CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-192

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

NDA NUMBER
022192

NAME OF APPLICANT / NDA HOLDER
Vanda Pharmaceuticals Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Fiapta

ACTIVE INGREDIENT(S)	STRENGTH(S)
Iloperidone (1-[4-[3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]propoxy]-3-methoxyphenyl]ethanone)	1, 2, 4, 6, 8, 10, 12 mg

DOSAGE FORM
Oral Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number RE39,198	b. Issue Date of Patent 7/18/2006	c. Expiration Date of Patent 11/15/2011
d. Name of Patent Owner Aventis Pharmaceuticals Inc.	Address *(of Patent Owner)* 55 Corporate Drive	
	City/State Bridgewater, NJ	
	ZIP Code 08807	FAX Number *(if available)*
	Telephone Number 800-981-2491	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

PSC Media Arts (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2	Patent Claim Number *(as listed in the patent)* 84	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes	☐ No
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* Indicated for the treament of schizophrenia	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

PSC Media Arts (301) 443-1090 EF

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
[signature]	Sept. 13, 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Paolo Baroldi, M.D., Chief Medical Officer Vanda Pharmaceuticals Inc.	
Address 9605 Medical Center Drive, Suite 300	City/State Rockville, MD
ZIP Code 20850	Telephone Number 240.599.4500
FAX Number *(if available)* 301.294.1900	E-Mail Address *(if available)* paolo.baroldi@vandapharma.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PSC Media Arts (301) 443-1090 EF

EXCLUSIVITY SUMMARY

NDA # 22-192 SUPPL # HFD # 130

Trade Name Fanapt

Generic Name iloperidone

Applicant Name Vanda Pharmaceuticals

Approval Date, If Known May 6, 2009

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Kimberly Updegraff, MS
Title: Regulatory Project Manager
Date: May 6, 2009

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Mitchell Mathis
5/7/2009 12:37:09 PM
For Dr. Laughren

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-192 Supplement Number: NA NDA Supplement Type (e.g. SE5): NA

Division Name: HFD-130; DPP PDUFA Goal Date: 5/6/2009 Stamp Date: 11/6/2008

Proprietary Name: Currently under review

Established/Generic Name: iloperidone

Dosage Form: tablets

Applicant/Sponsor: Vanda Pharmaceuticals

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Schizophrenia (adult)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☒ No: Please check all that apply:

☒ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☒ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☒	Neonate	_ wk. 0 mo.	__ wk. 1 mo.	☒	☐	☐	☐
☒	Other	0 yr. 1 mo.	12 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☒	Other	13 yr. 0 mo.	17 yr. 11 mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): March 1, 2014						

Are the indicated age ranges (above) based on weight (kg)? ☒ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☒ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

SECTION B: Partially Waived Studies Justification

There is a very low incidence of schizophrenia diagnosed prior to age 13 which makes it unlikely that it would be possible to conduct a sufficiently large study of the 0-12 age group within a reasonable time.

APPEARS THIS WAY ON ORIGINAL

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/s/

Kimberly Updegraff
2/11/2009 07:15:38 PM

1.3. Administrative Information

DEBARMENT CERTIFICATION

Vanda Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Paolo Baroldi, M.D.
Chief Medical Officer

9/13/2007
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	Please see attachments.	

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☒ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Paolo Baroldi, M.D.	Chief Medical Officer
FIRM / ORGANIZATION Vanda Pharmaceuticals Inc.	
SIGNATURE Paolo Baroldi	DATE 9/18/2007

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 17, 2009
TIME:	2:00 – 3:00 PM
LOCATION:	WO 22 RM 4201
APPLICATION:	NDA 22-192
DRUG NAME:	Iloperidone tablets (Vanda Pharmaceuticals)
TYPE OF MEETING:	Pre Approval Safety Conference (PSC)
MEETING CHAIR:	Thomas Laughren, DPP, Division Director
MEETING RECORDER:	Kim Updegraff, DPP, Project Manager

FDA ATTENDEES:

Thomas Laughren, DPP, Division Director
Mitchell Mathis, DPP, Deputy Division Director
Ni Khin, DPP, Clinical Team Leader
Silvana Borges, DPP, Clinical Reviewer
Ida-Lina Diak, OSE, DPV, Senior Regulatory Reviewer
Kim Updegraff, DPP, Project Manager

Not in Attendance:
Sonny Saini, DPP, Senior Safety Program Manager
Todd Bridges, OSE, DMEPA, Team Leader
Diane Smith, OSE, DMEPA, Reviewer
Abolade Adelou, OSE, DMEPA, Project Manager
Paul Loebach, OMP, DDMAC, Project Manager
Susannah Hubert, OMP, DDMAC, CSO
Amy Toscano, OMP, DDMAC, CSO

BACKGROUND:

Iloperidone is an atypical antipsychotic (5HT2 and D2 receptor antagonist). It is an immediate release formulation for twice daily administration. The NDA seeks a claim for both the acute and maintenance treatment of schizophrenia, in a total dose range of 12 to 24 mg/day. Iloperidone was developed under IND 36,827. This NDA was first submitted 9- 27-07. We issued a Not Approvable letter on 7-25-08. There were two major deficiencies that were the basis for this action, i.e., (1) lack of sufficient effectiveness data, and (2) lack of sufficient safety data in a relevant dose range. In addition to these not approvable issues, there were four other issues noted in the letter: (1) data from Dr. Gilliam's site; (2) need to repeat hepatic impairment study; (3) need for iloperidone and P-Gp interaction study; (4) need for safety update. We subsequently met with the sponsor on 9-10-08 (see meeting minutes) to discuss the Not Approvable action.

Vanda Pharmaceuticals submitted a complete response to our 7-25-08 action letter on 11-6-08. In the response, the sponsor argues that they have provided positive results for the effectiveness of iloperidone in the acute treatment of schizophrenia in 2 adequate and well-controlled trials, i.e., studies 3101 and 3004. They further argue that studies 3000 and 3005 provide supportive

evidence for the acute efficacy of iloperidone and that studies 3001, 3002, and 3003 provide evidence for the maintenance efficacy of iloperidone in schizophrenia. They acknowledge our arguments that they have not provided sufficient evidence for the acute and maintenance efficacy of iloperidone in schizophrenia, but note that they disagree. They indicate that they can show that iloperidone is effective for this indication in the US population, has comparable efficacy to other available antipsychotic agents, and has certain safety advantages over other available antipsychotic agents.

The Division of Psychiatry Products has reviewed the complete response and is now prepared to approve this NDA.

MEETING OBJECTIVES:

1. Ensure that OSE is aware of potential postmarketing safety problems related to the use of iloperidone.

2. Address the need for any special postmarketing analyses or postmarketing safety evaluations to be implemented by the sponsor.

3. Determine if there is any special information or feedback that the review division would like from OSE during the immediate post-launch of iloperidone.

DISCUSSION POINTS:

1. Safety Database:

The Division of Psychiatry Products discussed the safety signals that emerged in the clinical trial database. Such safety concerns included prolonged QT, weight gain, hyperglycemia, hyperprolactenemia, lipid changes and anemia.

The prolonged QT effect was discussed at length. DPP noted that the QTc effect of iloperidone is quite similar to ziprasidone and, as such, iloperidone is labeled similarly. The Division also noted that iloperidone must be titrated, and because of these two limitations (prolonged QT and titration schedule), the labeling suggests that iloperidone might not be considered as a first line agent.

DPP explained that the metabolic effects of iloperidone appear to be lower than those found with some other drugs in its class. Iloperidone appears to fall in the middle among the atypical antipsychotics with regard to weight gain and little, if no impact, was reported on triglycerides, cholesterol, or glucose levels in the short-term trials. It was also pointed out that iloperidone appears to be associated with less akathesia and extrapyramidal symptoms (EPS) than some others in the class.

