

Recommendations: Pharmacology and toxicology data support approval of this NDA.

Suggested labeling: Please see "Pharmacology Recommendation" above.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS:

IND 62,376 PHARMACOLOGY/TOXICOLOGY Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Herman Rhee
9/18/2006 09:59:44 AM
PHARMACOLOGIST

Karen Davis-Bruno
9/18/2006 10:25:27 AM
PHARMACOLOGIST
concur with recommendation

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Memorandum

9/5/06 forwarded to 2162 meeting

Date: 9/05/06
From: Karen Davis-Bruno
Subject: Draft Pharm/Tox Valtropin Labeling

To: NDA 21-905

Background:

Sponsor states 10 IU/kg/day corresponds to 3.3 mg/kg/day or 20 mg/m^2 in rat and 40 mg/m^2 in rabbit
MRHD (child) is 0.054 mg/kg or 1.35 mg/m^2
MRHD (adult) is 0.01 mg/kg or 0.37 mg/m^2

Labeling Recommendations:

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Karen Davis-Bruno
9/5/2006 01:32:40 PM
PHARMACOLOGIST

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA No. 21-905/LG Life Sciences/Valtropin(rh Growth Hormone)/January 20, 2006

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		

4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? **Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA** (None)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? N/A **Studies completed:** 1) 4-W tox study in monkeys/TK 2) 4-W tox study in rat 3) No carcinogenity study 4) Ames and micronucleus test 5) Reproductive studies 6) Skin irritation study 7) Antigenicity studies in rats & mice 8) Antigenicity study in guinea pig 9) Shock study in guinea pig

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		

7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Herman Rhee, Ph.D.
Reviewing Pharmacologist

Jeri Elhage, Ph.D.

Supervisory Pharmacologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Herman Rhee
1/23/2006 02:56:20 PM
PHARMACOLOGIST

Jeri El Hage
1/25/2006 09:24:24 AM
PHARMACOLOGIST