KING

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: June 4, 1999

Mike:
Minutes of 5/5/99 following...

Thanks,
-Crystal

TO:

Name Mike Bernstein, M.P.H.

Fax No. 512-487-2049

Phone No. 512-487-2018

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Location Sensus Drug Development Corporation

Pages (including this cover sheet): Six (6)

IND —
DIV File

ORIGINAL

Meeting Minutes

KING

IND # and Drug Name:	—
Meeting Date:	**March 17, 1999**
Time:	**9 am**
Location:	**PKLN 14B-56**
Indication:	**Acromegaly**
Sponsor:	**Sensus Drug Development Corp.**
Type of Meeting:	**Informational**
Project Manager:	Crystal King
FDA Participants:	Robert Perlstein, M.D. Saul Malozowski, M.D.
Sponsor Participants:	Bob Davis, Pharm.D. Mike Bernstein, M.P.H.

Meeting Objective:

Informational, informal meeting to provide an overview of the IND to Dr. Perlstein, new medical officer asssigned. Provide a recap and progression of the various IND studies.

Agreements: n/a

Unresolved Issues: n/a

Action Items: The division will consider a teleconference instead of the planned face-to-face pre-NDA meeting on 4/21. The sponsor has no new information to present; all present believed that this format would adequately provide for discussion of the electronic NDA submission and format. Any other issues by disciplines could be addressed at that time. Crystal King will notify Mike Bernstein.

Prepared by: /S/ , Regulatory Project Manager
Crystal King, P.D., M.G.A. date

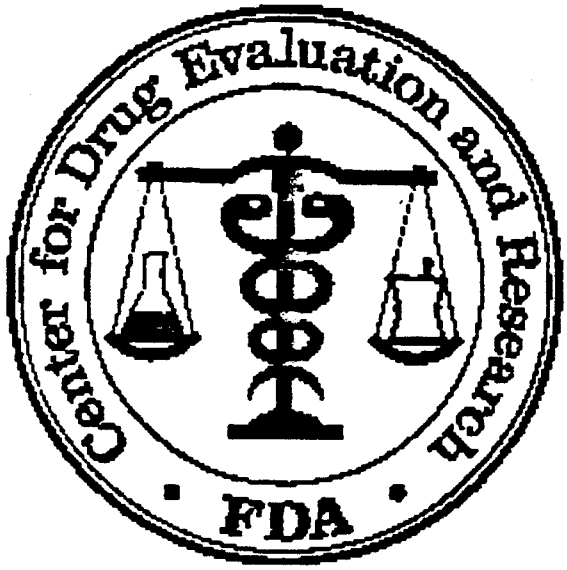
Concurrence: /S/ 3/19/99 , Medical Officer
Robert Perlstein, M.D. date

Concurrence: /S/ 3/20/99 , Team Leader (Acting)
Saul Malozowski, M.D., Ph.D.

cc: IND [redacted]
HFD-510: CKing/RPerlstein/SMalozowski

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: March 22, 1999



Mike:
Minutes of 3/17/99 following...

Thanks,
-Crystal

TO:

Name Mike Bernstein, M.P.H.

Fax No. 512-487-2049

Phone No. 512-487-2018

Location Sensus Drug Development Corporation

FROM:

Name Crystal King, P.D., M.G.A.

Fax No. 301-443-9282

Phone No. 301-827-6423

Pages (including this cover sheet): Two (2)

Meeting Minutes

IND # and Drug Name:	IND —— Trovert
Meeting Date:	December 8, 1998
Time:	2:00 pm
Location:	Parklawn Conference Room "A"
Indication:	Acromegaly
Sponsor:	Sensus Drug Development Corp.
Type of Meeting:	CMC
Meeting Facilitator:	William Berlin, Ph.D., Chemistry Reviewer
Sponsor Participant Lead:	Mike Bernstein, M.P.H., Senior Director, Regulatory Affairs
Regulatory Project Manager:	Crystal King, P.D., M.G.A.
Sponsor Participants:	William Bennett, Ph.D., Senior VP, Research Chief Scientific Officer
	Edward Calamai, Ph.D., Senior VP, Operations
	Nicholas Vrolilk, Ph.D., Project Manager

Meeting Objective:

To reach agreement on the proposed CMC development strategy for B2036-PEG in the treatment of acromegaly. To identify any additional information necessary to support an NDA.

Background:

Trovert is a growth hormone antagonist being developed for the treatment of adults with acromegaly. The original IND was submitted on March 18, 1997. An EOP2 meeting was held on July 1, 1998. Anticipated NDA submission is third quarter, 1999.

DISCUSSION OF MANUFACTURING PROCESS CHANGES AND SUPPORTING DATA

Agenda Item 1: Are the presented data and studies in progress adequate to demonstrate drug comparability between the current and previous manufacturing processes?

Response: An exhaustive review has not been performed; however, the package appears acceptable. Note that Process Validation data are very important in comparability analysis.

Comments: Dr. Berlin noted that it is important to revalidate what each step removes.

Action Items: None.

Trovert, IND —

12/0898

PROPOSED TESTING AND SPECIFICATIONS

Agenda Item 2: Does the division concur with the proposed testing and specifications for bulk drug substance and final product?

Response: Although a comprehensive pre-review of the material has not been performed, the following comments are offered: (1) bioassay is needed; (2) limits for individual product-related substance and impurities are needed.

Comments: Dr. Berlin noted that all standard results be included, even if not fully characterized. Limits need to be identified. There is an ICH document on specifications. Dr. Berlin indicated that the sponsor's specification limits should be for shelf life and are different from release specifications.

Action Items: **Sensus** will provide current chromatograms and a package indicating the current testing to Dr. Berlin.

Agenda Item 3: Is the company's strategy for quantitating process residuals, and validating their removal, including E. coli host cell proteins, suitable for showing that the process is free from contaminants?

Response: E. coli proteins assay should be kept on spec sheet until sufficient manufacturing history is obtained.

Comments: Dr. Berlin stated that the final specification on the final bulk product should include a footnote as to where it was run upstream. FDA usually asks for data to demonstrate broad specificity of the antibody. Limited detection for *E. coli* should be demonstrated. At least one process sample should be tested to see antigens disappear. The assay need to detect to 1 or 2 ppm.

Action Items: **Dr. Berlin** will check on the current level for *E. coli* detection.

STABILITY

Agenda Item 4: Does the Division concur that the stability data presented is adequate to support storage of clinical supplies (final product vials) at room temperature for 1 year?

Response: It appears to be adequate; however, bioassay at infrequent intervals needs to be performed.

Action Items: None.

Agenda Item 5: Are the company's plans for generating additional stability data adequate to support a label claim of room temperature shelf life for up to 2 years?

Response: The plans appear to be adequate. Again, bioassay at infrequent intervals should be performed.

Comments: Dr. Berlin noted that the Agency is getting stricter on shelf life extensions, so that as much as possible should be obtained with the initial NDA.

Action Items: **Dr. Calamai** will send in supportive stability data for the final product.

Trovert, IND ———

12/0898

PROCESS AND ANALYTICAL VALIDATION PLAN

Agenda Item 6: Are the plans for process and analytical validation, along with the proposed scheduled conformance lots, appropriate to support an NDA filing?

Response: A complete review of the plans has not been performed; nevertheless, we have several comments.

- (Sec. 6.2) Bioburden control
- (Sec. 6.3) Depending on assay conditions, USP test may need validation.
- (Sec. 6.4) What are the plans to include in original filing?

Comments: Dr. Bennett indicated that the diluent has been recently changed. Re-validation will need to be performed to demonstrate continued performance under the changes. Dr. Calamai noted that three qualification lots would be run with filing or inspection and then submitted as a supplement. Dr. Berlin stated that the first three lots should be incuded with the NDA package. (*Note: refer to ICH Q5c Stability Guidance.)

Action Items: **Dr. Berlin** will check out the timetable for the inspection.

PROPOSED CMC INDEX FOR NDA

Agenda Item 7: Is the proposed CMC index acceptable for the NDA?

Response: The proposed index appears acceptable. See also the guidance, "Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-derived Product or a Monoclonal Antibody Product for in vivo Use," dated August, 1996 (CBER website).

Action Items: None.

