CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-106 (N000 BM)	**Submission Date: 04-30-02, 10-01-02, 12-19-02**
BRAND NAME:	**Somavert®**
GENERIC NAME:	**Pegvisomant for Injection**
REVIEWER:	**Xiaoxiong "Jim" Wei, M.D., Ph.D.**
SPONSOR:	**Pharmacia & Upjohn, Kalamazoo, MI**
TYPE OF SUBMISSION:	**Clinical Response to Approvable Letter of 06/26/01**

Submission:

On April 30, 2002, Pharmacia & Upjohn submitted a correspondence to the Agency's approvable letter of June 6, 2001 of NDA 21-106 [pegvisomant/Somavert®]. Subsequently, the sponsor submitted their revised package insert on October 01, 2002.

In this submission, the sponsor responded all requests/comments raised by the review team including response to clinical pharmacology and biopharmaceutics and clinical sections. The original human pharmacokinetics reviewer, Dr. Robert Shore had 4 main comments to the sponsor for pegvisomant. These comments were related to (1) the drug product impurity and cross-reactivity in RIA detection, (2) potential drug interaction concerns between pegvisomant and cyclosporine, (3) information on elimination and metabolic pathways of pegvisomant, and (4) in vitro metabolism/drug interaction studies with pegvisomant. In the response, the sponsor indicated that they have worked on reduction of product impurity, potential difference in RIA cross-reactivity to product-related impurities becomes less significant. The sponsor described the interaction between octreotide and cyclosporine (CsA) was likely due to inhibition of the secretion of pancreatic lipase or bile acids and or through P-gp mediated interaction. Pegvisomant is different in mechanism from octreotide. Therefore, such interactions may not be likely to occur. The sponsor included a publication to support their position. Meanwhile, the sponsor submitted a study report on the effect of pegvisomant on P-gp. The results showed that pegvisomant is not an inhibitor of P-gp. The sponsor further indicated that pegvisomant is a pegylated protein comprising of 191 amino acids with significant structural similarities to human growth hormone (hGH). Proteins are metabolized by normal cellular catabolic mechanisms. Pegvisomant metabolism is expected to involve normal protein catabolism through peptide cleavage in the liver and other organs. It is generally recognized that proteins are not substrates of CYP450. The sponsor indicated that although pegylation slightly modifies the structure of the molecule (Lys pegylation modifies and removes two peptides from the tryptic map), it may not result in a significant alteration from the natural metabolic pathways for human growth hormone.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞indicates an explanation only and is not intended to be included in the labeling)

CLINICAL PHARMACOLOGY

1 page(s) of revised draft labeling has been redacted from this portion of the review.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the sponsor's responses and revised package insert submitted on 04/30/02, 08/01/02 and 12/19/02 to the Agency's approvable letter of 06/26/01on NDA21-106. Their response to original reviewer's comments is acceptable. This recommendation, reviewer's labeling changes and comments should be sent to the sponsor as appropriate.

Xiaoxiong (Jim) Wei, M.D., Ph.D.

RD/ FT initialed by Hae-Young Ahn, Ph.D., Team Leader

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

/s/

Xiao-xiong Wei
1/22/03 09:54:09 AM
BIOPHARMACEUTICS

Hae-Young Ahn
1/22/03 04:18:52 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-106 / N-000	Brand Name	Somavert
OCPB Division (I, II, III)	DPE 2	Generic Name	pegvisomant
Medical Division	DMEDP	Drug Class	
OCPB Reviewer	Robert M. Shore	Indication(s)	Acromegaly
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Injection
		Dosing Regimen	80mg LD then 10-30mg/QD titrated to IGF-1 response
Date of Submission	22-DEC-00	Route of Administration	SC
Estimated Due Date of OCPB Review	21-APR-00 to CSO	Sponsor	Sensus Drug Development Corp., Austin TX
PDUFA Due Date	24-JUN-00	Priority Classification	1P
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X	2 (3601/3623)	2	
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:	X	1 (3602)	1	
multiple dose:	X	5 (3611/3613/3613a/3614/3615)	1	
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	2 (3601/3602)	2	
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				

In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:	X	In PK/PD analysis	1	
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:	X			
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:	X			
Data sparse:	X	1	1	
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	1 (3623)	1	
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]			

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-106 / N-000	**SUBMISSION DATE:**	**22-DEC-00, 24-APR-01**
BRAND NAME:	**Somavert™**	
GENERIC NAME:	**Pegvisomant lyophilized powder 10, 15, and 20mg vials for SC injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
CONSULT:	**Sam H. Haidar, R.Ph., Ph.D.**	
SPONSOR:	**Sensus Drug Development Corp., Austin, TX**	
TYPE OF SUBMISSION:	**Original Application Code: 1P**	

RECOMMENDATION AND COMMENTS:

Recommendation :

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-106/N-000 submitted 22-DEC-00 and 24-APR-01. For the Human Pharmacokinetic Section of the NDA additional information is needed to satisfy 21CFR320. This recommendation, comments for the sponsor (p. 3), and labeling comments (p.18) should be sent to the sponsor.

Comments from other reviewers:

1) Dr Perlstein, MO, has informed me that the efficacy of this product is quite good. There is a soft hepatic signal regarding safety which labeling addresses.
2) There is concern from the Pharm/Tox team that the animal studies may not be adequate for approval.
3) The CMC team has major concerns over the characterization of the drug substance and presence of impurities in the drug product. It is unknown if these impurities are bioactive.

Comments to be sent to sponsor:

1) There is uncertainty as to the cross-reactivity of impurities in the drug product when using the RIA for detection of pegvisomant concentrations in serum. It is possible that some of these impurities are bioactive. The sponsor is to purify these impurities and evaluate their cross-reactivity with the RIA as well as their bioactivity. Together, these procedures will contribute to the understanding of the active components of Somavert™.

2) There are data that show an interaction between octreotide and cyclosporin which maybe growth hormone mediated. Since pegvisomant can cause an apparent decrease in growth hormone by blocking receptors, it is recommended that the sponsor conduct an in vivo drug interaction study to address any potential pharmacokinetic interaction between pegvisomant and cyclosporin.

3) There are no data submitted on the route of elimination of pegvisomant in humans. The sponsor needs to provide data showing the route of elimination and/or metabolic pathways of pegvisomant. These data may be the basis for future recommendations of pharmacokinetic studies in special populations (e.g. hepatic and/or renal impairment).

4) To further understand the metabolic effects that pegvisomant may have on other drugs, it is recommended that the sponsor conduct in vitro metabolism/drug interaction studies as per the guidance 'Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro' (http://www.fda.gov/cder/guidance/clin3.pdf).

APPEARS THIS WAY
ON ORIGINAL

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(Appendices and/or Attachments available from DMEDP filing room or DFS, if not included)

EXECUTIVE SUMMARY:

- ***What are the pharmacological, physical/chemical and formulation characteristics of the drug/drug products?***

Somavert™ (pegvisomant) is a competitive inhibitor of human growth hormone (GH) proposed as a treatment for acromegaly, a disease characterized by elevated GH levels which cause insulin-like growth factor 1 (IGF-1) elevations. Pegvisomant consists of a 191 amino acid protein to which polyethylene glycol polymers have been covalently bound in order to increase the size and decrease the clearance rate of the protein. The amino acid sequence of the engineered protein is the same as that for human growth hormone except that 9 residues have been mutated so that binding to the growth hormone receptor occurs, but growth hormone signal transduction is inhibited. The marketed formulations are lyophilized

vials of pegvisomant to be reconstituted with 1cc of diluent and administered subcutaneously. The proposed dosing regimen consists of an 80mg loading dose then 10mg daily. Patients are evaluated every 6-8 weeks until an appropriate IGF-1 response is seen without exceeding a maximum dose of 30mg. The dose can be titrated in 5mg increments.

There is data to show that the loading dose can be reduced to 40mg and possibly eliminated altogether. This has been discussed with the MO and the final decision about the loading dose needs to be made by the Clinical Division.

- ***Were the methods used to assess drug concentrations in biological matrices and/or drug pharmacodynamics adequate for the studies?***

The RIA used for detecting pegvisomant in human serum is acceptable but the sponsor needs to investigate the cross-reactivity of this assay with impurities which may be bioactive in the drug product. This investigation is to be completed by the sponsor within 6 months as a phase 4 commitment.

- ***What are the pharmacokinetics (ADME) of the drug?***

The pharmacokinetics of pegvisomant were calculated from single dose studies in healthy volunteers and acromegalic patients, and multiple dose studies in acromegalic patients. Population pharmacokinetic and pharmacodynamic modeling was performed. Compared to an intravenous dose, the bioavailability of a SC dose is 57%. The maximum concentration observed (Cmax) as well as area under the concentration-time curve (AUC) after administering 10, 15, or 20mg SC increased more than proportionality indicating possible saturable elimination. The route of elimination of pegvisomant has not been elucidated. The typical apparent volume of distribution is 7L and mean clearance is about 32 mL/h. Clearance of pegvisomant was directly related to body weight and inversely related to dose. From the population modeling it was found that patients receiving opioids may be less responsive to pegvisomant, lipid-altering drugs may decrease the clearance of pegvisomant by about 30%, and that baseline GH levels are directly related to the effective pegvisomant concentration (i.e. patients with higher baseline GH tended to need higher pegvisomant concentrations to achieve appropriate IGF-1 response).

QUESTION-BASED REVIEW

Terms and abbreviations:

ADME . ..... Absorption, distribution, metabolism, excretion
AUCa-b..... Area under the plasma-concentration-time curve from time a to time b
AUC_I.... ..... Total AUC after extrapolation from time 0 to time infinity
AUC_T... ..... Area under the serum concentration-time curve from time 0 to time T
C_{50}..... ..... Serum pegvisomant concentration that produces 50% of the maximum inhibition of IGF-1
Cmax .. .. Maximum observed plasma concentration
Css..... ..... Concentration at steady state
DMEDP..... Division of Metabolic and Endocrine Drug Products
GH .... Growth hormone
IGF-1... ..... Insulin-like growth factor 1
IV .... Intravenous
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics
PEG .... Polyethylene glycol
RIA..... ..... Radioimmunoassay
SC..... ..... Subcutaneous
Tmax... ..... Time at which Cmax is observed

Background:

Acromegaly is a chronic disorder resulting from excessive secretion of growth hormone (GH) which results in the secondary elevation of insulin-like growth factor-I (IGF-I) through positive feedback mechanisms. Current treatments include radiation and surgical removal of the GH-producing pituitary tumor and/or medication (e.g. bromocriptine, somatostatin analogues). Somavert™ (pegvisomant for injection) consists of an analog of human growth hormone that has been genetically altered at 9 residues to be a growth hormone receptor antagonist with PEG molecules covalently bound to this altered protein. The protein (B2036) blocks the action but not the secretion of the excess GH and the PEGylation extends the half-life of the protein *in vivo*.

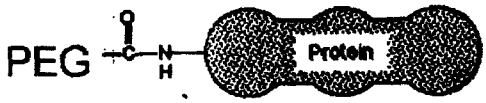
STUDY SUMMARY INDEX

3615	An open- label extension study of B2036- PEG in the treatment of acromegaly.	p. 40
3623	Absolute bioavailability and pharmacokinetics of subcutaneously-administered B2036- PEG.	p. 42

Drug Substance and Formulation:

- ***What are the physical/chemical characteristics of the drug substance?***

As per the submission, Somavert™ consists of a protein (B2036) containing 191 amino acid residues to which polyethylene glycol molecular weight 5000 polymers have been covalently bound in order to increase the size and decrease the clearance rate of the molecule. The amino acid sequence of the engineered protein is the same as that for human growth hormone except that 9 residues have been mutated so that binding to the growth hormone receptor occurs, but growth hormone signal transduction is inhibited. The B2036 protein is manufactured by expression in *E. coli* from which it is extracted and purified. The theoretical molecular formula of B2036 is $C_{980}H_{1519}N_{259}O_{303}S_7$. The structure of the PEGylated protein is shown below. The PEG molecule reacts with, and binds to, lysine residues of the B2036 protein.