2. Postapproval safety surveillance strategy.

The evaluation of the safety data did not reveal any particular safety issues that are unexpected for this class of drugs. DPP and OSE agreed that monitoring would be similar to of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole).

DPP would like to have additional data on the longer-term metabolic effects of iloperidone.

3. Labeling:

Iloperidone is labeled similarly to ziprasidone, per recommendation by the QT team, and is not labeled for first line use. The need for titration is appropriately outlined in the labeling as well. In addition, the following groups reviewed the label and provided recommendations on their respective sections: pharmacology/toxicology, chemistry, clinical pharmacology, statistics, DMEPA, SEALD, and QT.

It was noted that DMEPA performed labeling reviews for this NDA and their recommendations concerning labeling as well as the carton/container labeling were incorporated during the review process. DMEPA worked closely with Vanda Pharmaceuticals to ensure that the carton/container labeling was concise and clear.

DECISIONS (AGREEMENTS) REACHED:

OSE will monitor iloperidone and watch for issues similar to the others in the atypical class of drugs.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

Division Director Memo dated 3-27-09

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/s/

Kimberly Updegraff
4/23/2009 12:40:08 PM
CSO

Thomas Laughren
4/23/2009 01:45:58 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: March 16, 2009

APPLICATION NUMBER: NDA 22-192

BETWEEN:

Name: Jennifer Hamilton, Curt Wolfgang, John Feeney
Phone: (240)599-4515
Representing: Vanda Pharmaceuticals

AND

Name: Kim Updegraff, Diane Smith, Abolade Adeolu
DPP, HFD-130 & DMEPA, HFD-420

SUBJECT: Discussion concerning DMEPA recommendations for carton/container labeling

Kim Updegraff, project manager for NDA 22-192 contacted Jennifer Hamilton of Vanda Pharmaceuticals at the request of Diane Smith, DMEPA reviewer. Also present was Abolade Adeolu, project manager for DMEPA. Dr. Smith wanted to convey recommendations concerning Vanda's most recent submission on March 10, 2009 containing update carton and container labeling.

The following recommendations were relayed to the sponsor:

1) Titration Regimen Pack: Retail and Professional Sample
   Vanda recently added the name "[redacted]" to the labeling as the name for the titration regimen pack. DMEPA stated that the name would have to be reviewed prior to use. Vanda agreed to remove [redacted] from the label and will use "Titration Pack" in its place. b(4)

2) Professional/Commercial Container labeling:
   DMEPA is concerned that the hot pink color chosen for the graphics on the 6mg pack is very similar to the red used for the 1mg pack. DMEPA suggested using yellow outlined in black for the 6mg labeling graphic instead of the current hot pink color. Vanda agreed to the use of yellow outlined in black for the 6mg package.

3) Inside Card of Titration Pack:
   DMEPA requested that Vanda change the current "AM" and "PM" notations on the titration pack be changed to "morning" and "evening".

The Vanda representatives acknowledged and agreed to make all of the above changes as per

DMEPA's recommendations.

Kimberly Updegraff, RPh, MS
Regulatory Project Manager, DPP

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/s/

Kimberly Updegraff
4/5/2009 05:09:29 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-192

Vanda Pharmaceuticals
Attention: John Feeney, M.D.
Acting Chief Medical Officer
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Dear Dr. Feeney:

Please refer to your New Drug Application (NDA) dated and received on September 27, 2007 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for iloperidone tablets.

We also refer to your submission dated and received on November 6, 2008 containing a complete response to the Agency's July 25, 2008 action letter and your November 19, 2008 submission requesting review of your proposed proprietary name, Fanapt.

In a letter dated February 13, 2009, The Division of Medication Error Prevention and Analysis and the Division of Psychiatry Products informed you that the proprietary name, Fanapt, was found to be acceptable.