ADDITIONAL DISCUSSION ITEMS

- Dr. Berlin indicated that if Sterile Water for Injection was provided in the drug package the DMF must be referenced.
- Dr. Berlin suggested that Sensus consider a modified assay to measure activity at two or three levels. Alternatively, an assay to measure cAMP rather than cell growth inhibition could be developed. He stated that the use of a qualified, validated receptor binding assay was not adequate—more than affinity must be considered. This is FDA policy, not CDER policy.

Trovert, IND —

12/0898

Prepared by: /S/ 12/22/98
Crystal King, P.D., M.G.A. Regulatory Project Manager
date

/S/ 12/22/98
Concurrence: _____
William Berlin, Ph.D. Meeting Facilitator
date

Attachments:
A. CMC Meeting Package, #027, submitted 11/9/98
B. Overheads presented by Sensus on 12/8/98
C. Sensus Minutes of Meeting

cc: IND — Original File (With attachments)
HFD-510 Division File (without attachments)
HFD-510: SMoore/WBerlin/CKing (without attachments)

Meeting Minutes

IND# and Drug Name:	IND : ——— Trovert
Meeting Date:	July 1, 1998
Time:	1:00 pm
Location:	Parklawn Conference Room "B"
Indication:	Acromegaly
Sponsor:	Sensus
Type of Meeting:	End of Phase 2
Meeting Facilitator:	G. Alexander Fleming, M.D.
Sponsor Participant Lead:	John A. Scarlett, M.D.
Project Manager:	Crystal King, P.D., M.G.A.
FDA Participants:	Florence Houn, M.D., Deputy Office Director
	Solomon Sobel, M.D., Division Director
	G. Alexander Fleming, M.D., Medical Team Leader
	John Gueriguian, M.D., Medical Officer
	Robert Misbin, M.D., Medical Officer
	Saul Malozowski, M.D., Medical Officer
	Ronald Steigerwalt, Ph.D., Pharmacology Team Leader
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
	Lee-Ping Pian, Ph.D., Statistical Reviewer
	Robert Shore, Pharm.D., Biopharm Reviewer
Sponsor Participants:	John A Scarlett, M.D., CEO
	Robert Davis, Pharm.D, Exec. Vice President
	Mike Bernstein, M.P.H., Senior Director, Regulatory Affairs
	Ken Zib, Director, Project Management
	Jeff Pitts, Senior Director, Development Services
	Michael Thorner, M.B., B.S., D.Sc., F.R.C.P., Chairman, Department of Medicine, University of Virginia Health Science Center

Meeting Objective:

1. To reach agreement with the Division on the proposed development strategy for B2036-PEG in the treatment of acromegaly

2. To evaluate the Phase III plan and protocol

3. To identify any additional information necessary to support an NDA for the use under investigation

Background:

Trovert is a growth hormone antagonist being developed for the treatment of adults with acromegaly. The original IND was submitted on March 18, 1997. The purpose of this meting is to reach agreement on the Phase 3 program and acceptance of the pre-clinical and Phase 2 program.

PRE-CLINICAL

Agenda Item 1: Reproductive Toxicology - Does the Division concur that a Segment II in the rabbit is sufficient to satisfy the requirement for reproductive toxicology?

Agreements: Yes, the rabbit is sufficient.

Unresolved Issues: Additional comments have been received from the Reproductive Toxicology Committee and more will be forthcoming.

Action Items: Dr. Steigerwalt will forward the additional comments when received from the Committee.

Agenda Item 2: Does the Division concur with the hypothesis that decreasing the presence of IGF-I, a tumor mitogen, as does B2036-PEG, should reduce the mitogenic activity of IGF-I and could lead to an anticarcionogenic effect *in vivo*? Sensus to date has shown decreased IGF-I production by tumor cells *in vitro* and will be following up this set of experiments with *in vivo* tumor suppression studies. If B2036-PEG shows anti-tumor properties in human tumor cell line(s), would rodent bioassays for carcinogenicity be required?

Agreements: Additional mechanistic and Phase 4 studies would be expected for acromegaly.

Unresolved Issues: None.

Action Items: The sponsor should provide the following studies with the NDA submission for acromegaly: (1) GH binding experiments outlined at the May 22, 1998, meeting between the sponsor and the pharmacologist, Dr. Steigerwalt; and, (2) the PC-3 tumor cell transplant

study proposed during the June 8, 1998, teleconference. A single carcinogenicity study provided in Phase 4 will cover the acromegaly indication.

Agenda Item 3: Chronic Toxicity Testing - Does the Division concur that a three month study in rats, with daily dosing, satisfies all remaining requirements?

Agreements: A three-month, multiple study is satisfactory.

Unresolved Issues: None.

Action Items: None.

Agenda Item 4: Safety Pharmacology - Does the Division concur that safety pharmacology studies are not required unless we identify a target organ during the chronic rat study?

Agreements: Yes; companion studies to specific rat findings would be appropriate.

Unresolved Issues: None.

Action Items: None.

CLINICAL

Agenda Item 5: Does the Division concur that the single, 100 patient, placebo-controlled study as described in the development plan is adequate to support the NDA?

Agreements: Yes, with the following adjustments:

- Stratify patients only by the baseline IGF-I level and combine centers;
- Monitor patients beyond the control trial period for fall-off of response;
- Monitor patients beyond the control trial period for rising Growth Hormone levels;
- Perform multiple comparisons adjustment of different treatment groups vs. placebo;
- Provide normative data for IGF-I levels by age and sex strata; and,
- Address the durability effect through long-term Phase 4 studies.

Unresolved Issues: Further discussion is warranted regarding effect durability studies.

Action Items: Mr. Bernstein and Ms. King will arrange for a teleconference between Dr. Pian and the Sensus statistician, Suzanne Hackett.

Agenda Item 6: If not, does the Division agree that the Somatostatin-analogue Inadequate Response Study (SIRS), a study in which the effects of B2036-PEG will be studied in patients who have responded inadequately to octreotide acetate, will provide adequate supporting data for the NDA?

Agreements: Not discussed; the answer to Agenda Item 5 was affirmative.

Unresolved Issues: Not applicable.

Action Items: Not applicable.

Agenda Item 7: Does the Division agree that the patient exposure data (40 patient years at the time of NDA submission), plus a Phase IV surveillance study commitment proposed in the development plan, is sufficient to support the NDA?

Agreements: Based upon the explained calculation of patient years data and the fact that there will be close to 100 patient years data—yes.

Unresolved Issues: None.

Action Items: None.

Agenda Item 8: Are the studies proposed adequate to sufficiently characterize the PK of the proposed drug in the treatment of acromegaly?

Agreements: Yes, provided that:

- Multiple-dose kinetics are performed; and,
- Additional PK/PD data are provided.

Unresolved Issues: None.

Action Items: Sensus will submit more information and plans for pharmacokinetic and pharmacodynamic studies to Dr. Shore. Dr. [redacted] indicated that absolute bioavailability, renal impairment, and population PK/PD modeling studies would be pursued, using FDA guidances where applicable.

Prepared by: _____

Crystal King, Project Manager 7/7/8

Facilitator: _____

G. Alexander Fleming, Meeting Facilitator 7/7/98

Concurrence:	Florence Houn, Deputy Office Director	7/7/98
	Solomon Sobel, Division Director	7/17/98
	Robert Misbin, Medical Officer	7/14/98
	John Gueriguian, Medical Officer	7/16/98
	Saul Malozowski, Medical Officer	7/7/98
	Ronald Steigerwalt, Pharmacology Team Leader	7/7/98
	Hae-Young Ahn, Biopharmaceutics Team Leader	7/20/98
	Lee-Ping Pian, Statistical Reviewer	7/10/98
	Robert Shore, Biopharm Reviewer	7/20/98

Attachments: A) Overheads from Drs. Scarlett, Thorner,
B) Telecon memo, 7/9/98
C) Sensus Minutes of Meeting

cc: IND (with attachments)
HFD-510 Division File (without attachments)
HFD-510: CKing, GFleming, SSobel, RMisbin, JGueriguian, SMalozowski, RSteigerwalt, HAhn, LPian, RShore (without attachments)
HFD-102: JBilstad, FHoun (without attachments)

ATTACHMENT A

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

ATTACHMENT B

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: July 9, 1998
As per Dr. Pian's request during the July 1, 1998, meeting with Sensus, a Telecon was held with Suzanne Hackett, the Sensus statistician. Dr. Pian requested the sponsor to put down the algorithm of randomization and how the centers will be combined in case some centers have no patients in one or more treatment groups. She also requested that the sponsor do a multiple comparison for the primary analysis. ——— indicated that she would put them in the analysis plan and send it in for our review. Cc: Original IND —— file HFD-510 Division file HFD-510: CKing, LPian /S/ /S/ Name: Lee-Ping Pian, Ph.D. / Crystal King, PM	**IND#:** ——— **Telecon/Meeting initiated by:** ● Applicant/Sponsor ○ FDA **By:** Telephone **Product Name:** Trovert **Firm Name:** Sensus **Name and Title of Person with whom conversation was held:** ———

ATTACHMENT C

END-OF-PHASE-II (EOP-II) MEETING

DATE: 01 July 1998

TIME: 1:00 – 2:45 p.m.