In personal conversations the chemistry reviewer has indicated that the drug substance is not well characterized. The drug product may actually be a mixture of free as well as PEGylated B2036. The PEGylation is not well characterized as there maybe a range of PEG molecules bound to each B2036 protein molecule; there are nine potential binding sites on each B2036 molecule. In addition, there are a number of impurities in the drug substance and these have not been tested for biological activity or cross-reactivity in the pegvisomant serum RIA.

- ***What is the drug product formulation?***

The formulation for the 10, 15, and 20mg vials are as follows. The product is reconstituted with 1cc of supplied diluent before injection:

Ingredients	Quantity (per vial)[2]
B2036-PEG	10.00 mg
Glycine, USP	1.36 mg
Mannitol, USP	36.0 mg
Sodium Phosphate, Dibasic (Anhydrous), USP	1.04 mg
Sodium Phosphate, Monobasic (Monohydrate), USP	0.36 mg
Water for Injection, USP	2.00 mL[3]

Ingredients	Quantity (per vial)[2]
B2036-PEG	15.00 mg
Glycine, USP	1.36 mg
Mannitol, USP	36.0 mg
Sodium Phosphate, Dibasic (Anhydrous), USP	1.04 mg
Sodium Phosphate, Monobasic (Monohydrate), USP	0.36 mg
Water for Injection, USP	2.00 mL[3]

Ingredients	Quantity (per vial)[2]
B2036-PEG	20.00 mg
Glycine, USP	1.36 mg
Mannitol, USP	36.0 mg
Sodium Phosphate, Dibasic (Anhydrous), USP	1.04 mg
Sodium Phosphate, Monobasic (Monohydrate), USP	0.36 mg
Water for Injection, USP	2.00 mL[3]

[2] Each vial is reconstituted with 1 mL of Water for Injection.
[3] Water for Injection is removed from the finished drug product during the lyophilization.

The sponsor claims that the drug product manufacturing process has remained essentially unchanged throughout clinical and non-clinical development. However, the FDA Chemist (Janice Brown) has indicated that there have been some changes to the process but that these changes have introduced a number of new impurities rather than changing the drug substance itself. It is not known if any of these impurities are biologically active.

The proposed commercial batch size, as per the sponsor, is — vials. All batches used in biopharm and pivotal clinical trials were at least — of this commercial batch size.

Analytical methodology:

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Bioavailability

- ***What is the bioavailability of the product (absolute, relative)?***

Study SEN-3623 was a phase I, single-dose crossover study in healthy male and female volunteers. Twelve subjects (6 male and 6 female) each received 20 mg SC (single bolus dose) and 10 mg IV (infused over 6 hours) with a 4-week washout period between the two dosing regimens. The non-compartmental pharmacokinetic parameters from this study are presented in the table below.

	N	AUC_T (ng*hr/mL)	AUC_I (ng*hr/mL)	C_{max} (ng/mL)
SC, 20 mg B2036-PEG	12	186,320	207,752	1367 *
IV, 10 mg B2036-PEG	12	172,977	183,325	4271

Values are presented as geometric means.
* Statistically significant difference between treatments: F=6.45, P=0.048.

The absolute bioavailability of SC pegvisomant was calculated to be 54% using AUC_T and 57% using AUC_I.

There tended to be a gender effect on the mean dose-normalized values as shown below but it was not statistically significant and was not detected in the POP PK analysis.

	N	AUC_T (ng*hr/mL)	AUC_I (ng*hr/mL)	C_{max} (ng/mL)
SC, 20 mg B2036-PEG				
male	6	237,360	251,412	1825
female	6	139,280	164,091	950
IV, 10 mg B2036-PEG				
male	6	201,410	210,817	4338
female	6	144,543	155,833	4204

Values are presented as geometric means.

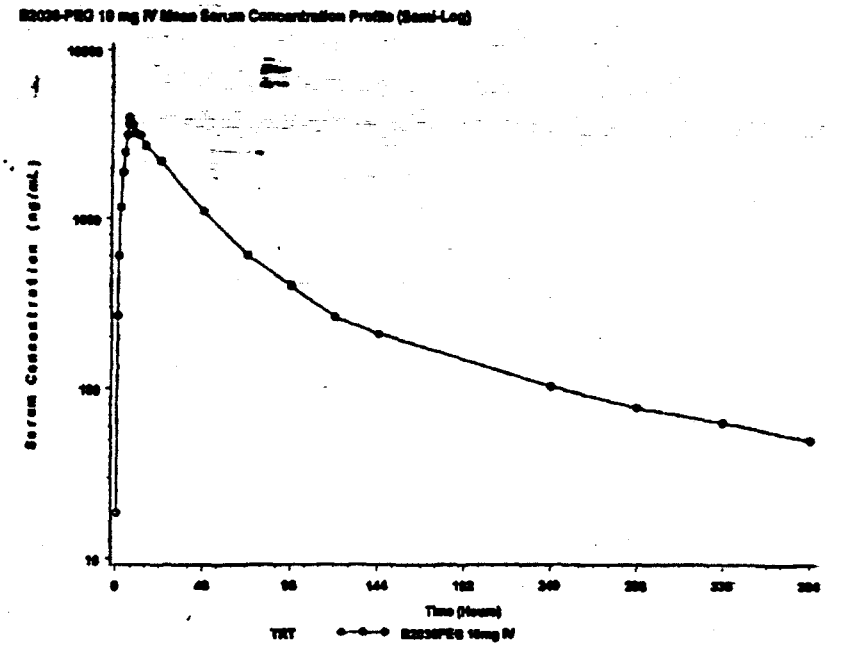
Half-life, elimination rate constant, and Tmax are summarized in the table below.

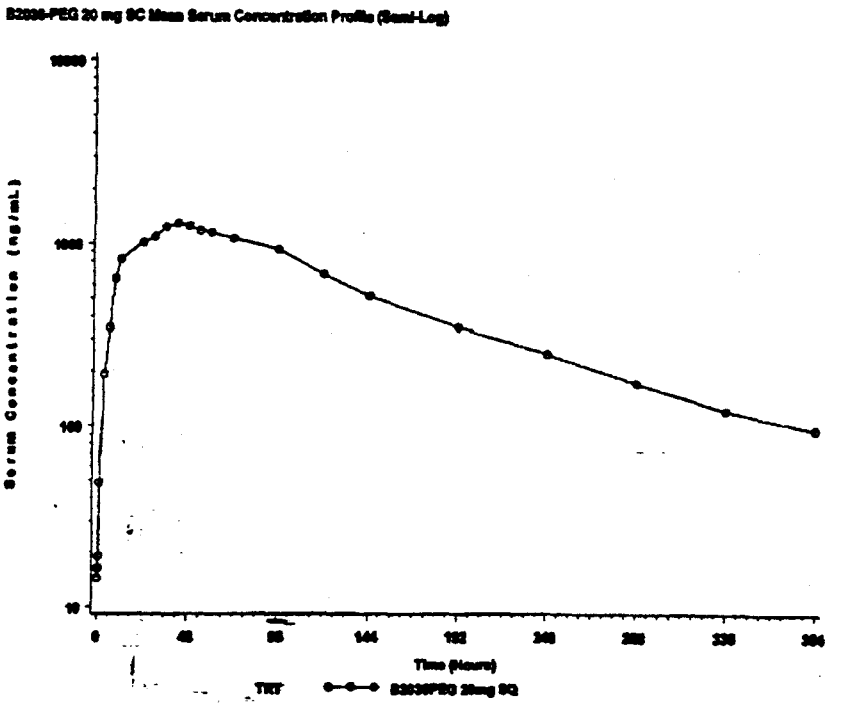
	N	$T_{\frac{1}{2}}$ (hr)	K_{el} (1/hr)	T_{max} (hr)
SC, 20 mg B2036-PEG	12	138.41 (49.34%)	0.0069 (39.54%)	49.02 (32.49%)
IV, 10 mg B2036-PEG	12	138.02 (26.02%)	0.0065 (38.96%)	6.45 (8.78%)

Values are presented as arithmetic means (coefficient of variation [CV%]).

There was a gender effect seen for the half-life also but only for the SC route. The half-life for females and males was 169 and 108 hours, respectively.

The plots below show the plasma profile of pegvisomant after IV and SC dosing.





As compared to the IV route, SC administration results in a diminished Cmax and a delayed Tmax.

Pharmacokinetics

- ***What are the basic pharmacokinetics of the drug in the volunteers/patient population?***
- ***Are the pharmacokinetics linear?***

Study SEN-3601 was a placebo-controlled, double-blind, single dose study in normal male volunteers. Pegvisomant doses of 0, 0.03, 0.1, 0.3, and 1.0 mg/kg SC were administered SC. The results indicated that the 0.3 mg/kg and 1.0 mg/kg doses suppressed IGF-I concentrations. The non-compartmental pharmacokinetic parameters from study SEN-3601 for pegvisomant are presented in the table below:

PK from study SEN-3601

	Dose (mg/kg)			
Parameter	0.03	0.1	0.3	1.0
C_{max} (ng/mL)	82.63 ± 23.66	461.6 ± 110.6	1832 ± 390	8962 ± 2186
T_{max} (hr)	12	36	36	60
AUC_{0-inf} (µg.hr/mL)	8.7 ± 1.5	37.4 ± 9.7	182.5 ± 46.5	1506.1 ± 549.6
$t_{½}$ (hr)	77.7± 22.3	99.1 ± 28.7	74.2 ± 33.2	79.8 ± 28.3

Data shown are mean ± SD for 6 subjects per dose group.
C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; AUC_{0-inf}, area under the serum concentration-time curve from time 0 to infinity; $t_{½}$, elimination half-life.

Study SEN-3602 was an open-label single-dose study of pegvisomant conducted in six acromegalic subjects to confirm the effects of pegvisomant on IGF-I and to study its pharmacokinetics in this population. Subjects received either 0.3 or 1.0 mg/kg subcutaneously. (subject weights ranged from 74 to 120 kg; the total dose administered ranged from 24.3 to 120 mg). Maximum suppression of IGF-I concentrations from baseline occurred 72-96 hours post dose and ranged from 7% to 24% in the 0.3 mg/kg group and from 26% and 61% in the 1.0 mg/kg group. The non-compartmental pharmacokinetic parameters from study SEN-3602 are presented in the table below:

PK from study SEN-3602

Dose	C_{max} (ng/L)	t_{max} (hrs)	AUC (µg•hr/mL)	$t_{1/2}$ (hrs)
0.3 mg/kg	1720.1 ± 288.6	33 ± 12.7	234 ± 52.7	109 ± 37.1
1.0 mg/kg	6545.7 ± 1983.8	77 ± 54.4	1060 ± 116.4	80 ± 36.3

Data shown are mean ± SD for 3 subjects per group.
C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; AUC, area under the serum concentration curve; $t_{1/2}$, elimination half-life.

In general the pharmacokinetic parameters were similar in healthy volunteers and acromegalics showing a more than proportional increase in Cmax and AUC with increasing dose.

From a population pharmacokinetic analysis, the clearance of pegvisomant is estimated to be about 32mL/h with an apparent volume of distribution of 7L.

Metabolism

- ***What is/are the route(s) of metabolism elimination?***

The disposition of pegvisomant has not been studied in humans.

Dose

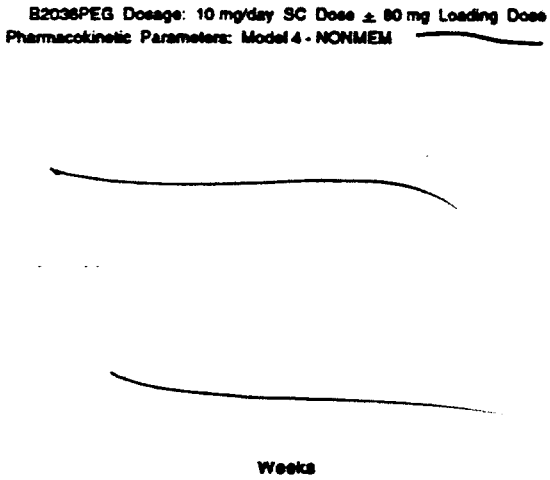
- ***What is the recommended dosing regimen?***

Since the calculated half-life of pegvisomant from early studies was a few days, Phase 2 clinical studies investigated weekly dosing regimens. It was discovered that effective IGF-1 suppression was not

achieved with up to 80mg weekly dose. The sponsor indicated that a pharmacokinetic/pharmacodynamic analysis suggested higher trough concentrations of pegvisomant would be needed to reduce IGF-1 more effectively. An increase in the weekly dosing was not feasible (limited by the number and volume of injections) so patients were converted to daily dosing.