The results of the Label and Labeling Risk Assessment found that the presentation of information on the proposed container labels is vulnerable to confusion that could lead to medication errors. Based upon the assessment of the labels and labeling, we have the identified the following areas that are in need of improvement:

All Labels and Labeling:

1. Decrease the prominence of the "F" that appears above the proprietary name; Fanapt, ensuring it is not more prominent than the proprietary name or the established name.
2. Increase the size of the established name, ensuring it is 1/2 the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

Trade Container Labels

1. The lavender color on the 4 mg product strength is too similar to the light grey color used for the 10 mg product strength. There are similar concerns involving the colors utilized

for the 6 mg and 12 mg strengths. Revise the colors used for these strengths to provide better differentiation.

2. The light yellow color used for the 2 mg product strength is difficult to read on the white background. Revise the color for the 2 mg product strength to increase the color contrast between the yellow text and the white background color. Ensure that the revised color is not similar to appearance of any other product strength. (See previous comment)

Professional Sample Container Labels

1. The container configuration will likely be small and when the label is placed on the container, the current presentation of the product strength may not be visible when looking at the front panel of the container label (i.e., the portion of the label containing the product strength may wrap around to the side panel). Relocate the strength to immediately follow the established name ensuring it appears on the principal display panel (i.e., as presented on the trade size container labels).
2. The statement "Professional sample" is small and difficult to read. Increase the size of this statement.

Titration Package Configuration

1. The use of the term [redacted] on the professional samples in not in accordance with [redacted]. A drug product which is to be given to a patient by a physician as a sample cannot not use the term [redacted] Delete the term "[redacted]" from the professional samples. b(4)
2. The current insert labeling recommends that all patients are titrated to 6 mg two times a day on days [redacted]. However, some patients may require further titration up to maximum daily dose of 12 mg two times a day. The proposed titration package configuration includes additional doses of 6 mg BID on [redacted] We believe the titration package should stop after day four to eliminate potential confusion in patients who require additional increases in dose. Revise the titration package configuration so that the package configuration only contains a four day supply which is congruent with the recommended starting titration dose schedule.
3. The white text font on the green background is difficult to read (i.e., white lettering on green background). Increase the size of the font to improve readability of important information such as the instructions for use and contents of the package.
4. We note the utilization of the "sun" and "moon" graphic to depict when the tablets should be taken in the morning and evening. The use of these graphics can be a source of confusion because patients can misinterpret exactly when the tablets should be taken. Remove the "sun and moon" graphics.
5. The front cover does not adequately convey to healthcare practitioners the specific contents of each titration pack. Revise the product strength statement so healthcare practitioners and patients understand the exact strengths and quantities contained in the titration carton. Revise to read:

This package contains:
Two 1 mg tablets
Two 2 mg tablets
Two 4 mg tablets
Two 6 mg tablets

6. We note your November 19, 2008, submission references the inclusion of a commercial titration pack. However, upon review of the file, we note that the carton labeling is for a professional sample titration pack. Please clarify whether or not you plan to market a commercial titration pack.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}
Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
3/6/2009 12:39:29 PM

Updegraff, Kimberly

From: Jennifer Hamilton [Jennifer.Hamilton@vandapharma.com]
Sent: Wednesday, February 11, 2009 2:16 PM
To: Updegraff, Kimberly
Cc: Curt Wolfgang; John Feeney
Subject: RE: NDA 22-192 Iloperidone
Attachments: Proposal for Pediatric Development Plan_Final.pdf

Dear Kim

Please find attached Vanda's updated plan. We have agreed to the dates you proposed below. Please let me know if you have any other questions.

Thanks,
Jennifer

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Wed 2/11/2009 1:26 PM
To: Jennifer Hamilton
Cc: Updegraff, Kimberly
Subject: NDA 22-192 Iloperidone

Hi Jennifer,

We are requesting the following revisions to your proposed pediatric development plan for iloperidone. Please note, the revised dates are not linked to an action date, but show your agreement to conduct pediatric studies with iloperidone in the future.

Protocol submission date: March 1, 2010
Study start date: September 1, [redacted]
Final Report submission date: March 1, 2014 b(4)

Please respond as soon as possible to our request.