PLACE: FDA – Parklawn Building – Conference Room B, 5600 Fishets Lane, Rockville, MD 20857

Attendees:

FDA Participants

Solomon Sobel, M.D., Division Director	(SS)
G. Alexander Fleming, M.D., Team Leader	(GAF)
Robert Misbin, M.D.	(RM)
John Gueriguian, M.D.	(JG)
Saul Malozowski, M.D., Ph.D.	(SM)
Ronald Steigerwalt, Ph.D., Team Leader	(RS)
Rob Shore, Pharm.D., Biopharmaceutics	(RSh)
Lee-Ping Pian, PH.D., Statistician	(LP)
Crystal King, P.D., M.G.A., Project Manager	(CK)

Sensus Participants

John A. Scarlett, M.D., President & CEO	(JS)
Robert Davis, Pharm.D., Executive Vice President	(RD)
Kennith Zib, Director, Project Management	(KZ)
Jeff Pitts, Senior Director, Development Services	(JP)
Mike Bernstein, M.P.H., Senior Director, Regulatory Affairs	(MB)
Michael Thorner, MB, BS, DSc, FRCP, Medical Consultant	(MT)

Mr. Bernstein (MB) opened the meeting by thanking the Division for the opportunity to present the progress of Sensus' development of B2036-PEG and to get further advise on the proposed Phase III program. After self-introduction of all participants, Dr Scarlett (JS) began with an overview of the clinical development to date and our proposed Phase

III program. JS began by describing the mechanism by which hGH binds to its receptor. The hGH molecule is then modified by amino acid substitution to develop the proposed drug product, B2036-PEG. JS described how the drug is PEGylated to increase half-life and decrease immunogenicity. He explained that Trovert has a different mechanism of action to that of Sandostatin. Trovert blocks GH action while Sandostatin inhibits its release. JS then presented the Trovert Phase II acromegaly study. Dr Gueriguian (JG) asked if there was any cross-reactivity of GH and Trovert? JS stated there may have been some cross-reactivity because of the assay, but Sensus is developing a very specific assay for GH without interference from Trovert and we are awaiting the results from this new assay. JS then described the open-label extension study with daily dosing and said that IGF-I had normalized in 56% of patients as of 5/31/98. JS indicated that no serious ADEs attributed to drug and no significant anti-body formation has occurred. The longest exposure to date now is around 11 months. JS discussed the patient who overdosed on 80 mg/day rather that 80 mg/week.

JS then presented the Phase III study. It is a 100 patient study in 12-14 U.S. and European centers comparing placebo vs. Trovert 10, 15 and 20 mg/day. It is a 3-month double-blind study with a rollover to open-label extension. The primary endpoint is percent reduction of IGF-I with secondary endpoints being percent normalization of IGF-I and clinical/quality of life measures. JG asked if there has been an attempt at combination therapy? JS explained the difficulty of a double-dummy study and the difficulty of getting the octreotide sponsor to supply matching placebo.
RM asked if there was a rise in IGF-I when patients came off Sandostatin therapy prior to randomization in the Phase IIb (SEN-3611) study. JS said there were rises in many patients, but that the baseline was stable by the time of randomization, as demonstrated by the stable IGF-I values throughout the treatment period in the placebo group.

MT then commented that acromegaly is hard to treat because many patients have it for 15 years before being diagnosed. Thus the tumors are usually macroadenomas and therefore cannot be cured by surgery alone. The tumors have often invaded the surrounding structures. Only ~15-30% of patients are cured by surgery alone. Today the standard of care is that surgery is first line of therapy, then somatostatin analogues, and radiotherapy and now we have the possibility of GHA. MT said he does not routinely advise conventional radiation but is recommending gamma knife radiation in some patients. Additionally, Sandostatin does lower GH but it is virtually impossible to lower GH secretion sufficiently to lower IGF-I levels in normal subjects. Even with newer analogues MT expressed his opinion that it was unlikely that the clinical outcome would be changed. MT continued to say that with somatostatin analogues 50% of acromegalic patients would normalize their IGF-1 levels with long acting, as is the case with TID administration of somatostatin analogues. Trovert is a major addition and first new approach in 20 years and he is very impressed with the results.

JG stated he felt that a good number of patients will respond to Trovert monotherapy but some may need combination therapy.

Clinical Questions

1) Does the Division concur that the single, 100 patient, placebo-controlled study as described in the development plan is adequate to support the NDA?

Division's Response

Yes; with the following adjustments:

a) Stratify patients only by the baseline IGF-I level and combine centers
b) Monitor patients beyond the control trial period for fall-off of responses
c) Monitor patients beyond the control trial period for rising GH levels

d) Perform multiple comparisons adjustment of different treatment groups vs. placebo

e) Provide normative data for IGF-I levels by age and sex strats

f) Address the durability effect through long-term Phase IV studies

2) If not, does the Division agree that the Somatostatin – analogue Inadequate Response Study (SIRS), a study in which the effects of B2036-PEG will be studied on patients who have responded inadequately to octreotide acetate, will provide adequate supporting data for the NDA?

Division's Response:

Comparison with octreotide acetate failure is appropriate

Discussion

It was felt that this study would not be required for the NDA.

3) Does the Division agree that the patient exposure data planned (40 patient years at the time of NDA submission), plus a Phase IV surveillance study commitment proposed in the development plan, is sufficient to support the NDA?

Division's Response:

Based upon the explained calculation of patient year's data and the fact that there will be close to 100 patient years data – yes.

RD stated that patient years were based on continuous exposure to drug from first dose through March 1998. He said that at the time of filing the NDA, Sensus would have 40-80 years of exposure.

4) Are the studies proposed adequate to sufficiently characterize the PK of the proposed drug in the treatment of acromegaly?

Division's Response:

a) Multiple dose kinetics should be performed.

b) Additional PK/PD data are requested.

Pre-Clinical Questions

1. Reproductive Toxicology – Does the Division concur that a Segment II in the rabbit is sufficient to satisfy the requirement for reproduction toxicology.

Division's Response:

a) Yes, the rabbit is sufficient

b) Additional comments have been reviewed from the Reproductive Toxicology Committee and more will be forthcoming.
Action Item: Dr Steigerwaldt will forward the additional comments when received from the Committee

2. Carcinogenicity – Does the Division concur with the hypothesis that decreasing the presence of IGF-I, a tumor mitogen, as does B2036-PEG, should reduce the mitogenic activity of IGF-I and could lead to an anticarcinogenic effect in-vivo? Sensus is investigating IGF-I production by tumor cells in vitro and will be following up this set of experiments with in vivo tumor suppression studies. If B2036-PEG shows anti-tumor

properties in human tumor cell line(s), would rodent bioassays for carcinogenicity be required?

Division's Response:

Additional mechanistic and Phase IV studies would be expected for Acromegaly.

Action Items: Sensus should provide the following studies with the NDA submission for Acromegaly: (1) GH binding experiments outlined at the May 22, 1998 meeting between Sensus and Dr. Steigerwaldt; and (2) the PC-3 tumor cell transplant study proposed during the June 8, 1998 teleconference. A single carcinogenicity study provided in Phase IV will cover the acromegaly indication.

3) Chronic Toxicity Testing – Does the Division concur that a three month study in rats, with daily dosing, satisfies all remaining requirements?

Division's Response:

A 3-month, multiple study is satisfactory.

4) Safety Pharmacology – Does the Division concur that safety pharmacology studies are not required unless we identify a target organ during the chronic rat study?