A preliminary population pharmacokinetic analysis was performed on pegvisomant concentrations from an early clinical trial (SEN-3611; weekly dosing) pegvisomant concentrations. The pharmacokinetic parameters obtained from this analysis were used to simulate concentration-time profiles of pegvisomant. Among other predictions, this analysis showed that the use of an 80 mg loading dose would lead to near steady-state conditions achieved approximately 2 weeks sooner as compared to no loading dose (see plot below).

Pharmacokinetic model prediction of effect of loading dose on time to reach steady-state plasma pegvisomant concentrations



The primary clinical trial (SEN-3614) which supports the efficacy of Somavert™ was conducted with an 80mg loading dose and then daily maintenance doses of 10, 15, or 20mg (parallel groups). This study was 12 weeks in length with an extension of an additional 6 months. There is also clinical data using titration schemes for treating patients where 10mg was the starting dose. Starting at the 10mg dose will help prevent overshooting the dose (titration determines the least effective dose) but there is no *a priori* method to determine who will end up at a higher dose. In addition, the 10mg dose was shown to be effective for many patients.

Patients will be monitored for IGF-1 suppression every 6 to 8 weeks until appropriate IGF-1 suppression is achieved. Titration occurs at these visits in 5mg increments.

Through a telecon with Bob Davis of Sensus it was learned that the sponsor used the loading dose to 'increase exposure' to the drug due to the short duration of the clinical studies. Furthermore, he indicated that eliminating the loading dose altogether was acceptable because it places a burden on the patient to return to the physician's office after obtaining the drug for administration of the loading dose.

The NDA included simulations of the effect of no loading dose or loading with 40, 60, or 80mg. These data tend to indicate that, after 6 weeks, the loading dose is irrelevant. The pharmacokinetics and pharmacodynamics of pegvisomant are comparable at 6 weeks whether or not a loading dose is given.

The following points were made in a discussion with the medical officer:

- The nature of the illness is such that a loading dose is not necessary for clinical treatment. These patients are not in crisis and do not need pharmacological treatment in the same time frame as, for example, a patient who needs a loading dose of digoxin or theophylline;

- The elimination of the loading dose will decrease overall exposure to the drug without decreasing efficacy.

It may be feasible to eliminate the loading dose but there is no clinical data to support this. Due to a mistake in the clinical trial, some patients did receive a loading dose of either 40mg or 60mg and, according to the medical officer, these patients had comparable efficacy as those patients who received the 80mg loading dose.

There are clinical as well as pharmacokinetic/pharmacodynamic data to support the diminution of the loading dose to 40mg. This same pharmacokinetic/pharmacodynamic data can also be use to support the elimination of the loading dose since the patient will be monitored every six weeks and the PK/PD effects of the loading dose will be gone at that time. However, to eliminate the loading dose altogether would need to be a clinical decision.

Special Populations

- ***Are the pharmacokinetics/pharmacodynamics of the drug similar in different human populations?***

Pegvisomant has not been studied in children, the elderly, or in subjects with impaired hepatic or renal function.

The analysis of study SEN-3623, a single-dose absolute bioavailability study in healthy volunteers, showed a slight gender effect on some pharmacokinetic parameters but this effect was not borne out in POP PK modeling.

Drug Interactions / Protein Binding

Not submitted.

Population Pharmacokinetics

A population pharmacokinetic analysis was submitted based on a model developed with single dose data and applied to the clinical study SEN-3614. A Pharmacometrics consult was obtained from Dr. Sam Haidar (HFD-870) and is located in the Appendix. Covariates tested for an effect on the observed inter-subject variability in apparent systemic clearance of pegvisomant included age, gender, race, birth control method, baseline IGF-I stratification, baseline IGF-I concentration, baseline GH concentration, baseline concentration of endogenous cross-reactant, presence of diabetes, height, weight, body surface area, body mass index, blood chemistries (including AST, ALT, alkaline phosphatase, bilirubin and serum creatinine) and baseline overall health status obtained from the health status survey. The influence of previous treatments for acromegaly, including prior surgery, radiation treatment, gamma-knife treatment, sandostatin therapy and bromocriptine therapy were tested. Concomitant drug therapies were examined to evaluate the possibility of drug-drug interactions. Specific drugs (or drug classes) being used by at least 5% of the study population were included in the pharmacokinetic analysis.

The population analysis concluded that the clearance of pegvisomant:

- increases with increasing body weight
- decreases with increasing dose
- decreases by about 30% if a patient is also receiving lipid-altering drugs

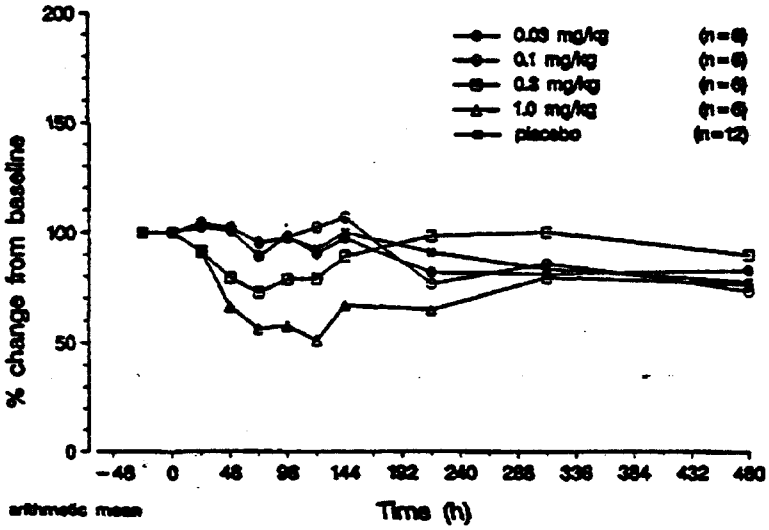
There is a suggestion from the population pharmacokinetic/pharmacodynamic analysis that patients receiving opioids may have a higher C_{50} than patients not receiving such medications. The implication is that opioid-receiving patients may need higher doses of pegvisomant but this has not been confirmed clinically and the result is considered exploratory, not definitive.

This same analysis shows a direct relationship between concentration of pegvisomant and baseline GH levels. Patients with high baseline GH levels tended to need greater concentrations of pegvisomant to achieve appropriate levels of IGF-1 as compared to patients with lower baseline GH levels.

Pharmacokinetic / Pharmacodynamic Relationships

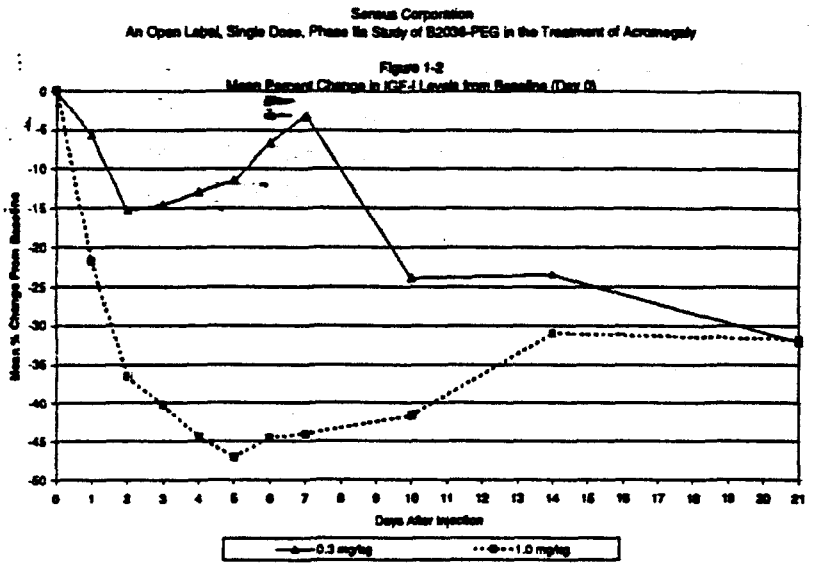
- ***Is there a pharmacokinetic/pharmacodynamic relationship?***

From study SEN-3601 the following response was seen for IGF-1 at the four different dose levels in healthy volunteers. There is evidence that higher doses do result in greater suppression of IGF-1 for longer periods of time (0.3 vs. 1.0 mg/kg doses).



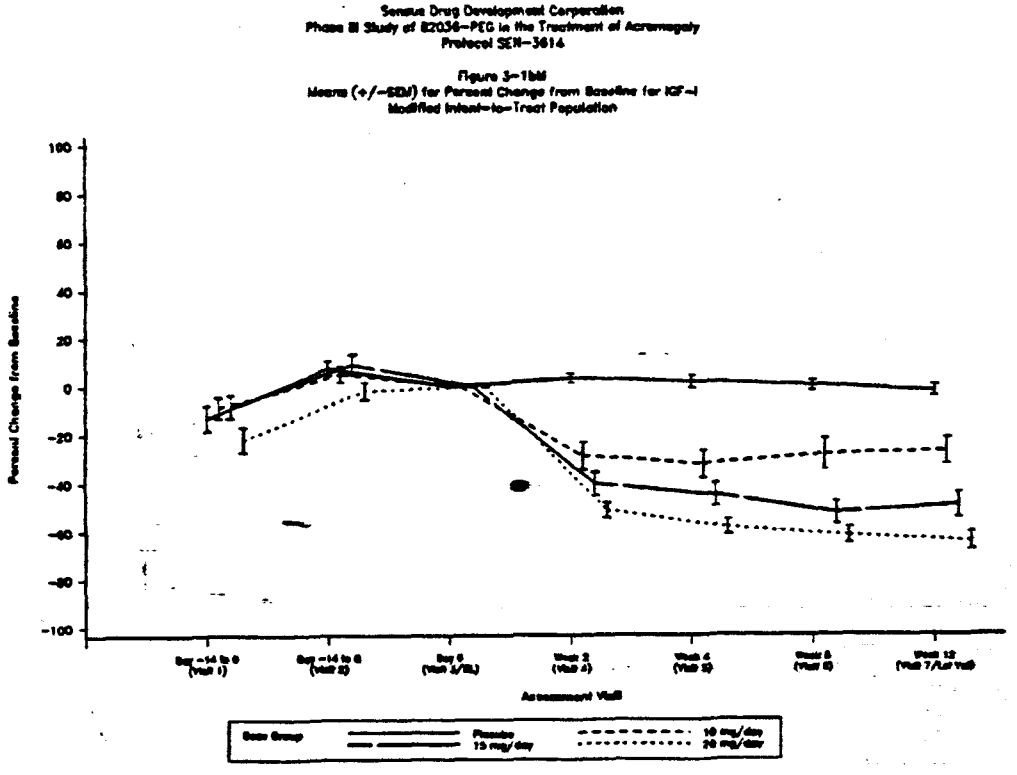
Combined group mean curves of IGF-1 as percentage from baseline

The following plot shows a similar IGF-1 response from study SEN-3602 in acromegalics.



Subjects in these two studies had an average body weight between 70 and 120 kg. The 80mg dose was probably chosen as a typical dose from these study data.

The plot below is from the clinical trial SEN-3614 and shows the general response seen in all the clinical trials. Generally, as the dose increases the effect is a greater diminution in IGF-1.



The results of a pharmacokinetic/pharmacodynamic model for the 20mg dose from study SEN-3614 are shown in the plot below. Pegvisomant is assumed to exert its effect by an indirect, saturable mechanism

that inhibits IGF-1 production. The final model is considered to be exploratory and did show a tendency for higher C_{50} concentrations in patients receiving concomitant opioid therapy.