Best regards,

Kim

From: Jennifer Hamilton [mailto:Jennifer.Hamilton@vandapharma.com]
Sent: Tuesday, February 10, 2009 4:41 PM
To: Updegraff, Kimberly
Cc: Curt Wolfgang; John Feeney
Subject: FW: NDA 22-192 Iloperidone

Dear Kim,

Please find attached Vanda's proposal for the pediatric development plan for iloperidone (updated timelines). Please let us know if you need additional details.

Thanks,
Jennifer

Jennifer B. Hamilton, M.S.
Clinical Research Scientist
Vanda Pharmaceuticals Inc.
9605 Medical Center Dr.
Suite 300
Rockville, MD 20850
t. 240-599-4515
f. 301-294-1900

APPEARS THIS WAY ON ORIGINAL

Updegraff, Kimberly

From: Jennifer Hamilton [Jennifer.Hamilton@vandapharma.com]
Sent: Friday, April 24, 2009 1:14 PM
To: Updegraff, Kimberly
Cc: Curt Wolfgang; John Feeney
Subject: RE: NDA 22-192 (Iloperidone): P95 study

Hi Kim,

The P95 carcinogenicity study is still on track for all dates shown in the table below. The audited draft report will be issued to Vanda by our vendor on 16 April 2010; therefore Vanda would like to request extending the final report submission date to the FDA to May 31, 2010. That will allow us time to finalize the report with the vendor and then format the document for publishing to the eCTD. Please let me know if the below dates are acceptable:

Study completion date: by February 28, 2010
Final report submission date: by May 31, 2010

Please let me know if you have any questions.

Best regards,
Jennifer

Jennifer B. Hamilton, M.S.
Clinical Research Scientist
Vanda Pharmaceuticals Inc.
9605 Medical Center Drive
Suite 300
Rockville, MD 20850
p. 240-599-4515
c. 301-803-8640
f. 301-294-1900

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Friday, April 24, 2009 12:50 PM
To: Jennifer Hamilton
Subject: NDA 22-192 (Iloperidone): P95 study

Hi Jennifer,

Please confirm that you are in agreement with the dates submitted on January 15, 2009 in relation to the ongoing P95 carcinogenicity study.

Study completion date: by February 28, 2010
Final report submission date: by [redacted] b(4)

Best regards,

Kim

From: Jennifer Hamilton [mailto:Jennifer.Hamilton@vandapharma.com]
Sent: Thursday, January 15, 2009 12:24 PM
To: Updegraff, Kimberly
Cc: Curt Wolfgang; John Feeney

Subject: RE: NDA 22-192 (Iloperidone): Information request

Dear Kim,

Regarding your question below, the P95 carcinogenicity study is ongoing and is in Month 17 of treatment. Below is a list of key milestones and dates for the study:

Animals to arrive (experimental start date)	30 August 2007
Treatment to commence	11 September 2007
Terminal sacrifice to commence	
Bioanalysis report (audited)	
Pharmacokinetic report to be completed	
Histopathology completed	
Histopathology external peer review completed	
Draft report to QA for audit	
Experimental finish date (estimated)	February 2010
Audited draft report to be issued	

b(4)

Please let us know if there are any additional questions or information that we can provide the review team.

Best regards,
Jennifer

Jennifer B. Hamilton, M.S.
Clinical Research Scientist
Vanda Pharmaceuticals Inc.
9605 Medical Center Dr.
Suite 300
Rockville, MD 20850
t. 240-599-4515
f. 301-294-1900

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Thursday, January 15, 2009 11:35 AM
To: Jennifer Hamilton
Cc: Updegraff, Kimberly
Subject: NDA 22-192 (Iloperidone): Information request

Dear Jennifer,

Please refer to your new drug application (NDA) for iloperidone tablets. Also refer to your resubmission dated and received on November 6, 2008.