Division's Response:

Yes; comparison studies to specific rat findings would be appropriate.

Other Issues:

RD asked if Sensus could go beyond 20 mg/day to treat some patients who are not responding to this dose.

SM said that we should submit an amendment to the protocol to do this.

There being no further business, the meeting adjourned at 2:45 PM.

/S/ 7/24/98

IND [redacted]	DATE RECEIVED:	07/24/98
BRAND NAME:	Trovert	
GENERIC NAME:	B2036-PEG	
REVIEWER:	Meeting Participants	
SPONSOR:	Sensus Drug Corp.	
SUBMISSION TYPE:	Informal Meeting Minutes	

Our meeting participants have reviewed your informal End-of-Phase 2 meeting minutes of July 1, 1998, sent to us via FAX on 7/24/98. Following are the comments.

Attendees:
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader should be added to the FDA list.

Clinical Question 1, Division's Response:
Item (a) should read, "Stratify patients only by the baseline IGF-I level and *provide an algorithm how to* combine centers, *if necessary.*"
Item (e) – "strats" should be "*strata*".

Clinical Question 2, Division's Response:
The response should read, "*A* comparison ~~with~~ *in patients who have failed on* octreotide acetate ~~failure~~ is appropriate."

Clinical Question 4, Division's Response:
Item (b) should be amended, "Additional PK/PD data are requested. *As indicated by KR, these data would include: absolute bioavailability, renal study, population PK/PD modeling. KR stated he is aware of the FDA guidances.*"

Should you have any questions, please do not hesitate to contact me at 301-827-6423.

/S/

Crystal Anne King, P.D., M.G.A.
Project Manager

/S/

Fax Clearance:

Gloria Troendle, M.D.
Deputy Director

Paul

pre-IND
B2036-PEG
Sensus Drug

January 24, 1996

Memorandum of Pre-IND Meeting

Sensus Drug Representatives:

Richard Hawkins - Founder and Chairman of the Board
John (Chip) Scarlett, M.D. - Founder and Chief Executive Officer
Robert F. Butz, Ph.D. - President and Chief Operating Officer
William Bennett, Ph.D. - Sr. VP, Research and Manufacturing and Chief Scientific Officer
Kenneth Zib - Director, Project Management and Chief Information Officer
William Clementi, Pharm.D., F.C.P. - President, Clementi & Associates, Ltd. (CRO)

FDA:

Solomon Sobel, M.D. - Director, Division of Metabolism and Endocrine Drug Products (DMEDP), HFD-510
Gloria Troendle, M.D. - Deputy Director I, DMEDP(HFD-510)
Saul Malozowski, M.D., Ph.D., - Medical Officer, DMEDP(HFD-510)
Elizabeth Koller, M.D. - Medical Officer, DMEDP(HFD-510)
Robert Misbin, M.D. - Medical Officer, DMEDP(HFD-510)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DMEDP(HFD-510)
Ronald Steigerwalt, Ph.D. - Pharmacologist, DMEDP(HFD-510)
Duu-Gong Wu, Ph.D. - Chemist, DNDC II (HFD-820) @ HFD-510
Stephen Moore, Ph.D. - Acting Chemistry Supervisor II, DNDC II (HFD-820) @ HFD-510

Purpose:

The meeting was requested by Sensus Drug to discuss the drug development of a PEGylated growth hormone agonist, B2036-PEG.

Discussion and Conclusions:

After self-introduction of all participants, Dr. Scarlett began with an overview of the information to be presented.

He began by discussing the mechanism by which hGH binds to its receptor. The hGH molecule is then modified by amino acid substitution to develop the proposed drug product, B2036-PEG.

Dr. Scarlett indicated that PEGylation of the molecule increases the molecular size and at the same time increases the half-life in systemic circulation.

Dr. Butz then discussed the manufacturing program. He indicated that Sensus is a "virtual company" (i.e., it has no intention of manufacturing its own drug). At present, Genentech, Inc. will perform the fermentation, purification, protein characterization, PEGylation, final characterization, and release of the bulk drug substance. —— will perform fill and finish, labeling, stability testing, and release of the final drug product.

Due to a change in procedure at Genentech, Dr. Butz indicated that the drug prepared for the completed toxicology studies is slightly different than that which will be prepared for human use.

Dr. Steigerwalt asked if the gradations between the lot size used for the toxicity studies and that to be used for human use would be performed. Sensus responded affirmatively. Dr. Moore asked about the availability of the chemistry and manufacturing information. Sensus indicated that Genentech and —— would generate their own DMFs. In addition, all firms involved would provide letters allowing the FDA to cross-reference their manufacturing processes.

Dr. Wu asked what bioassay would be used. Senesu indicated that it would be the inhibition of the growth hormone cellular assay.

Dr. Jordan asked whether Sensus had studied the differences between agonist and antagonist activity and the PEGylated molecules. Sensus responded that increasing PEGylation decreases binding but the final product will be unifoirm in the number of PEG molecules/peptide.

Dr. Butz then continued with an overview of the studies performed in rhesus monkeys. The results demonstrated a dose response. He then discussed the preliminary assessment of the immunogenicity. The results demonstrated that IGF-I is suppressed by B2036-PEG but NOT the unPEGylated form, B2036. Dr. Scarlett indicated that they chose to PEGylate the molecule due to a general decrease in immunogenicity.

Dr. Butz continued with the proposed toxicology program (already initiated). He stated that acute and subchronic mouse studies will be performed, as well as subchronic monkey studies. The studies will be supported with GLP PK in both mouse and monkey. Dr. Butz asked for input about additional studies (repro/tox and neuropharm studies). Dr. Jordan indicated that the proposed tox studies to be performed in monkeys

should be sufficient. In regard to teratology, Dr. Jordan indicated that the studies should be performed in a species in which the drug works.

Dr. Scarlett continued with the potential medical applications of the drug. He suggested that weekly dosing (to increase compliance) for the treatment of patients with acromegaly will be the first indication, followed by data to support an

Dr. Butz then discussed the proposed initial clinical program. He indicated that there would be a single (rising dose) study in healthy volunteers followed by a multiple dose study in acromegalic patients (16) and a

Ms. Pauls indicated that, for administrative purposes,

Dr. Scarlett indicated that in regard to the study proposed for acromegalic patients, changes in IGF-I as well as morphometric changes would be measured as endpoints.

Dr. Butz then asked for input regarding the safety (and length of follow-up required) for these studies (presuming that the application would continue to the NDA stage). Dr. Malozowski decided to defer this question until the results from the tox studies were available. Dr. Koller indicated that Sensus should consider evaluating different subsets a trend to develop the various complications. In addition, hypoglycemia may be more problematic in patients with autonomic neuropathy. Dr. Scarlett responded by indicating that they would take Dr. Koller's advice under consideration. However, at present, the proposed phase II study was designed to include 260 patients with non-severe to severe retinopathy. Dr. Misbin indicated that decreased insulin levels could be used as a measure of drug effect because high insulin levels are observed in patients with acromegaly and low insulin levels are observed in patients with growth hormone deficiency. He also indicated that patients who had already received laser therapy once should be included in the study to determine if the drug decreases the need for additional laser treatment.

Ms. Pauls indicated that in regard to the questions asked in the pre-meeting package, she could provide the following responses (see attached):

Q1: Orphan drug . . .

A1: The Division supports the indication. However, OODPD makes the final decision regarding whether orphan drug status will be granted.

Q2: The design . . .

A2: As discussed above.

Q3: The possibility of . . .
A3: OODPD has the ability to provide grant money; they should be contacted directly.

Q4: Subpart E . . .
A4: _____ would be eligible under the auspices of Subpart E.

Dr. Jordan indicated that eventually, carcinogenicity studies would be required,

Dr. Butz indicated that the IND (for acromegaly) would be submitted by the end of August. Ms. Pauls referred Sensus to the new Guidance for Industry document for preparing INDs.

The meeting concluded at 11:45 AM.