DISCUSSION:

Somavert™ is proposed for use to treat acromegaly, a disease characterized by excessive growth hormone secretion and elevated IGF-1 levels. The mechanism of action is though competitive blockade of the growth hormone receptor and subsequent reduction of IGF-1 production. The sponsor has submitted pharmacokinetic studies performed in healthy volunteers and patients. The assay used for the detection of pegvisomant in human serum is acceptable but the sponsor needs to complete phase 4 study involving cross-reactivity of impurities in the assay. The pharmacokinetics of the drug are affected by body weight and dose as well as the concomitant administration of lipid-altering drugs. Patients on opioids may need higher concentrations of pegvisomant to achieve appropriate IGF-1 response.

During the Clinical Pharmacology and Biopharmaceutics Briefing on 24-APR-01 the possibility of a drug-drug interaction was mentioned. Dr. Huang cited an interaction with octreotide and cyclosporin noted in the Sandostatin® labeling in which the blood concentrations of cyclosporin were decreased. Theoretically this could be the result of decreased growth hormone (GH) levels on GI transit/absorption. Since pegvisomant would cause an apparent decrease in GH by blocking GH receptors, it is possible that a similar interaction could arise between pegvisomant and cyclosporin. As such, the sponsor will be asked to address this issue.

LABELING COMMENTS:

1) The sponsor's proposed labeling under 'Pharmacokinetics/Pharmacodynamics' should be eliminated and replaced with the following:

Pharmacokinetics

1 page(s) of revised draft labeling has been redacted from this portion of the review.

/S/ 24-APR-01

Signatures:

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by John Hunt, Deputy Director, DPE2 23-APR-01

CPB Briefing 24-APR-01
attendees:Malinowski, HuntJ, HuangS, Lazor, SahajwallaC, Ahnh, StrongJ, PeristeinR

FT initialed by John Hunt, Deputy Director, DPE2 /S/ 4/25/01

CC: NDA 21-106/N-000 (orig.,1 copy), HFD-510(King, Peristein, Malozowski), HFD-870(Ahnh, Malinowski), HFD-850(Lesko) CDR.

DFS Code: AE

APPENDIXES

Appendix 1. Draft labeling

7 page(s) of revised draft labeling has been redacted from this portion of the review.

REFERENCES

[1] SEN-209 (binding to hepatocytes from mouse, rat rabbit, dog, rhesus monkey and humans)

[2] Maamra M, Finidori J, Von Laue S, et al. Studies with a growth hormone antagonist and dual-fluorescent confocal microscopy demonstrate that the full-length human growth hormone receptor, but not the truncated isoform, is very rapidly internalized independent of Jak2-Stat5 signaling. J Biol Chem 1999; 274:14791-8.

[3] SEN-204 (including adrenergic α_{2A}, β_1, β_2, β_3; dopamine D_1, D_{2L}, D_{2S}, D_3; interleukin-6; leukotriene B_4; Muscarinic M_1, M_2; tachykinin Nk_1, Nk_2; opiate δ, κ, μ; and serotonin 5-HT_{1A} receptors).

[4] Goffin V, Bernichtein S, Carriere O, Bennett WF, Kopchick JJ, Kelly PA. The human growth hormone antagonist B2036 does not interact with the prolactin receptor. Endocrinology 1999; 140:3853-6

[5] SEN-3614

[6] SEN-121

Appendix 2. Study summaries

SUMMARY OF CLINICAL STUDY REPORT

NAME OF SPONSOR Sensus Corporation NAME OF FINISHED PRODUCT NAME OF ACTIVE INGREDIENT B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume Page	(FOR NATIONAL AUTHORITY USE ONLY)

Study Title : SINGLE RISING DOSE PHASE I STUDY ON THE SAFETY, TOLERABILITY, PHARMACODYNAMICS AND PHARMACOKINETICS OF B2036-PEG AFTER SUBCUTANEOUS ADMINISTRATION IN HEALTHY MALE VOLUNTEERS

Study Code : [redacted]

Sponsor : Sensus Corporation, Austin, Texas, USA
Study director : C.L. Delmonte, M.D., F.C.P. / Robert J. Davis, Pharm. D.
Study monitor : K. Zib

Investigator : [redacted]

Publication : not applicable

Study Period : November 1996 – April 1997 Clinical Phase I

Objectives : to determine the safety, tolerability, pharmacodynamics and pharmacokinetics of B2036-PEG after single dose subcutaneous administration at four rising dose levels

Design : placebo-controlled, double-blind randomized study with four sequential groups of healthy male volunteers receiving ascending single subcutaneous doses of B2036-PEG or placebo at two-week intervals, with interim safety evaluation between successive dose groups

Subjects : 36 healthy young male volunteers (9 per dose group; 6 active/3 placebo (planned and actual = analyzed)
Age : mean 25 yr; range 18-37 yr
Weight : mean 74.9 kg, range 56.7-92.4 kg

Medication 1. : Name : Somavert™
Active component : B2036-PEG
Activity : recombinant human growth hormone receptor antagonist (rhGHA)
Indication : acromegaly, diabetes (diabetic retinopathy and nephropathy) and IGF-I and/or GH-sensitive tumours
Strength : 10 mg/mL
Dosage form/Route : solution for subcutaneous injection
2. : placebo, visually matching medication 1

Treatment : subcutaneous administration of B2036-PEG or placebo as a single dose:
Group I : 0.05 mg/kg
Group II : 0.1 mg/kg
Group III : 0.3 mg/kg (two injections if volume is more than 1.5 mL)
Group IV : 1.0 mg/kg (up to six injections of maximum 1.5 mL)

Procedures and Assessments : Eligibility screening and follow-up (= day 21): clinical laboratory, full physical examination, ECG, fasting insulin; at eligibility screening: tests on drugs of abuse, barbiturates, benzodiazepines, tricyclic antidepressants, HBsAg, anti-HCV and anti-HIV1/2
Observation period: in clinic from -41 h up to 168 h (day 8) after drug administration and from day 13 (13:00 h) to day 14 (10:00 h) after drug administration, ambulant visits on days 10, 21, 60 and 90 (antibody tests on day 60 and 90)
Blood sampling: for B2036-PEG: pre-dose and at 0.25, 0.5, 1, 2, 4, 9, 12, 24, 36, 48, 72, 96, 120 and 144 h after drug administration (15 samples per subject, total 540 samples); for IGF-1 and IGF-BP3: on day -1 and on days 1-7, 10, 14 and 21 (total 396 samples); for 6-h growth hormone profiles (samples every 20 minutes), TSH and prolactin: days -1, 3, 6 and 14 (total 2736 growth hormone samples, 144 prolactin samples); for B2036-PEG and hGH antibodies: on days 60 and 90 (total 72 samples)
Urine sampling: for urinary Cr excretion: a blank sample (24 h) was collected before dosing (day -1); 24 h urine was collected on days 3, 7 and 21 (total 144 samples)
Safety assessments: adverse events and vital signs on day -1, pre-dose, 12, 24 and 36 hours post-dose and daily on days 3 to 7 and on days 10, 14 and 21; physical examination on days 1 and 7; clinical laboratory tests including fasting glucose and lipid profile: on days -1, 3, 7, 10, 14 and 21, fasting glucose and insulin on days 4, 5 and 6; telemetric cardiac monitoring up to 6 hours post-dose

SUMMARY OF CLINICAL STUDY REPORT (continued)

NAME OF COMPANY Sensus Corporation NAME OF FINISHED PRODUCT NAME OF ACTIVE INGREDIENT B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume Page	(FOR NATIONAL AUTHORITY USE ONLY)

Bioanalysis : B2036-PEG concentrations were measured in 540 samples using a radioimmunoassay; growth hormone concentrations were measured in 2736 samples; IGF-1 and IGF-BP3 concentrations were measured in 396 samples using an immunoradiometric assay; TSH and prolactin concentrations were measured in 144 samples using assay; insulin concentrations were measured in 180 samples using an immunoenzymatic assay

Criteria for Evaluation : Safety/Tolerability parameters: adverse events: listing by treatment; clinical laboratory: values outside reference range and descriptive statistics; vital signs: descriptive statistics and combined plot of group mean curves

Pharmacokinetic parameters: descriptive statistics for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, k_{el}, $t_{½}$ and t_{max}; regression analysis (factor dose) on the log-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$; group-wise plots of individual serum concentration-time curves and combined plot of group mean curves

Pharmacodynamic parameters: descriptive statistics, group-wise plots of individual values, combined plots of group mean curves for IGF-1, growth hormone AUC, IGF-BP3, prolactin, insulin and TSH; effective dose: 50% suppression of IGF-1, maximum effect dose: >90% suppression of IGF-1

Results : Safety/Tolerability parameters: neither serious nor severe adverse events leading to poor or moderate tolerability were observed. In total 52 adverse events occurred. Of these, nine were considered to be possibly and one probably related to the study medication (five during active treatment and four during placebo treatment). No clinically relevant alterations in vital signs, clinical laboratory test results, physical examination, continuous electrocardiographic monitoring and 24-h urine calcium excretion were observed.

Pharmacokinetic parameters: B2036-PEG was detected in plasma in all four dose groups. Arithmetic means for C_{max} were 0.08, 0.46, 1.83 and 8.98 µg/mL for the four dose groups, respectively; for $AUC_{0-\infty}$ these values were 8.7, 37.4, 183 and 1506 µg.h/mL, respectively. The mean B2036-PEG serum concentration-time curves show a more than dose-proportional increase in C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Statistical analysis (log-linear regression analysis) confirmed this observation. P-values for treatment effect were 0.0001 for all three parameters.

Pharmacodynamic parameters: IGF-1 did not show any decrease from baseline in Groups I and II, a slight decrease (27.7% from baseline at 72.00 h post-dose) was seen in Group III, and a more marked decrease was seen in Group IV (43.95% from baseline at 72.00 h post-dose). The maximum effect dose was not reached. GH values showed a large intra-individual variation. No clear treatment effect can be observed. IGF-BP3, insulin, prolactin and TSH did not show any consistent changes at any time after dosing compared to the pre-dose values.

Conclusions :
- All four doses tested were well tolerated and considered safe;
- B2036-PEG was detected in plasma;
- B2036-PEG C_{max} and AUC showed a more than dose-proportional increase;
- B2036-PEG half-life and elimination rate constant were similar for all dose groups;
- The effective dose, causing a 50% suppression of IGF-1, was 1.0 mg/kg;
- The maximum effect of >90% suppression of IGF-1 was not reached;
- Growth hormone AUCs showed a large intra-individual fluctuation;
- IGF-BP3, insulin, prolactin and TSH concentrations did not show a consistent change from baseline.

Date of Report : April 20, 1998

Report Number SEN-3602

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: B2036-PEG NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open Label, Single Dose, Phase IIa Study of B2036-PEG in the Treatment of Acromegaly

Investigators:

Aart J. van der Lely, M.D., Ph.D.; Steven W. Lamberts, M.D., Ph.D.

Study center:

Publications:

Van der Lely AJ, Zib KA, Lamberts SWJ. Subcutaneous administration of the GH-receptor antagonist B2036-PEG (Trovert®) decreases IGF-I concentrations in active acromegalic patients. Abstract P2-494. The Endocrine Society 80th Annual Meeting. June 24-27, 1998, New Orleans, Louisiana.

Rodvold KA, van der Lely AJ. Pharmacokinetics and pharmacodynamics of B2036-PEG, a novel growth hormone receptor antagonist, in acromegalic subjects. Abstract P1-049 (submitted and accepted). The Endocrine Society 81st Annual Meeting. June 12-15, 1999, San Diego, California.

Study period: April 23, 1997 - June 2, 1997	Clinical phase: IIa

Objectives:

To determine the safety, tolerability, pharmacokinetics, and efficacy of a single subcutaneous dose of two selected dose levels of B2036-PEG in subjects with acromegaly.

Methodology:

This study consisted of three phases. During the screening/eligibility phase, evaluations were conducted within 2 weeks before the start of the study (Days -14 to -2) to determine the eligibility of each subject for study inclusion. Enrolled subjects were hospitalized on Day -1 for a 7-day dosing/observation period. During this phase, subjects underwent the administration of a single dose of study medication (Day 0); blood sampling for the assessment of pharmacokinetic parameters (Days 0 though 7); and safety, tolerability, and efficacy assessments (Days 0 through 7). Subjects were then discharged from the hospital (Day 7) but returned on an outpatient basis on Days 10, 14, and 21 for follow-up blood sampling for the determination of growth hormone (GH), insulin-like growth factor I (IGF-I), free IGF-I, and IGF binding protein 3 (IGFBP-3) levels, and for pharmacokinetic analysis.