/S/

Lana L. Pauls, M.P.H.
Project Manager

cc: HFD-510/growth hormones
HFD-510/EGalliers/AFleming/Attendees (including chemists)
HFD-510/LPauls/01.25.96/Sensus.MTG

Concurrences:
SMalozowski, EKoller, RMisbin 01.25.96/AJordan, RSteigerwalt, DWu, SMoore 01.26.96/GTroendle, SSobel 01.29.96

COMPLETE RESPONSE EVALUATION

NDA Number: 21-106, Somavert (pegvisomant) 10 mg, 15 mg and 20 mg for injection

Applicant: Pharmacia & Upjohn

"Complete Response"
Date of Application: August 29, 2002 October 1, 2002, Labeling in EDR
Date of Receipt: August 30, 2002
Date of Filing Meeting: October 9, 2002
Filing Date: N/A due response (class II- 6 mo.) to a June 26, 2001 AE letter

Indication(s) requested: Treatment of aromegaly

Type of Application: Full NDA ___X_ Supplement _____
(b)(1) ____X___ (b)(2) _____
[

Therapeutic Classifications: S_____ P___X__
Resubmission after a withdrawal or refuse to file ___No____
Chemical Classification: (1,2,3 etc.)___1P___
Other (orphan, OTC, etc.)__orphan___

User Fee Status: no fee for response to AE letter_____ Waived (e.g., small business, public health) _____ Exempt (orphan, government) ____X____
Form 3397 (User Fee Cover Sheet) submitted: YES_____ NO_____
User Fee ID#_____N/A_____
Clinical data? ___ NO __X_ Referenced to _____
Date clock started after UN _____

User Fee Goal date: ___March 31, 2003_____

Note: If an electronic NDA: all certifications require a signature and must be in paper.

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.
- Submission complete as required under 21 CFR 314.50? YES, CR letter issued Oct 7, 2002
- If electronic NDA, does it follow the Guidance? YES
- Patent information included with authorized signature? N/A
- Exclusivity requested? N/A
- Correctly worded Debarment Certification included with authorized signature? N/A

- Financial Disclosure included with authorized signature? N/A
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign or submit a separate certification.

- Pediatric Rule appears to be addressed for all indications? N/A

- Pediatric assessment of all ages? N/A
  (If multiple indications, answer for each indication.)
  If NO, for what ages was a waiver requested? _____
  For what ages was a deferral requested? _____

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES

Drug name/Applicant name correct in COMIS YES

List referenced IND numbers: _____

End-of-Phase 2 Meeting? N/A
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? N/A
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name and labeling (PI) sent to ODS? N/A, done on first review cycle

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NO

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
- EA consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) package submitted? YES

MEMORANDUM OF TELECON

DATE: July 18, 2001

APPLICATION NUMBER: NDA 21-106, Somavert (pegvisomant for injection)

BETWEEN:

Name: Robert Davis, Pharm.D., Executive Vice President, Sensus Corp.
Richard Wolfe, Ph.D., Director of CMC Operations, Bioprocess & Formulation Technology, Pharmacia
Roger Nosal, Senior Director, Global Regulatory Affairs, Pharmacia
Gary Bild, Ph.D., Associate Director of Analytical Development, Bioprocess & Formulation Technology, Pharmacia
John Landis, Ph.D., Senior Vice President, Preclinical Development, Pharmacia
Arthur Campbell, Ph.D., Vice President, Bioprocess Development & Manufacturing, Pharmacia

Phone: 847-982-7250

Representing: Sensus Drug Development Corporation

AND

Name: Crystal King, P.D., M.G.A., Regulatory Project Manager
Stephen Moore, Ph.D., Chemistry Team Leader
Janice Brown, Ph.D., Chemistry Reviewer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Discussion of two deficiencies in the Approvable Letter of June 26, 2001

Following the Approvable Letter the Agency issued on June 26, 2001, the sponsor submitted a meeting request on July 3, 2001. The Division denied the meeting request on July 5, 2001, on the basis that the meeting was unnecessary since the specific questions the sponsor proposed essentially requested an opinion on the approvability of the planned resubmission. However, the Agency agreed to discuss two deficiencies that were adequately identified in the sponsor's meeting request. The June 26 deficiencies, the sponsor's questions, and the agreements reached are as follows.

Item 1:

Deficiency 8c: Add MALTI-TOF analysis and establish a specification for characterizing a pegylated-B2036.

2 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/

Crystal King
8/3/01 09:33:25 AM

Memorandum of Telecon

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics

Date of Telecon:	23-JAN-01
From:	Robert M. Shore, Pharm.D.
Re:	NDA 21-106/N-000 Somavert pegvisomant
Participants:	Robert M. Shore (FDA); Mike Bernstein, Sensus (512-487-2018)

I called Mike and conveyed the following two comments from my filing memo for this NDA:

1. No assay validation data could be located for study SEN 3623. Please either submit these data or indicate where in the submission these data can be located.

2. Data files used in the NONMEM analyses could not be located in the submission. Please either submit these files on disk or indicate where in the submission these files can be located

(The third comment from the memo was that the labeling be submitted in Word format; the sponsor has already done this)

He indicated that he "will get back to me shortly" regarding these items.

CC: NDA 21-106 / N-000 (orig., 1 copy), HFD-510(King)

/s/

Robert Shore
1/23/01 11:19:53 AM
BIOPHARMACEUTICS
TC memo. Conveyed two comments to sponsor.

MEMORANDUM OF TELECON

DATE: October 12, 2000

APPLICATION: IND —— Somavert (pegvisomant)

BETWEEN:

Name: Ed Calamai, Senior VP, Operations
Nick Vrolijk, Director, Manufacturing Services
Mike Bernstein, Senior Director, Regulatory Affairs

Phone: 512-487-2018

Representing: Sensus Drug Development Corporation

AND

Name: Crystal King, P.D., M.G.A., Regulatory Project Manager
Stephen Moore, Ph.D., Chemistry Team Leader
Janice Brown, Ph.D., Chemistry Reviewer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Follow up of Teleconference of October 3, 2000, regarding various CMC issues

J. Brown noted that all specifications should be addressed prior to the NDA submission. This would include quantitative monitoring for the pegylation and for impurities. The test statistics and times provided by Sensus are acceptable; however, we don't see test specs for degradation, thus we are unable to comment. Sensus should also consider the site inspection and manufacturing schedule.

Sensus has made much progress since the October, 1999, meeting. N. Vrolijk and E. Calamai reviewed technical information regarding degradation, deamidation, high molecular weight aggregates, and impurity specifications. J. Brown responded with the following concerns:

1) Degradation: identification by qualification is acceptable, however, to monitor degradation, it is necessary to have a quantitative method.
2) High molecular weight proteins: should be supported by data from clinical batches.
3) Deamidation: Sensus should try to detect certain species and must identify which sites are deamidated.
4) Impurity specifications: we target less than or equal to —— for host cell protein.

Finally, J. Brown encouraged Sensus to have all specifications in place include validated results with the NDA submission.

Crystal King
Regulatory Project Manager

Janice Brown
Review Chemist

/s/

Crystal King
1/17/01 04:45:18 PM
CSO

Janice Brown
1/24/01 04:50:57 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2001

To: Mike Bernstein	**From:** Crystal King
Company: Sensus Drug Development Corporation	Division of Division of Metabolic and Endocrine Drug Products
Fax number: 512-487-2049	**Fax number:** 301-443-9282
Phone number: 512-487-2018	**Phone number:** 301-827-6423

Subject: Telecon minutes for October 12,2000

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 3, 2000
FDA participants: Stephen Moore, Ph.D., Chemistry Team Leader Janice Brown, Ph.D., Chemistry Reviewer Crystal King, P.D., M.G.A., Regulatory Project Manager Sensus sent a FAX outline of the proposed experimental designs for stability studies for the NDA on 9/14/00. Draft specifications for bulk drug substance and drug product were also presented. This telecon discussed these proposals. Concerns were voiced by the Division relating to the monitoring/analysis for product related substances, specifications for PEG/protein ratios, and stability monitoring. Specifically: 1. Specifications should be established for product related substances —— (Refer to FDA comments for item 2 for the 12/8/98 FDA meeting minutes and item 2 for the 10/7/99 Sensus meeting minutes.) 2. Specifications should be established for the hGHR antagonist:PEG ratio, free PEG, and free hGHR antagonist. 3. Specifications should be established for impurities until enough manufacturing history has been established (DNA, *E.coli* proteins, purification and PEGylation reagents). (Refer to FDA comments to items 1 and 3 in the 12/8/98 FDA meeting minutes.) The test stations and times proposed are acceptable. *Following the telecon, the Division discussed concerns with manufacturing and inspections. The sponsor must verify that the facility is "ready for inspection" in the submitted NDA. "Ready for inspection" means that the product is being actively manufactured and that a proposed manufacturing schedule is submitted. The determination of*	**IND#:** — **Telecon/Meeting initiated by:** ● Applicant/Sponsor ○ FDA **By:** Telephone **Product Name:** B2036-PEG **Firm Name:** Sensus **Name and Title of Person with whom conversation was held:** Ed Calamai, Ph.D., Sr. VP, Operations Nick Vrolijk, Ph.D., Director, Manufacturing & Controls Mike Bernstein, M.P.H., Sr. Director, Regulatory Affairs **Phone:** 512-487-2018

the inspection dates is made at or near the filing date of the application. (These comments will be relayed through the Division's meeting minutes provided to Sensus.) /S/ 10-11-00 **Stephen Moore, Meeting Chair** /S/ 10/11/00 **Crystal King, Recorder**	

Attachment

cc: IND ——
Div Files
HFD-510: S.Moore/J.Brown/C.King

ADRA Review #2 of Action Package for NDA 21-106, Somavert (pegvisomant) for Injection.

Reviewer: Lee Ripper, HFD-102
Date: March 14, 2003

Date package received in HFD-102: March 12, 2003

Indication: Tx of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these treatments are not appropriate.

Approval letter from HFD-510 — Drug Classification: 1PV
RPM: Monica Johnson/Enid Galliers
Fast Track Granted: Mar 18, 1999 — Rolling Rev Granted: Dec 7, 1999
Date original NDA received: Dec 26, 2000
505(b)(1) application — Patent Info: Yes
User fee goal date: March 31, 2003 — **ACTION GOAL DATE: MARCH 25, 2003**

EER: AC 3/17/03
Clinical Inspection Summary: Adequate
DMETS review of tradename: 3/21/01 OPDRA review rejected Somavert as a tradename due to many look-alike and/or sound-alike products. 5/15/01 medical team leader review overruled OPDRA review. 6/20/01 DD review concurred with TL. No review by DMETS during current review cycle. *3/17/03: LR email to Jerry Phillips asking if DMETS wants to comment at this time. Sammie Beam to review and respond Monday, March 24. Review received 3/25/03. FU memo from Dr. Orloff.*
DDMAC review of PI and PPI: 5/11/01 (not in DFS) and 12/10/02

EA: Categorical exclusion
Financial disclosure information/review: Adequate response to AE letter
120-day safety update dated 2/22/01, reviewed in MOR#1, also see separate safety update memo

Comments:

1. Pediatric Page should be completed.
2. See comments on letter and labeling.

Lee Ripper
March 25, 2003

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

/s/

Leah Ripper
3/25/03 03:45:33 PM
CSO

ADRA Review of Action Package for NDA 21-106, Somavert (pegvisomant) for Injection.

Reviewer: Lee Ripper, HFD-102
Date: June 14, 2001

Date package received in HFD-102: June 14, 2001

Indication: Tx of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these treatments are not appropriate.

Approvable letter from HFD-510
Drug Classification: 1PV
Fast Track Granted: Mar 18, 1999
Date original NDA received: Dec 26, 2000
505(b)(1) application

RPM: Crystal King, 7-6423

Rolling Rev Granted: Dec 7, 1999
User fee goal date: June 26, 2001
Patent Info: Yes

EER: Pending, district withhold recommendation on ——— site (drug substance manufacturer); inspection ongoing at ——— site (testing), there appear to be some lab methods issues with this facility.
EER signed 6/26/01. Withhold recommendation. ——— sites not satisfactory

Clinical Inspection Summary: Adequate

OPDRA review of tradename in package
DDMAC review of PI and PPI not in package or in DFS; package states that comments were incorporated into labeling recommendation

EA: Categorical exclusion
Financial disclosure information/review: Inadequate, see comment #2 below
120-day safety update dated 2/22/01, reviewed in MOR#1, also see separate safety update memo

Comments:

1. Did DDMAC provide a written review of the PI and PPI? If so, needs to be added to package and DFS. If not, package should explicitly say so.

2. Applicant should be asked to explain why, on the forms 3455 for ——— DRClemmons, KEFriend, and SMelmed, they checked the box for outcome payments.
Deficiency added to letter

3. Even though it's an orphan drug, Pediatric Page should be completed at AP stage.

4. What is submission date of carton and container labels that are in the action package? No vial label for the water for dilution. Was it submitted?
Vial label for the water for dilution requested in letter

5. See comments on draft letter.

6. Review of DFS:

Not in DFS:
Perlstein, Review of SU – *Added to DFS*

Other DFS comments:
DD Memo needs to be signed in DFS - *Done*
P/T filing memo is in DFS twice; copy not signed by TL should be removed - *Done*
Electronic signature page for RPM filing memo should be added to package
Electronic signature page for Biopharm filing memo should be added to package

Lee Ripper
June 15, 2001

Lee Ripper
July 3, 2001

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

/s/

Leah Ripper
7/3/01 06:29:28 PM
CSO

MEMO TO THE FILE

Fred Alavi, Ph.D.
March 19, 2003

NDA: 21-106
Drug: Pegvisomant
Class & Mechanism: Growth hormone antagonist
Indication: Acromegaly
Sponsor: Pharmacia
Meeting Date: July 12, 2001
Type of Meeting: Tcon

In the original discipline review letter issued on May 17, 2001, the pre-clinical deficiencies for NDA 21-106 were communicated to the sponsor. In the letter, the agency had requested a new rabbit reprotoxicity study using doses high enough to produce maternal toxicity in rabbits. In the original study, the highest dose of pegvisomant (10 mg/kg/d, 10X MRHD based on AUC) did not cause significant maternal toxicity, although a 2 fold increase in post-implantation loss was observed.
The sponsor responded to our request with data from an additional rabbit dose-finding study conducted as follow up to the definitive embryofetal toxicity study. The issue was discussed at the teleconference meeting on July 12, 2001. Since pegvisomant interferes with IGF-I levels, and IGF-I levels are required for normal fetal development, we agreed that another rabbit reprotoxicity study with higher doses is unlikely to yield new information. The agency agreed to waive the request for another reprotoxicity study in rabbits. For Tcon meeting details please see the minutes appended on the next page.

Memo to File

To: Monika Johnson, Pharm.D.
Division of Metabolic and Endocrine Drug Products

From: Laura Pincock, Pharm.D., Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Date: 12/10/02

Re: Consult Request for the Somavert labeling

Somavert (pegvisomant), NDA 21-106

DDMAC's comments are based on the proposed Somavert labeling (package insert and patient package insert) received by the Division and dated August 29, 2002. We reviewed this version and compared it to the previous version with previous DDAMC comments by Margie Kober dated 5/11/02.

-We note the indication has included a new statement that " This statement could be used in promotion to overstate the efficacy of Somavert and be exploited to claim other benefits We recommend you remove the last part of the statement. Likewise, we recommend you remove the similar statement from the PPI that Somavert

-we have no additional new comments on the proposed package insert and patient package insert.

-we have no comments on the labels or cartons for Somavert 10 mg, 15 mg, or 20 mg.

Please contact me if you have further questions at (301) 827-3903.

Signature: _____

(Laura Pincock, Pharm.D.)

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

/s/

Monika Johnson
1/25/03 02:41:09 PM
CSO
Entering into DFS for Laura Pincock

FILING MEETING MINUTES
January 22, 2001

Drug/Application: NDA 21-106 SOMAVERT™ (Pegvisomant)
Sponsor: Sensus Drug Development Corporation

1. Filing Discussion:

- Clinical – No filing issues per Robert Perlstein and Saul Malozowski. There is a review concern regarding substantially elevated liver enzymes in 2 acromegalic patients.

- Pharmacology – The application is filable per Jeri El-Hage and Fred Alavi. However, there are some review issues as described below:

  The major concern was that sponsors are supposed to complete 6-month toxicity studies in two species for biotechnology-derived products prior to NDA filing (according to ICH S6 document). The PTCC also advised that carcinogenicity testing should be performed on this product.

  The 6 month rat study appears to have used adequate dose levels, duration, and frequency of administration (daily). The monkey study used relatively low doses (less than human on mg/sq. meter basis), and only once per week dosing. Clinical dosing frequency is daily, therefore, the 6-month monkey study is inadequate.