Number of subjects: Subjects entered - 6 Subjects completed - 6

Three subjects per dose group. Three subjects, 0.3 mg/kg B2036-PEG; three subjects, 1.0 mg/kg B2036-PEG.

Diagnosis and criteria for inclusion:

Male or female (post-menopausal or surgically sterile) subjects between 18 and 65 years of age (inclusive) with a previous diagnosis of acromegaly. All subjects had an IGF-I level greater then 50% above the upper limit of age-matched normal values.

Test product, dose and mode of administration, batch no:

The study drug B2036-PEG is a recombinant protein of human DNA origin and act as a growth hormone receptor antagonist indicated for the treatment of acromegaly. B2036-PEG was prepared as a sterile solution for subcutaneous or parenteral injection (10 mg/mL) and was administered as a single dose of either 0.03 mg/kg or 1.0 mg/kg; batch no. 003007

Duration of treatment:

Only a single dose was administered; the duration of the entire study was approximately 3 weeks.

Reference therapy, dose and mode of administration, batch no:

None

Report Number SEN-3602

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: B2036-PEG NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open Label, Single Dose, Phase IIa Study of B2036-PEG in the Treatment of Acromegaly

Criteria for evaluation:

Efficacy evaluations: IGF-I levels, signs and symptoms of acromegaly, ring size, and the levels of other endocrine hormones.

Safety/tolerability evaluations: Repeated physical examinations, clinical laboratory testing, and adverse event monitoring.

Pharmacokinetics: B2036-PEG serum concentrations measured on Days 0 - 7, 10, 14, and 21.

Summary:

Efficacy: In the three low-dose (0.3 mg/kg) subjects, IGF-I levels decreased from baseline values of 1688, 872, and 762 ng/mL, respectively, to nadirs of 1402, 567, and 424 ng/mL, respectively (56-83% of baseline). In the three high-dose (1.0 mg/kg) subjects, IGF-I levels decreased from baseline values of 1006, 465, and 1162 ng/mL, respectively, to nadirs of 389, 214, 714 ng/mL, respectively (39-61% of baseline). In the 1.0 mg/kg group, there were also substantial decreases seen in free IGF-I levels (19%-42% of baseline). In three of the six subjects (two in the 1.0 mg/kg group and one in the 0.3 mg/kg group), an impressive improvement was seen in signs and symptoms of acromegaly 2-5 days after receiving the single injection of B2036-PEG. Using a quantitative score for disease activity, a more pronounced clinical improvement was observed in the 1.0 mg/kg group. Very little change and no directional trends were observed for GH in either dose group.

Safety/tolerability: Because subject weights ranged from 74 to 120 kg, the total dose administered ranged from 24 to 120 mg. B2036-PEG was well tolerated, and no adverse events or clinically significant laboratory results were reported during the study.

Pharmacokinetics: Mean (±SEM) serum B2036-PEG concentrations (as determined by [redacted] in the 0.3 mg/kg group peaked on Day 1 (24 hours following drug administration) at 1720.1 ± 288.6 ng/mL (1.72 µg/mL). Mean B2036-PEG concentrations in the 1.0 mg/kg group peaked on Day 2 at 6545.7 ± 1983.8 ng/mL (6.55 µg/mL). These values were similar to those seen after single doses in healthy male volunteers in Study SEN-3601 (maximum concentrations of 1.83 µg/mL for 0.3 mg/kg and 8.98 µg/mL for 1.0 mg/kg). The noncompartmental pharmacokinetics (as determined by a consultant pharmacokineticist) showed similar maximum concentrations as the [redacted] results but showed a time to maximum concentration of 33 ± 7 hours in the 0.3 mg/kg group and 77 ± 31 hours in the 1.0 mg/kg group.

Conclusions:

B2036-PEG, administered as a single subcutaneous dose of 0.3 mg/kg or 1.0 mg/kg, was well tolerated and decreased total and free serum IGF-I concentrations in a dose-dependent manner. Clinical improvement (demonstrated by the signs and symptoms of acromegaly) varied between subjects at the doses tested.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: Pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open Label Extension Study of B2036-PEG in the Treatment of Acromegaly (Interim Report, Data up to 31 May 1999)

Investigators:

G. Michael Besser; Aart van der Lely; Shlomo Melmed; Mary Lee Vance; David Clemmons; Ariel Barkan

Study centers:

St. Bartholomew's Hospital, London; Erasmus University, Rotterdam; Cedars-Sinai Hospital, Los Angeles, CA; University of Virginia, Charlottesville, VA; University of North Carolina, Chapel Hill, NC; University of Michigan, Ann Arbor, MI.

Publications:

Barkan A, Dimaraki E, Besser GM, et al. Treatment of acromegaly with B2036-PEG, a growth hormone receptor antagonist. Abstract OR14-6. The Endocrine Society 81st Annual Meeting. June 12-15, 1999, San Diego, California.

Rose DR, Jr., Clemmons DR. Growth hormone receptor antagonist induces improvement in insulin resistance in acromegaly. Abstract P1-47. The Endocrine Society 81st Annual Meeting. June 12-15, 1999, San Diego, California.

Hutson RK, Lipper M. The novel growth hormone receptor antagonist B2036-PEG does not stimulate growth of pituitary tumors in acromegalic patients [Abstract, p. 74]. Sixth International Pituitary Congress, June 15-17, 1999, Long Beach, California.

Vance ML, Dimaraki E, Trainer P, et al. B2036-PEG, a growth hormone (GH) receptor antagonist, lowers insulin and glucose in acromegalic patients [Abstract, p. 75]. Sixth International Pituitary Congress, June 15-17, 1999, Long Beach, California.

Study period: Ongoing; 24 February 1998 to 31 May 1999 Data included in this Report	Clinical phase: IIb

Objectives:

To determine the long-term safety of B2036-PEG therapy in subjects with acromegaly.

Design:

Open-label extension study in subjects with a diagnosis of acromegaly who successfully completed SEN-3611. Subjects received from 10 to 40 mg B2036-PEG daily by subcutaneous administration. This is an extension study of SEN-3611 and SEN-3613.

Methodology:

Each subject received a dose from 10 to 40 mg B2036-PEG (titrated in 5-mg increments) daily administered subcutaneously in an open-label fashion. Each subject was to complete a visit every other week (± 2 days) until insulin-like growth factor-I (IGF-I) concentrations were normalized at two consecutive visits or until the maximum dose (40 mg/day) was achieved, whichever came first, and then one visit every month (± 1 week) thereafter. At each visit, subjects were to receive study drug and undergo study assessments. Additional safety assessments were also to be performed at 6 and 12 month (±1 month) intervals after the subject's enrollment into the previous double-blind study, SEN-3611.

Number of subjects: Subjects entered - 38 Subjects completed - 0 (Ongoing) Subjects Active - 35

Diagnosis and criteria for inclusion:

Subjects with a diagnosis of acromegaly who had successfully completed Sensus Study SEN-3611 and/or had participated in SEN-3613.

Test product, dose, mode of administration, and lot numbers:

B2036-PEG was provided as a lyophilized powder, which was prepared as a solution for subcutaneous injection (20 mg/mL) by reconstituting with sterile water for injection. B2036-PEG was administered as an initial 80-mg bolus loading dose followed by single daily doses from 10 to 40 mg for an indeterminate period of time. Lot numbers used in this study to date are: 472153A and 523153A.

Duration of treatment:

Ongoing, for an indeterminate period of time

Reference therapy, dose and mode of administration, batch no:

None

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: Pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open Label Extension Study of B2036-PEG in the Treatment of Acromegaly (Interim Report, Data up to 31 May 1999)

Criteria for evaluation:

Safety evaluations - The long-term safety of B2036-PEG was evaluated through laboratory tests, B2036-PEG antibody evaluations, growth hormone (GH) antibody evaluations, magnetic resonance imaging (MRI) of the pituitary, electrocardiograms (ECGs), chest x-ray, and adverse event monitoring.

Efficacy evaluations - No formal efficacy evaluations were performed. Descriptive statistics were prepared for IGF-I concentrations, signs and symptoms of acromegaly, and ring size.

Summary:

Safety - B2036-PEG administered as daily subcutaneous doses of up to 40 mg was well tolerated. A total of 31 of the 38 study subjects (81.6%) reported 217 adverse events. The most common adverse events were asthenia, headache, infection, pain, diarrhea, nausea, vomiting, peripheral edema, dizziness, and increased cough. Three subjects withdrew from the study because of adverse events (autoimmune hepatitis not related to study drug; lipohypertrophy believed possibly drug-related; and death due to an unrelated myocardial infarction). Nine subjects reported serious adverse events, one of which (hospitalization for investigation into panic attacks) was considered possibly related to study drug. Trends in decreased mean insulin and glucose and in increased total cholesterol were observed over time; the clinical significance of these trends is not known. Overall, there were no clinically significant changes over time with respect to vital signs, weight, ECGs, chest x-rays, or pituitary tumor volumes (as measured by MRI). There was no apparent trend in type or frequency of adverse events when previous weekly dosing regimens of B2036-PEG were compared with the current long-term daily dosing regimen. Also, there was no apparent dose relationship in the incidence of adverse events.

Efficacy - Although no formal efficacy analyses were performed, potentially clinically important decreases in IGF-I concentrations were noted. To date, normalization of IGF-I concentrations has occurred in 35 of the 38 subjects (92.1%) who have participated in SEN-3613A.

Conclusions:

B2036-PEG in doses of 10 to 40 mg delivered as daily subcutaneous injections was well tolerated by subjects with acromegaly.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of B2036-PEG in the Treatment of Acromegaly

Investigators:

G. Michael Besser, Aart van der Lely, Shlomo Melmed, Mary Lee Vance, David Clemmons, Ariel Barkan, Keith Friend, Gudmundur Johannson, Anne Klibanski, Larry Phillips, Paul Stewart, Christian Strasburger, Peter Trainer, David Cook, Pamela Freda, David Kleinberg.

Study centers:

St. Bartholomew's Hospital, London, England; Erasmus University, Rotterdam, The Netherlands; Cedars-Sinai Hospital, Los Angeles, CA; University of Virginia, Charlottesville, VA; University of North Carolina, Chapel Hill, NC; University of Michigan, Ann Arbor, MI; MD Anderson Cancer Center, Houston, TX; Sahlgrenska University Hospital, Goteborg, Sweden; Massachusetts General Hospital, Boston, MA; Emory University School of Medicine, Atlanta, GA; Queen Elizabeth Hospital, Birmingham, England; Klinikum Innenstadt der Ludwig-Maximilians-University, Munich, Germany; Christie Hospital, Manchester, England; Oregon Health Sciences University, Portland, OR; Columbia Presbyterian Medical Center, New York, NY; Bellevue Hospital, New York, NY.

Publication:

Trainer PJ, Besser GM, Klibanski A, et al. A phase III study of B2036-PEG, a growth hormone receptor antagonist, in the treatment of acromegaly. Abstract HT-7. The Endocrine Society 81st Annual Meeting. June 12-15, 1999. San Diego, California.

Study period: 20 July 1998 – 07 April 1999	Clinical phase: III

Objectives:

To determine the tolerability and efficacy of B2036-PEG therapy in subjects with acromegaly.

Design:

Randomized, multicenter, double-blind, placebo-controlled study with subjects with the diagnosis of acromegaly receiving either placebo or B2036-PEG (one of three dose levels) by subcutaneous injection in a single bolus loading dose and then once daily for 12 weeks, with safety and efficacy assessments performed at Weeks 2, 4, 8, and 12.

Methodology:

Prior to dosing, subjects were withdrawn from previous acromegaly therapies and screened for study eligibility. Subjects were qualified for enrollment at the second screening visit if their serum IGF-I, drawn after the required drug washout period, was ≥1.3 times the upper limit of the age-adjusted normal range. Subjects were randomly assigned at the baseline visit (Visit 3/Week 0) to one of four treatment groups (placebo, 10 mg/day, 15 mg/day, or 20 mg/day of B2036-PEG). Assessments throughout the study included signs and symptoms of acromegaly; quality of life; ring size; magnetic resonance imaging (MRI) of the pituitary; adverse events; and laboratory sampling for growth hormone (GH), insulin-like growth factor I (IGF-I), free IGF-I, acid labile subunit (ALS), insulin-like growth factor binding protein-3 (IGFBP-3), hematology, chemistry profile, lipid profile, urinalysis, B2036-PEG serum drug concentrations, and GH antibody development.

Number of subjects: Subjects entered – 112 Subjects completed - 108

Four subjects withdrew prematurely: two in the placebo group (protocol violation and lack of efficacy, respectively) and two in the 15 mg/day group (lack of efficacy and adverse event of transaminitis, respectively).

Diagnosis and criteria for inclusion:

Male or female (not pregnant or lactating) volunteers 18 years of age or older with a diagnosis of acromegaly and an IGF-I value 30% or greater above the upper limit of normal at screening.

Test product, dose and mode of administration, lot no:

B2036-PEG, a recombinant human growth hormone receptor antagonist, was prepared as a solution for subcutaneous injection (10, 15, or 20 mg/mL) and was administered as a single bolus loading dose of 80 mg and then as a single daily dose of 10, 15, or 20 mg for 12 weeks. The lot numbers of B2036-PEG used in this study were 413303A (10-mg dose), 413353A (15-mg dose), and 423503A (20-mg dose).

Duration of treatment:

Approximately 12 weeks, outpatient.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of B2036-PEG in the Treatment of Acromegaly

Reference therapy, dose and mode of administration, lot no:

The placebo, a visually matching test product, was administered as a single 4-mL bolus loading dose and then as a single 1-mL daily dose for 12 weeks. The lot number of placebo used in this study was 003628.

Criteria for evaluation:

Efficacy evaluations – Percent suppression in IGF-I concentrations from baseline (primary); incidence of normalization of IGF-I, reduction in acid labile subunit (ALS) and free IGF-I, acromegaly signs and symptoms score, ring size, and quality of life (secondary).

Safety evaluations – Clinical laboratory tests, pituitary MRI, ECGs, physical examinations, vital signs, adverse events, GH, and GH antibodies.

Summary:

All three B2036-PEG treatment groups had reductions in IGF-I compared with baseline that were statistically significantly different from the placebo treatment group at each post-treatment time point. The mean percent reduction in IGF-I at Week 12 was 4% for the placebo group compared with 27%, 50%, and 63% for the B2036-PEG 10 mg/day, 15 mg/day, and 20 mg/day groups, respectively. The analysis of covariance showed no statistically significant effects for baseline IGF-I, entry strata, baseline GH, or gender; however, baseline body weight was a significant factor in the pairwise treatment comparison of B2036-PEG treatments versus placebo. B2036-PEG treatment was also associated with a dose-dependent increase in the incidence of IGF-I normalization, which was statistically significantly different from placebo at each time point. The percentage of subjects who achieved normal IGF-I concentrations at any time during the study was 54%, 81%, and 89% for the B2036-PEG 10 mg/day, 15 mg/day, and 20 mg/day groups, respectively, compared with 10% for the placebo group. Dose-dependent, statistically significant reductions in free IGF-I, IGFBP-3, and ALS were also observed at all post-baseline visits in the B2036-PEG treatment groups.

The mean values for the individual clinical signs and symptoms ratings and for the total signs and symptoms score showed worsening in the placebo-treated subjects and dose-dependent improvement in the B2036-PEG-treated subjects, with statistically significant differences from placebo observed at Week 12 for categorical changes (improved, worsened, unchanged) in soft tissue swelling, excessive perspiration, fatigue and total signs and symptoms score in the 15 mg/day and 20 mg/day groups. Ring size decreased significantly at Week 12 in the B2036-PEG 15 mg/day and 20 mg/day treatment groups compared with the placebo group.

Overall, B2036-PEG was well tolerated, and the incidence of adverse effects was similar in all four treatment groups. One subject treated with B2036-PEG 15 mg/day withdrew from the study due to elevated liver transaminases. Adverse events thought to be related to treatment that were reported by two or more subjects in any B2036-PEG treatment group included liver function abnormality, asthenia, injection site reaction, rash, sweating, diarrhea, and nausea. None of the eight serious adverse events occurring during treatment with B2036-PEG were related to the study medication. Serum GH increased and then plateaued in the B2036-PEG-treated subjects in a manner that coincided with the magnitude and timing of the fall in serum IGF-I. This was not accompanied by any clinically significant changes in pituitary tumor size (as measured by MRI). There were no clinically significant trends toward changes in other laboratory values. No subjects developed clinically significant treatment-emergent GH antibodies.

Conclusions:

B2036-PEG is a novel, genetically engineered human GH receptor antagonist that is a highly effective in blocking GH action, thus reducing both the biochemical abnormalities and the clinical signs and symptomatology observed in acromegalic subjects. Based on the efficacy and adverse effect profile observed to date, it has the potential to become a primary medical therapy for acromegaly.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: Pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open-Label Extension Study of B2036-PEG in the Treatment of Acromegaly (Interim Report, Data up to 30 April 1999)

Investigators:

G. Michael Besser; Aart van der Lely; Shlomo Melmed; Mary Lee Vance; David Clemmons; Ariel Barkan, Keith Friend, Gudmundur Johannson, Anne Klibanski, Larry Phillips, Paul Stewart, Christian Strasburger, Peter Trainer, David Cook, Pamela Freda, David Kleinberg.

Study centers:

St. Bartholomew's Hospital, London, England; Erasmus University, Rotterdam, The Netherlands; Cedars-Sinai Hospital, Los Angeles, CA; University of Virginia, Charlottesville, VA; University of North Carolina, Chapel Hill, NC; University of Michigan, Ann Arbor, MI; MD Anderson Cancer Center, Houston, TX; Sahlgrenska University Hospital, Goteborg, Sweden; Massachusetts General Hospital, Boston, MA; Emory University School of Medicine, Atlanta, GA; Queen Elizabeth Hospital, Birmingham, England; Klinikum Innenstadt der Ludwig-Maximilians-University, Munich, Germany; Christie Hospital, Manchester, England; Oregon Health Sciences University, Portland, OR; Columbia Presbyterian Medical Center, New York, NY; Bellevue Hospital, New York, NY.

Publication:

There are no publications based on this study.

Study period: 27 October 1998 to 30 April 1999 (for data included in this report); the study is ongoing.	Clinical phase: III

Objectives:

To assess the long-term safety, tolerability, and efficacy of B2036-PEG therapy in subjects with acromegaly.

Design:

This investigation is a multicenter, open-label, dose-titration extension study to evaluate the safety, tolerability, and efficacy of B2036-PEG (5-30 mg/day) therapy in subjects with acromegaly. The study was designed with a dose-titration phase (to normalize IGF-I concentrations) and a maintenance phase to mimic eventual clinical practice.

Methodology:

At Week 0 subjects were screened for study eligibility, underwent safety and efficacy assessments, and entered into an 8-week dose-titration cycle. Eligible subjects who had received placebo in Study SEN-3614 (and those who had not participated in SEN-3614) were administered a blinded bolus loading dose of study drug (80 mg) at the first open-label visit (Week 0). Starting the day after the bolus loading dose, subjects were to self-administer study drug daily via subcutaneous injection. The initial dose for all subjects was 10 mg/day. At Week 8, the dose could be titrated up or down in 5-mg/day increments based on IGF-I concentrations collected at Week 6. (No changes in dose levels could be made during the 8-week cycle except for safety reasons.) The cycle was repeated until IGF-I concentrations decreased to within the normal range for age-adjusted controls, or until the minimum or maximum dose level was reached. Subjects then entered the maintenance phase of the study during which daily drug administration continued at that dose level, and returned to the study site every 4 weeks thereafter for a repeat of all safety and efficacy assessments.

Number of subjects: Subjects entered - 101 Subjects completed - 0 (Ongoing) Subjects Active - 97

Diagnosis and criteria for inclusion:

Male or female (not pregnant or lactating) volunteers 18 years of age or older with a diagnosis of acromegaly who successfully completed Study SEN-3614 or who were allowed to participate by special permission of the sponsor.

Test product, dose and mode of administration, batch no:

B2036-PEG was provided as a lyophilized powder, which was prepared as a solution for subcutaneous injection (10, 15, or 20 mg/mL) by reconstituting with sterile water for injection. B2036-PEG was administered as a single bolus loading dose of 80 mg (in those who received placebo in Study SEN-3614) and then as a single daily dose of 10 mg/day for 8 weeks and then titrated up or down in 5 mg/day increments for 8-week cycles (minimum 5 mg/day, maximum 30 mg/day). Lot numbers used in this study to date are: 423553A, 003007, 413303A, 452653A, 500703A, 413353A, 481753A, 442253A, 472153A, 523153A.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: Pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

An Open-Label Extension Study of B2036-PEG in the Treatment of Acromegaly (Interim Report, Data up to 30 April 1999)

Duration of treatment:

Ongoing, for an indeterminate period of time

Reference therapy, dose and mode of administration, batch no:

Placebo, a visually matching test product, was administered as a blinded single bolus loading dose via subcutaneous injections in those subjects who received B2036-PEG in Study SEN-3614. The placebo lot number used in this study was 003628.

Criteria for evaluation:

Safety evaluations – Clinical laboratory tests, pituitary MRI, physical examinations, vital signs, adverse events, GH and B2036-PEG antibodies.

Efficacy evaluations – Percent suppression in IGF-I concentrations from baseline of Study SEN-3614 (primary); normalization of IGF-I, reduction in ALS, IGFBP-3, and free IGF-I, acromegaly severity score, and ring size (secondary).

Summary:

Safety - B2036-PEG has been generally well-tolerated among study subjects. Overall, the most frequently reported adverse events were flu syndrome, infection, accidental injury, pain, somnolence, and flatulence. Most events were mild to moderate in intensity and not considered to be related to the study medication. Five subjects receiving B2036-PEG 10 mg/day experienced serious adverse events; none were considered to be related to study medication. One subject (#1707) discontinued because of an adverse event of severe headaches, which was considered probably related to the study medication.

No clinically significant trends in change-from-baseline values were noted for any laboratory parameter. Randomly drawn serum GH rose in a fashion that coincided with the magnitude and timing of the decrease in serum IGF-I. No clinically significant trends over time were observed with respect to vital signs, weight, or pituitary tumor volumes. None of the subjects developed clinically significant GH antibodies during treatment.

Efficacy - *No formal efficacy conclusions can be drawn from the limited amount of interim data from this ongoing safety study.* Potentially clinically important effects in reducing IGF-I concentrations were noted. Mean pretreatment IGF-I concentrations (705.4 ng/mL) decreased 24% at the end of double-blind treatment in SEN-3614 and 44% at the data cutoff point of SEN-3615. A total of 66 subjects (70.2%) had IGF-I concentrations that normalized by the time of data cutoff. Most subjects' (57.4%) IGF-I concentrations first became normal at the initial B2036-PEG dose level of 10 mg/day. Treatment with B2036-PEG also slightly improved the clinical indices of acromegaly.

Conclusions:

The interim results of this open-label follow-up study further support the safety and efficacy of B2306-PEG in subjects with acromegaly. Dose titration is a safe and reliable approach to finding the appropriate individualized B2036-PEG dose needed to normalize IGF-I concentrations in acromegalic subjects.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

Absolute Bioavailability and Pharmacokinetics of Subcutaneously-Administered B2036-PEG

Investigators:

Study center:

Publication:

None

Study period: April 6, 1999 to June 9, 1999	Clinical phase: I

Objectives:

To determine the absolute bioavailability of subcutaneously administered B2036-PEG and to profile the pharmacokinetics of the compound after intravenous and subcutaneous administration.