  In addition, only limited genotoxicity and reproductive toxicity studies were conducted rather than those in the ICH standard batteries.

  Despite all the inadequacies, Dr. Ron Steigerwalt (the previous Pharmacology/Toxicology team leader) had agreed that Sensus could submit their NDA for acromegaly with the studies provided and a Phase IV commitment to perform a carcinogenicity study.

- Chemistry – The application is filable per Janice Brown. However, the applicant has not sent in the requested information for a complete review.

  1. The immunogenicity of the product - in addition to the 9 amino acid changes made to the native growth hormone, the sponsor submitted data indicating that seven other variant forms are produced during manufacturing.

2. No information provided on the diluent used. The sponsor indicated that it is an approved diluent manufactured by Abbott. No letter of authorization was submitted.

3. The firm, in a recent submission of 1/17/01, states they are ready for inspection.

4. The sponsor did not include the number of PEG moieties attached to the molecule in the release and stability specifications.

5. Many of the assays used to test the product on stability were not validated and some of the stability indicating assays did not have acceptance criteria. The sponsor did not state in the stability section whether any changes were made to the method due to the validation.

6. There are no specifications for [redacted] and the clipped form of the bulk intermediate.

7. There is no process validation supporting the removal of tetracycline (2.4 - 2.6 mg/ml) in the culture medium.

- Microbiology – no filing issues per Neal Sweeney

- Biopharmaceutics – no filing issues per Robert Shore and Hae-Young Ahn

- Biostatistics – no filing issues per Lee Pian and Todd Sahlroot

- DSI – no filing issues per Roy Blay. One previously selected site (the largest) had to be replaced since DSI has recently inspected that investigator.

- Electronic Submission – no filing issues per George Liao

- OPDRA – no filing issues per Sammie Beam (by e-mail)

- DDMAC – no filing issues per Margie Kober. A Patient Package Insert may be requested (only a patient instruction sheet is included).

- Regulatory – All necessary components of the submission are present.

2. Priority or Standard Review schedule: Priority ~~Standard~~

3. Clinical Audit sites (list): Three clinical sites will be audited

4. Advisory Committee Meeting: ~~Yes~~ No

5. Review Timelines/Review Goal Date (with labeling):
The UF_6 for this priority submission is June 24, 2001. Final review from team leaders is due on or before April 21, 2001 to Crystal King. Package is due to the Division Director on May 12, 2001 and to the Office Director on May 26, 2001.

/S/ 1/30/01
Crystal King, Regulatory Project Manager

/S/ 1-30-01
David Orloff, Division Director

Cc: Original NDA 21-106

/s/

Samuel Wu
2/6/01 02:58:20 PM
CSO

David Orloff
2/6/01 05:59:40 PM
MEDICAL OFFICER

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES

505(b)(2) NO___X_____

FILING MEETING MINUTES

DATE: October 9, 2002

BACKGROUND:

Sensus Drug Development Corporation submitted Somavert, a new molecular entity, on December 16, 1999 (submission #1) after receiving fast track designation and orphan drug status. The Agency acknowledged the full NDA on January 24, 2001. The application was approvable pending chemistry, and pharmacology deficiencies on June 26, 2001. Pharmacia & Upjohn, new owner of this application, submitted a complete response to our approvable letter on September 27, 2002.

ATTENDEES: Janice Brown, Steve Moore, Hae Young Ahn, Jeri El Hage, Fred Alavi, Robert Perlstein, David Orloff, Enid Galliers, Monika Johnson

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Robert Perlstein, MD
Secondary Medical:	David Orloff, MD
Statistical:	Todd Sahlroot, PhD
Pharmacology:	Fred Alavi, PhD
Statistical Pharmacology:	
Chemist:	Janice Brown, MS
Environmental Assessment (if needed):	Janice Brown, MS
Biopharmaceutcal:	Jim Wei, MD, PhD
Microbiology, sterility:	Jim McVey, PhD
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Project Manager:	Monika Johnson, PharmD
Other Consults:	Sandra Birdsong (ODS, PSC meeting) Laura Governale — DDMAC

Is the application affected by the application integrity policy (AIP) NO X

Per reviewers, all parts in English, or English translation? YES_____

Establishment ready for inspection YES

Monika Johnson, PharmD
Project Manager, HFD-510

+ Waiting immunogenicity study reports.

[illegible] ? P4 Commitment:
① Renal toxicity - additional monitoring (no longer a concern)
② 2 yr [illegible] study.
③ liver toxicity

45 Day Meeting Checklist

NDA 21-106, Pegvisomant (Somavert®)

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		adequate
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? No, <u>Tests submitted:</u> Ames test in E.coli, Salmonella Chrome Abs using human lymphocyte Acute IV, SC tox study in mice. 14 Day IV, SC tox CD-1 mice 28 Day SC monkey studies 26 Week SC rat study Insufficient 26 Week monkey study * Early embryonic to implantation in rabbits A dose–range finding study in rabbits Embryonic/fetal development in rabbits Effects on Breast cancer cell lines Effects on human meningioma growth in vitro and in vivo Treatment of liver metastases with or without pegvisomant * The 26-WK monkey study was insufficient since animals were dosed once a week at lower doses compared to proposed daily dose in humans.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

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

_____

Reviewing Pharmacologist

_____

Supervisory Pharmacologist

/s/

Fred Alavi
1/25/01 11:02:12 AM
PHARMACOLOGIST
The 45-day checklist for NDA 21-106, pegvisomant [Somavert] was checke
d and found fileable by the Pharm/Tox reviewer.
Jeri, Please sign the modified Checklist for pegvisomant, NDA 21-106

Jeri El Hage
1/25/01 11:06:12 AM
PHARMACOLOGIST

Electronic Mail Message

Date: 3/8/01 4:57:29 PM
From: bob davis (bob@sensuscorp.com)
To: Crystal King (kingc@A1)
Subject: Press Release

Crystal,
Attached is the news release sent out today by Pharmacia announcing the merger between our companies. I know there is some paperwork that must be submitted to the agency, and would like to set up a call with you tomorrow if possible to discuss. I would be joined on the call by Mark Mannebach and Leslie Frank from Pharmacia.
I will retain the responsibility for the interactions and communications for our product.
Regards,
Bob Davis

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-01 to CSO	Sponsor	Sensus Drug Development Corp., Austin TX
PDUFA Due Date	24-JUN-01	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				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2 (3601/3623)		
multiple dose:				
Patients-				
single dose:	X	1 (3602)		
multiple dose:	X	5 (3611/3613/3613a/3614/3615)		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	2 (3601/3602)		
Drug-drug interaction studies -				
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		
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			
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	1 (3623)		
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]			

Background: Pegvisomant is a pegylated recombinant protein which is similar to human growth hormone in structure. However some mutations have been introduced into the amino acid chain which causes Somavert to act as a GH antagonist after binding to the GH receptor site. As such it is being proposed for the treatment of acromegaly, a disease often caused by pituitary tumors and characterized by elevated GH levels in the body.

This submission is wholly electronic. Section 6 contains eight studies for review. These studies are summarized in the following tables from the NDA. The sponsor indicates that the clinical and to be marketed formulations are the same. The pharmacokinetics of pegvisomant are non-linear and the drug substance does not seem to be cleared renally. The half-life is about 100-150 hours and the bioavailability of a SC dose is about 57% of an intravenous dose. The proposed dosing regimen is

80mg SC loading dose followed by 10mg/day SC. The dose is titrated up in increments of 5mg/day to a maximum of 30mg/day based on clinical IGF-1 levels. Although the half-life of the drug substance is about 100 hours the daily dosing regimen allows trough concentrations of pegvisomant to reach effective steady-state levels.