Design:

A single-dose crossover study in healthy male and female volunteers. In study period 1, half of the subjects of each gender were randomly assigned to receive 20 mg B2036-PEG subcutaneously, and the other half received 10 mg B2036-PEG intravenously. There was then a 4-week washout period. In study period 2, the opposite treatment was administered to each subject. The safety of B2036-PEG was determined on the basis of physical examinations, laboratory tests, and reported adverse events on Days 1-6, 8, 10, 12, 14, and 16 of each study period.

Methodology:

Subjects entered the facility at 8 p.m. the day before administration of the medication for each study period, and remained in the facility until after the 96-hr. post-dosing urine collection on Day 4. Clinical chemistry, hematology, urinalysis samples were collected on Days 0, 5, 10, and 16. Blood samples were collected for measurement of B2036-PEG concentrations as follows: for subjects receiving IV drug - pre-dose, during the infusion (at 0.5, 1, 2, 3, 4, 5, 5.75, 5.95, 6.0 hr), and at 6.033, 6.083, 6.17, 6.25, 6.5, 6.75, 7, 8, 9, 12, and 15 hr after the start of the infusion, and once daily on Days 1-6, 8, 10, 12, 14, and 16; for subjects receiving SC drug - pre-dose, and at 0.25, 0.5, 1, 3, 6, 9, and 12 hr after treatment, and once daily on Days 1-6, 8, 10, 12, 14, and 16. Blood samples were collected for IGF-I and GH concentration determination pre-dose, on Days 1-4, 8, 10, 12, 14, and 16. B2036-PEG antibodies and GH antibodies blood sample collection: pre-dose and on Day 16. Urine samples were collected from all subjects for the determination of B2036-PEG concentrations over the following periods: 0-12 hr, 12-24 hr, 24-48 hr, 48-72 hr, and 72-96 hr post-dose.

Number of subjects: Subjects entered – 12 (6 male, 6 female) Subjects completed - 12

Diagnosis and criteria for inclusion:

Male and female subjects, 18 to 40 years of age, with all physical and biochemical parameters within normal limits.

Test product, dose and mode of administration, batch no:

B2036-PEG was prepared as a solution for SC injection with sterile distilled water or intravenous infusion with 5% dextrose in water. The dosing solution was administered as a single bolus dose (SC injection, 20 mg dose) or was infused over a 6-hr. period (intravenous infusion, 10 mg dose); lot number 372753A.

Duration of treatment:

One day (single SC dose or 6-hr. IV infusion).

Reference therapy, dose and mode of administration, batch no:

None.

Criteria for evaluation:

Pharmacokinetic and pharmacodynamic evaluations – Pharmacokinetics parameters, endocrine hormone concentrations (GH, IGF-I, free IGF-I, and free IGF-I %).
Safety evaluations – Physical examinations, vital signs, clinical laboratory tests (chemistry, hematology, urinalysis), B2036-PEG antibodies, growth hormone antibodies, adverse events.

NAME OF COMPANY: Sensus Drug Development Corporation NAME OF FINISHED PRODUCT: pegvisomant NAME OF ACTIVE INGREDIENT(S): B2036-PEG	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title:

Absolute Bioavailability and Pharmacokinetics of Subcutaneously-Administered B2036-PEG

Summary:

Safety

B2036-PEG administered as single doses of 10 mg intravenous infusion or 20 mg subcutaneously was well tolerated. Few of the adverse events reported during the study were considered treatment-related; all adverse events were mild in severity and resolved without significant sequelae. No serious adverse events were reported, and no subjects discontinued study participation due to adverse events. No clinically significant chemistry, hematology, or urinalysis findings were noted during study treatment. No positive antibody test results were seen for growth hormone.

Pharmacokinetics and Pharmacodynamics

The extent of absorption of subcutaneously administered B2036-PEG based on dose-normalized AUC_T and AUC_I was 54.4% and 56.7%, respectively. Bioavailability of B2036-PEG when dosed via SC route was 56.7%. The dose-normalized C_{max} for subcutaneously administered B2036-PEG was also lower compared to intravenously administered B2036-PEG, indicating a lower rate of absorption. The C_{max} for subcutaneously administered B2036-PEG was 1387 ng/mL, and the ratio of the dose-normalized C_{max} and the ite-associated 90% confidence interval was 16% (10% - 23%). There appeared to be a difference between males and females in the mean C_{max} values of B2036-PEG after SC drug administration (1825 ng/mL vs. 950 ng/mL for male vs. female subjects, respectively). However, the large variability observed and the limited number of subjects preclude any conclusions based on these differences. Elimination half-lives were similar, with ratio of SC to IV treatments being 1.0028. The half-life for B2036-PEG was approximately 136 hours for either SC or IV dosing routes. However, the mean half-life for B2036-PEG administered via SC route was 108 hr and 169 hr for male and female subjects, respectively.

Subcutaneous treatment produced similar serum clearance, a similar fraction excreted in the urine, and a similar renal clearance when compared to IV treatment. The fraction excreted in the urine was less than 0.01 for both routes of administration and indicates that urinary excretion is probably not the major route of elimination of B2036-PEG. The B2036-PEG data for all subjects treated with IV dosing appear to have two-compartmental characteristics. The data from SC dosing appeared to be one-compartmental for some subjects and two-compartmental for others.

For both routes of B2036-PEG administration, the clinically significant maximal increase in IGF-I occurred by Day 4 (15% increase for IV dosing, 19% increase for SC dosing), with IGF-I concentrations decreasing to below pre-treatment values by Day 8. By Day 16, both SC and IV dosing group IGF-I concentrations had returned to baseline values. Due to the small subject populations, interpretation of these data is not possible.

Conclusions:

B2036-PEG, when administered as a single IV infusion dose of 10 mg or a single SC dose of 20 mg, was well tolerated and considered safe. B2036-PEG half-life and elimination rate constants were similar for the two dosing regimens. Concentrations of B2036-PEG achieved were inadequate to lower serum IGF-I values in normal volunteers. By-gender analysis of the IGF-I findings showed little difference between male and female subjects when evaluated as percent change from baseline in serum IGF-I concentration.

study 3623

Subject No.	Age	Sex	Height (cm)	Weight (kg)
All Subjects Mean ± SEM	29.3 ± 1.5		173.9 ± 2.5	64.7 ± 3.4
Female Subjects Mean ± SEM	26.7 ± 1.4		167.8 ± 2.8	56.5 ± 2.1
Male Subjects Mean ± SEM	31.8 ± 2.3		180.1 ± 2.4	72.8 ± 4.3

[a] S = small frame, M = medium frame.

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Appendix 3. Assay performance

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Appendix 4. Formulation

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Appendix 5. Pharmacometrics Consult and Data

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Division of Pharmaceutical Evaluation II

NDA:	**21-106**
Brand® Name	**Somavert™ Injection**
Generic	**Pegvisomant**
Submission Date:	**December 22, 2000**
Sponsor:	**Sensus Drug Development Corp.**
Consult:	**Population PK, PK-PD**
Pharmacometrics Scientist:	**Sam H. Haidar, R.Ph., Ph.D.**

Background

NDA 21-106 for pegvisomant (Somavert™) injection was submitted by Sensus Drug Development on December 22, 2000. The proposed indication for Somavert™ is the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy or for whom surgery or radiation therapy is not appropriate. The recommended daily dose is 10 mg administered subcutaneously following an 80 mg loading dose. According to the sponsor, the dose may be adjusted up or down every six to eight weeks in order to maintain the serum IGF-I (Insulin-like growth factor I) concentration within the age-adjusted normal range and alleviate the signs and symptoms of acromegaly.

According to the sponsor, "SOMAVERT™ (pegvisomant for injection), is an analog of human growth hormone that has been genetically engineered to be a growth hormone receptor antagonist. SOMAVERT™ consists of a protein containing 191 amino acid residues, to which several polyethylene glycol molecular weight 5000 polymers have been covalently bound in order to increase the size and decrease the clearance rate of the molecule. The amino acid sequence of the SOMAVERT™ protein is the same as that for human growth hormone, except that 9 residues have been mutated so that binding to the growth hormone receptor occurs, but growth hormone signal transduction is inhibited."

This NDA submission included population PK and PD studies, which were the subject of this pharmacometrics consult.

Study SEN-3614 evaluated the pharmacokinetics and pharmacokinetic-pharmacodynamic (PK-PD) relationship of pegvisomant (B2036-PEG) and IGF-I in patients. The influence of patient covariates on the PK and PD parameters was also investigated.

Details of the study are given below.

Study SEN-3614

Title: Pharmacokinetic-Pharmacodynamic analysis of B2036-PEG: Analysis of SEN-3614, a randomized multicenter double-blind placebo controlled study of B2036-PEG in the treatment of acromegaly.

Objectives: The goals of this study were:

1) to characterize the PK-PD of B2036-PEG, and
2) to identify patient characteristics that contribute to variability in B2036-PEG PK-PD

Methods:
This was a multicenter, randomized, placebo controlled, double-blind study. One hundred twelve adult acromegalic subjects were randomized to receive 10, 15, 20 mg of B2036-PEG per day or placebo. Doses were administered daily by subcutaneous injection for a period of 12 weeks. According to the sponsor, all subjects randomized to receive placebo received a placebo loading dose while all subjects randomized to receive B2036-PEG (all dose levels) were intended to receive a bolus loading dose of 80 mg B2036-PEG. However, a total of 24 subjects (11 subjects in the 10 mg/day group and 13
subjects in the 15 mg/day group) did not receive the correct loading dose. Instead, these subjects received four times their assigned daily dose, i.e., 40 mg and 60 mg of B2036-PEG in the 10 mg/day and 15 mg/day groups, respectively.

Sampling:
Plasma levels for the determination of concentrations and IGF-I levels were collected pretreatment (baseline), and at 2, 4, 8, and 12 weeks of treatment. B2036-PEG concentrations were measured using a radioimmunoassay (RIA).

Pharmacokinetics:
Pharmacokinetic analysis was performed using nonlinear mixed effect modeling and first order maximum likelihood in NONMEM. Because the assay was not 100% specific for the drug (interference by an endogenous substance), modeling of the placebo dose was also performed. A model was developed to describe the disposition of B2036-PEG using data from an intensively sampled bioavailability study (SEN-3623). Mixed effects modeling was used to simultaneously fit serum concentration vs. time data collected after a single 10 mg intravenous infusion and after a single 20 mg subcutaneous dose. The model was then applied to Study SEN-3614. Covariates tested include the following: age, gender, race, birth control method, baseline IGF-I stratification, baseline IGF-I concentration, baseline GH concentration, baseline concentration of endogenous cross-reactant, presence of diabetes, height, weight, body surface area, body mass index, blood chemistries (including AST, ALT, alkaline phosphatase, bilirubin and serum creatinine) and baseline overall health status obtained from the health status survey.

Pharmacodynamics:
A PK-PD model was constructed to describe the pharmacological effect of B2036-PEG on the inhibition of the

apparent production rate of circulating IGF-I. The drug is assumed to exert its effect by an indirect mechanism [Dayneka et al., 1993; Sun et al., 1999]. The general form of the model is given below:

$$\frac{dC_{IGF-1}}{dt}i = k_{in_i} \cdot \left(1 - \frac{C_{B2036-PEG_{ij}}}{C_{50,B2036-PEG_i} + C_{B2036-PEG_{ij}}}\right) - k_{out_i} \cdot C_{IGF-1_{ij}}$$

in which $C_{B2036-PEG}$ represents the jth serum B2036-PEG concentration for the ith subject, C_{IGF-I} is the serum IGF-I concentration, $C_{50,B2036-PEG}$ drug concentration causing 50% inhibition. The pharmacodynamic parameters to be estimated are k_{in}, the apparent rate of IGF-I production, and k_{out}, the first order rate of elimination of IGF-I in the circulation, and $C_{50,B2036-PEG}$.

Results:

Modeling of the placebo dose provided a mean concentration of the endogenous cross-reactant of 32.5 ng/mL (CV = 59.9%). Levels did not fluctuate to a significant extent over the course of the study. Figure 1 provides individual as well as mean profiles of the endogenous cross-reactant.

For analysis of the active dose, the sponsor applied a 2-compartment model, which was developed previously using data rich studies, to the sparse data collected in study SEN-3614. Additionally, according to the sponsor, the 2-compartment was collapsed into a one-compartment model without a significant effect on the parameter estimates. Population PK parameters are listed in Table I.