Table 1. Human Pharmacology/Pharmacokinetics and Bioavailability/Bioequivalence Studies

Study Number	Study Design	Population and Study Site Location	Treatment Regimen	Pegvisomant Doses	Pegvisomant Lot/Batch Number	Number of Subjects (M / F)
SEN-209	A pre-clinical, in vitro growth hormone receptor binding study	Human hepatocytes and microsomal membranes United States	In vitro, single treatment	0.1 nM – 100 µM	I1812004-B	3 samples/ test
SEN-3601	A Phase I, double-blind, placebo-controlled, single rising-dose study	Healthy male volunteers Netherlands	Single SC dose	0 mg/kg 0.03 mg/kg 0.1 mg/kg 0.3 mg/kg 1.0 mg/kg	- 003007 003007 003007 003007	12 (12 / 0) 6 (6 / 0) 6 (6 / 0) 6 (6 / 0) 6 (6 / 0)
SEN-3602	A Phase II, open-label, single-dose study	Male and female subjects with acromegaly Netherlands	Single SC dose	0.3 mg/kg 1.0 mg/kg	003007 003007	3 (3 / 0) 3 (2 / 1)
SEN-3611	A Phase IIb, double-blind, randomized, placebo-controlled multicenter study	Male and female subjects with acromegaly United States and Europe	SC dosing, once weekly for 6 weeks	0 mg 30 mg 80 mg	- 003007 003007	15 (5 / 10) 16 (10 / 6) 15 (13 / 2)
SEN-3613	A Phase IIb, open-label, dose-titration, multicenter study	Male and female subjects with acromegaly who had participated in study SEN-3611 United States and Europe	SC dosing, once weekly for 6 weeks	30 mg - 80 mg	442253A 423553A 472753A 362053A 372753A	36 (21 / 15)
SEN-3613A	A Phase IIb, open-label, dose-titration, multicenter study	Male and female subjects with acromegaly, including those who had participated in study SEN-3613 United States and Europe	Initial 80-mg SC bolus/loading dose, followed by daily SC dosing	10 mg – 30 mg	472153A 523153A	38 (22 / 16)
SEN-3614	A Phase III, double-blind, randomized, placebo-controlled study	Male and female subjects with acromegaly United States and Europe	Initial placebo or 80-mg SC bolus dose, followed by daily SC dosing for 12 weeks	0 mg 10 mg 15 mg 20 mg	- 413303A 413353A 423503A	32 (19 / 13) 26 (15 / 11) 28 (14 / 12) 28 (15 / 13)

SC = subcutaneous IV = intravenous

Table 1. Human Pharmacology/Pharmacokinetics and Bioavailability/Bioequivalence Studies - continued

Study Number	Study Design	Population and Study Site Location	Treatment Regimen	Pegvisomant Doses	Pegvisomant Lot/Batch Number	Number of Subjects (M / F)
SEN-3615	A Phase III, open-label, dose-titration, extension study	Male and female subjects with acromegaly who had completed study SEN-3614 United States and Europe	Initial 80-mg SC bolus dose, followed by daily SC dosing for 8 week cycles	10 mg – 30 mg	10 mg - 003007 413303A 452653A 500703A 15 mg - 413353A 481753A 20 mg - 423553A 442253A 472153A 523153A	101 (57 / 44)
SEN-3623	A Phase I, open-label, single-dose crossover study	Healthy male and female volunteers United States	Single SC or IV dose	20 mg SC 10 mg IV	372753A 372753A	12 (6/6) 12 (6/6)

SC = subcutaneous IV = intravenous

Table 2. Pharmacokinetics of B2036-PEG in Volunteers and Acromegalic Subjects								
Study	Subject Group	Dose	N (male/female)	C_{max} (ng/mL)	Trough Pegvisomant Concentration (ng/mL)	t_{max} (hrs)	AUC (ng-hr/L)	$t_{1/2}$ (hrs)
SEN-3601	Healthy volunteers	0.03 mg/kg	6 (6/0)	82.53 ± 23.66	ND	~12	8.7 ± 1.5	77.7 ± 22.3
		0.1 mg/kg	6 (6/0)	461.8 ± 110.8	ND	~36	37.4 ± 9.7	99.1 ± 28.7
		0.3 mg/kg	6 (6/0)	1832 ± 390	ND	36	182.5 ± 46.5	74.2 ± 33.2
		1.0 mg/kg	6 (6/0)	8982 ± 2186	ND	60	1506.1 ± 549.6	79.8 ± 28.3
SEN-3602	Acromegalic subjects	0.3 mg/kg	3 (3/0)	ND	1720.1 ± 288.6	33 ± 12.7	234 ± 52.7	109 ± 37.1
		1.0 mg/kg	3 (2/1)	ND	6545.7 ± 1983.8	77 ± 54.4	1060 ± 118.4	80 ± 36.3
SEN-3611	Acromegalic subjects	30 mg/wk	18 (10/8)	ND	1021.2 (160-4164)	ND	ND	ND
		80 mg/wk	15 (13/2)	ND	5290.3 (840-15,003)	ND	ND	ND
SEN-3613	Acromegalic subjects	30-80 mg/wk	36 (21/15)	ND	5324.9 ± 785.8 (80 mg steady-state dose regimen)	ND	ND	ND
SEN-3613A	Acromegalic subjects	10-30 mg/d	36 (22/16)	ND	12,547 ± 843 (10 mg/d) 18,366 ± 743 (15 mg/d) 21,315 ± 923 (20 mg/d)	ND	ND	ND
SEN-3614	Acromegalic subjects	10 mg/d	28 (15/11)	ND	6595.8 [1333.0]	ND	ND	133.6
		15 mg/d	28 (14/12)		16,342.8 [2212.6]	ND	ND	150.2
		20 mg/d	28 (15/13)		27,207.2 [3056.1]	ND	ND	171.7
SEN-3615	Acromegalic subjects	10-30 mg/d	101 (57/44)	ND	8238.1 ± 755.5	ND	ND	ND
SEN-3623	Healthy volunteers	10 mg (IV)	12 (6/6)	4270.9 ± 624.8	ND	6.45 ± 0.56	183.3 ± 79.9	136.0 ± 35.9
		20 mg (SC)	12 (6/6)	1367.2 ± 628.7	ND	49.02 ± 15.93	207.8 ± 89.5	138.4 ± 68.3

Data shown are mean ± SD, mean (range), or mean [SEM].
C_{max}, maximum concentration; t_{max}, time to C_{max}; AUC, area under the concentration curve; $t_{1/2}$, elimination half-life; ND, not determined.

Studies include single dose in healthy subjects as well as single and multiple dose in acromegalic patients. A PK/PD NONMEM analysis using data from the clinical studies has also been submitted. Assay validation data have been included for all but one study.

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	X	1. No assay validation data could be located for study SEN 3623. Please either submit these data or indicate where in the submission these data can be located. 2. Data files used in the NONMEM analyses could not be located in the submission. Please either submit these files on disk or indicate where in the submission these files can be located. 3. The sponsor needs to submit the proposed labeling in Word format.
QBR questions (key issues to be considered)	**Are there covariates that could predict a starting dose of Somavert?** **What are the exposure-response relationships for efficacy/safety?**	
Other comments or information not included above		

Primary reviewer Signature and Date	/S/	22-JAN-01
Secondary reviewer Signature and Date		1/22/01

CC: NDA 21-106, HFD-850(Electronic Entry or Lee), HFD-510(King), HFD-870(Ahnh, Malinowkski), CDR

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

[6] SEN-121

APPEARS THIS WAY
ON ORIGINAL

/s/

Robert Shore
1/24/01 03:12:27 PM
BIOPHARMACEUTICS
Filing memo for Somavert. Filable.
electronic copy of finalized hardcopy

Hae-Young Ahn
2/2/01 12:55:56 PM
BIOPHARMACEUTICS

DDMAC

Electronic Mail Message

Date: 5/11/01 8:39:57 AM
From: Margaret Kober (KOBERM)
To: Crystal King (KINGC)
Subject: Somavert Labeling

Crystal,

This e-mail summarizes my comments on the proposed labeling for Somavert (pegvisomant for injection), NDA 21-106. They pertain to the version I received in an e-mail dated 4-24-01. I will forward Karen's comments on the proposed PPI in a separate e-mail to you this morning. I will be happy to provide further explanation/clarification during our meeting Monday. Thank you again for consulting DDMAC!

Clinical Pharmacology - Mechanism of Action

Are the decrease in growth factors and the increase in serum GH at 2 weeks clinically significant? This does not seem to correlate with the dosing adjustment recommendation to evaluate levels every 6 to 8 weeks and could be exploited in a "time-to-effect" claim.

Clinical Pharmacology - Pharmacokinetics/Pharmacodynamics

Precautions - General

Precautions - Monitoring of Liver Function

n

Precautions - Drug Interactions

How Supplied

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