Testing of different covariates suggested that weight, dose, and concomitant use of lipid lowering drugs had a significant effect on clearance. The effect of dose was decreased clearance with higher doses, suggesting non-linear PK. Weight was inversely related to clearance. Patients who weighed more tended to have lower serum levels of B2036-PEG compared to those with a lower weight (Figure 2). As for the effect of lipid lowering drugs (LLD), clearance was decreased by about 30%, although the number of patients on LLD was small (6 out of 80 subjects).

The final model of the PK-PD analysis indicated that baseline values of growth hormone (GH) as well as concomitant use of opioids had a significant effect on response. Subjects with a high baseline value of GH, or on concomitant opioid therapy would require higher levels of B2036-PEG to achieve the same effect as those with a lower GH baseline or no concomitant opioid therapy. This was reflected by higher $C_{50,B2036}$ values. The PD parameters are listed in Table II.

The PD model was used to evaluate the effect of different loading doses on response, through the use of simulations. Results are listed in Table III.

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Table I. Population PK parameters for Study SEN-3614.

Parameter*	Mean	%CV
CL (mL/h) for a subject of average weight (94 kg) on 15 mg dose	32.3	8.0
CL (mL/h) for a subject of average weight on 15 mg dose and taking lipid lowering drugs	21.4	24.2
Change in CL (mL/h) for each kg that a subject's weight differs from the average weight	0.51	14.8
Change in CL (mL/h) for each mg increment in dose	-0.81	55.1
V (L)	7.0	12.8
Baseline concentration of endogenous cross-reactant (ng/mL)	42.2	4.2
Ka (h^{-1})	0.0184	7.2
F	0.639	7.1
Absorption Lag-time (h)	0.404	22.1
Inter-subject variability (%CV) in		
CL	64.0	23.7
V	78.2	44.5
Baseline concentration of endogenous cross-reactant	4.2	29.3
Ka	29.5	37.2
F	22.7	49.2
Absorption Lag-time	30.0	89.2
Residual variability		
%CV	20.4	28.3

* CL = apparent systemic clearance, V = apparent volume of the distribution, Ka = absorption rate constant, F = absolute bioavailability, %CV = coefficient of variation (expressed as a percentage).

Table II. PK-PD parameter estimates with and without concomitant use of opioids.

	Model Not Including Concomitant Opioids	Model Including Concomitant Opioids	
Parameter*	Mean	Mean	Coefficient of Variation (%)
k_{in}/k_{out}	650.3	652.0	–
$C_{50,B2036\text{-}PEG}$ (ng/mL) in subjects not taking opioids	14600	13400	7.8
$C_{50,B2036\text{-}PEG}$ (ng/mL) in subjects taking opioids	–	24100	29.8
Change in $C_{50,B2036\text{-}PEG}$ (ng/mL) per ng/mL of endogenous cross-reactant greater than the average baseline concentration (9.08 ng/mL)	324	218	40.9
Inter-subject variability (%CV) in			
k_{in}	33.9	34.0	16.6
$C_{50,B2036\text{-}PEG}$	45.8	43.5	25.3
Residual variability			
%CV	17.8	17.7	12.5

* k_{in} = apparent rate of IGF-I production. k_{out} = the rate of elimination of IGF-I. $C_{50,B2036\text{-}PEG}$ = the serum B2036-PEG concentration that produces 50% of the maximum effect.

Table III. The effect of different loading doses on response (IGF-I), using simulations.

Dose	LD	Ratio of IGF-I_4 to IGF-I_3*	Ratio of IGF-I_5 to IGF-I_3*	Ratio of IGF-I_7 to IGF-I_3*
10	0	0.73	0.66	0.65
15	0	0.62	0.54	0.52
20	0	0.54	0.44	0.42
10	40	0.69	0.65	0.65
15	40	0.59	0.54	0.52
20	40	0.51	0.44	0.42
10	60	0.67	0.65	0.65
15	60	0.58	0.53	0.52
20	60	0.50	0.44	0.42
10	80	0.65	0.65	0.65
15	80	0.56	0.53	0.52
20	80	0.49	0.43	0.42

* IGF-I_3 = serum IGF-I concentration at the pretreatment visit (visit 3), IGF-I_4 = serum IGF-I concentration at visit 4, IGF-I_5 = serum IGF-I concentration at visit 5, IGF-I_7 = serum IGF-I concentration at visit 7.

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Figure 2. Effect of weight on serum concentration profiles of B2036-PEG. ( ) is average body wt, (Δ) is above average, and (+) is below average weight. In this study, average weight is 91 kg.

Reviewer's Comments:

1. Based on the results of simulations, it appears that a loading dose of 40 mg achieves nearly the same effect at two weeks of treatment as the proposed loading dose of 80 mg. Based on the results of a Phase III clinical trial and following a discussion with Dr. Robert Shore (HFD-870) and Dr. Robert Perlstein (HFD-510), it was decided that a loading dose of 40 mg would be appropriate. This would reduce drug exposure without significantly altering efficacy.

2. In addition to weight, concomitant use of lipid-altering drugs and opioids had an effect on the PK and PD of B2036-PEG, respectively. It is recommended that information about the possible effect of concomitant use of opioids or lipid altering drugs be included in the Drug Interaction section of the labeling. This information may be helpful to clinicians, although B2036-PEG is to be titrated to the appropriate efficacy endpoint in each patient.

3. B2036-PEG exhibited non-linear PK over the dose range studied.

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

cc:

HFD-870 (Malinowski, Shore, Ahn, Haidar)
HFD-510 (Perlstein, King)
HFD-850 (Lee P.)
CDR

Data from SEN-3614:

Table 1. Covariates Tested in the Population Analyses of Active Doses of B2036-PEG in SEN-3614

Covariate	Mean ± SEM or Count			
Dose Group	10 mg	15 mg	20 mg	Total
Number per group	26	26	28	80
Age (y)	46. 9 ± 2.4	46.0 ± 2.9	47.8 ± 2.5	46.9 ± 1.5
Gender (M:F)	15:11	14:12	15:13	44:36
Weight (kg)	93.6 ± 3.8	93.5 ± 3.5	93.6 ± 4.1	93.6 ± 2.2
Body Surface Area (m^2)*	2.01 ± 0.04	1.99 ± 0.05	2.04 ± 0.06	2.01 ± 0.03
Body Mass Index (kg/m^2)**	34.1 ± 1.5	35.1 ± 1.6	32.6 ± 1.6	33.9 ± 0.9
Height (cm)	166.5 ± 2.3	164.5 ± 2.9	170.1 ± 3.0	167.1 ± 1.6
Baseline IGF-I (ng/mL)	626.7 ± 49.2	648.8 ± 57.6	731.6 ± 38.7	670.6 ± 28.2
Baseline IGF-I Strata (low:high)	15:11	16:10	13:15	44:36
Baseline GH concentration (ng/mL)	7.4 ± 1.6	11.6 ± 4.6	8.2 ± 2.1	9.1 ± 1.7
GH concentration (ng/mL) over period of study	11.9 ± 1.4	22.0 ± 2.5	21.5 ± 2.2	18.5 ± 1.2
Race				
Caucasian	22	22	22	66
African American	0	2	1	3
Hispanic	3	2	3	8
Other	0	0	1	1
Asian	1	0	1	2

* Body Surface Area = $71.84 \cdot (\text{Weight})^{0.425} \cdot (\text{Height})^{0.725}$

** Body Mass Index = $\text{Weight}/(\text{Height})^2$

Table 1 continued.

Covariate	Mean ± SEM or Count			
Dose Group	10 mg	15 mg	20 mg	Total
Diabetes Mellitus				
Absence	19	21	21	61
Presence	6	5	6	17
Type 1	1	0	0	1
Type 2 – Active	5	4	6	15
Type 2 – Not Active	0	1	0	1
Diabetes Insipidus	1	0	1	2
Baseline Overall Health Status				
0 = worst possible	1	0	0	1
1	0	0	3	3
2	3	3	2	8
3	2	2	2	6
4	3	4	3	10
5	5	6	7	18
6	3	4	4	11
7	3	2	1	6
8	2	1	3	6
9	4	2	0	6
10 = best possible	0	1	3	4
Previous Treatment				
Surgery	22	22	23	67
Radiation	11	14	15	40
Gamma-Knife	0	3	1	4
Sandostatin	15	21	21	57
Bromocriptine	15	9	14	38

Table 1 continued.

Covariate	Mean ± SEM or Count			
Dose Group	10 mg	15 mg	20 mg	Total
Birth Control (Females Only)				
Medication	2	0	0	2
Barrier	2	2	1	5
Post-Menopause	1	5	5	11
Surgically Sterile	3	0	2	5
Sterile Secondary to Surgery/ Radiation	1	3	1	5
Other	2	2	4	8
Abstinence, Husband vasectomy	2	1	2	5
Other hormone deficiency (hysterectomy, ammenorhea)	0	0	3	3
Blood Chemistries				
Baseline Bilirubin (µmol/L)	11.54 ± 1.40	8.91 ± 0.66	10.58 ± 0.96	10.35 ± 0.61
Bilirubin (µmol/L) over period of study	10.46 ± 0.57	8.04 ± 0.35	9.98 ± 0.47	9.53 ± 0.28
Baseline Serum Creatinine (µmol/L)	78.58 ± 5.80	73.04 ± 4.15	74.50 ± 3.57	75.35 ± 2.61
Serum Creatinine (µmol/L) over period of study	80.54 ± 2.75	73.54 ± 2.12	76.42 ± 1.92	76.87 ± 1.32
Baseline Alkaline Phosphatase (U/L)	88.04 ± 8.47	84.08 ± 6.95	78.68 ± 6.16	83.48 ± 4.13
Alkaline Phosphatase (U/L) over period of study	92.93 ± 4.44	86.32 ± 3.71	80.25 ± 2.03	86.34 ± 2.02
Baseline ALT (U/L)	19.62 ± 1.42	25.23 ± 3.98	32.14 ± 12.31	25.83 ± 4.51
ALT (U/L) over period of study	33.39± 3.03	28.79 ± 5.53	24.16 ± 1.03	28.65 ± 2.04
Baseline AST (U/L)	20.62 ±1.38	24.00 ± 2.54	20.64 ± 1.66	21.70 ± 1.10
AST (U/L) over period of study	27.01 ± 1.97	23.63 ± 2.72	20.97 ± 0.49	23.79 ± 1.09

Table 1 continued.

Covariate	Count
Concomitant Drug Therapy	
Any hormone	43
Glucocorticoids	29
Thyroxine	27
Testosterone	15
Estrogen/Progestagen	11
Oral hypoglycemic drugs for diabetes	6
Insulin	6
Liver enzyme inhibitors	18
Lipid lowering agents	6
Antihypertensives	25
Calcium channel blockers	8
Angiotensin converting enzyme inhibitors	13
α- or β-blockers	15
Diuretics	15
Analgesics	13
Nonsteroidal anti-inflammatory drugs	15
Opioids	9
Ulcer treatments	15
Serotonin uptake inhibitors	8
Other antidepressants	8
Benzodiazepines	7
Oral antihistamines	4
Vitamins	12
Minerals	11

Table 3. Summary of Serum B2036-PEG Concentrations in SEN-3614

Group	n	Visit	Average	SEM
Placebo*	30	3	30.13	3.94
		4	32.20	3.96
		5	31.21	5.70
		6	30.81	5.63
		7	30.05	5.49
10	26	3	36.55	7.66
		4	6509.69	873.76
		5	6842.28	1130.28
		6	7047.43	1370.13
		7	6595.61	1333.02
15	24	3	52.10	9.91
		4	10480.42	1644.57
		5	14369.42	1881.84
		6	16868.80	2402.93
		7	16342.83	2212.62
20	27	3	39.67	7.53
		4	18354.30	2053.69
		5	21473.74	2109.88
		6	25601.06	2819.44
		7	27207.18	3056.05

* excludes outlier (#1504)

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/s/

Robert Shore
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Section 6 not complete. Need for moe info to satisfy 21CFR320.
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