The review team is requesting an update on the status of your ongoing carcinogenicity study of the iloperidone metabolite, P95.

Thanks,

Kim

Kimberly Updegraff

Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Phone: (301)796-2201
email: Kimberly.Updegraff@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

Updegraff, Kimberly

From: Updegraff, Kimberly
Sent: Wednesday, April 15, 2009 4:58 PM
To: Jennifer Hamilton
Cc: Updegraff, Kimberly
Subject: RE: NDA 22-192 (iloperidone) Post Marketing Requirement Agreement

Hi Jennifer,

I acknowledge receipt of your agreement with the proposed postmarketing requirements and associated dates.

Thank you,

Kim

From: Jennifer Hamilton [mailto:Jennifer.Hamilton@vandapharma.com]
Sent: Wednesday, April 15, 2009 4:47 PM
To: Updegraff, Kimberly
Cc: Jennifer Hamilton; Curt Wolfgang; John Feeney
Subject: RE: NDA 22-192 (iloperidone) Post Marketing Requirement Agreement

Hi Kim,

Please find below the requested dates. For a number of the dates, we changed them by – nonths based on original communications that we had and we are now assuming an approval in May 2009 and not [redacted] However, we left the PREA as agreed upon previously. b(4)

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17.

Final Protocol Submission:	by March 1. 2010
Study Start Date:	by [redacted]
Study Completion Date:	by September 1, 2013
Final Report Submission:	by March 1, 2014

2. Conduct a study investigating the possible in vitro interaction of iloperidone and P-Glycoprotein (P-Gp).

Final Protocol Submission:	by August 1, 2009 (original communication was 3 months from approval)
Study Start Date:	by [redacted] 009
Study Completion Date:	by October 1, 2009
Final Report Submission:	by November 1, 2009 (original communication was 6 months from approval)

b(4)

3. Your clinical trial CIL0522A0103, conducted in subjects with normal, mildly and moderately impaired hepatic function, was inconclusive because the exposure for mild subjects was greater than for moderately impaired subjects.

You will, within 2 years of approval, repeat the trial in a group of subjects with moderately impaired hepatic function, comparing them to normals in the same trial.

Final Protocol Submission: by November 1, 2009
Study Start Date: by [redacted]
Trial Completion Date: by November 1, 2010
Final Report Submission: by May 1, 2011 (original communication was 2 years from approval)

b(4)

4. Long-Term Efficacy Trial

You have agreed to conduct and submit the results of a randomized withdrawal clinical trial to address longer-term efficacy for your drug at appropriate doses.

Protocol Submission: by November 1, 2009 (original communication was 6 months from approval)
Trial Start Date: by May [redacted] original communication was [redacted] months from approval)
Trial Completion Date: by November 1, 2012
Final Report Submission: by May 1, 2013 (original communication was 4 years from approval)

b(4)

Please let me know if you have any questions or concerns about the dates above.

Thanks,

Jennifer

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Wed 4/15/2009 4:23 PM
To: Jennifer Hamilton
Cc: Updegraff, Kimberly
Subject: NDA 22-192 (iloperidone) Post Marketing Requirement Agreement

Dear Jennifer,

Please refer to your new drug application (NDA) for iloperidone tablets as well as your resubmission dated and received November 6, 2008. The previously agreed upon postmarketing commitments have been reviewed and are now considered postmarketing requirements. We will need for you to propose timeframes for the following areas highlighted in red:

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17.

Final Protocol Submission: by March 1, 2010
Study Start Date: by [redacted]
Study Completion Date:
Final Report Submission: by March 1, 2014

b(4)

2. Conduct a study investigating the possible in vitro interaction of iloperidone and P-Glycoprotein (P-Gp).

Final Protocol Submission: by ———
Study Start Date:
Study Completion Date:
Final Report Submission: by ———

b(4)

3. Your clinical trial CIL0522A0103, conducted in subjects with normal, mildly and moderately impaired hepatic function, was inconclusive because the exposure for mild subjects was greater than for moderately impaired subjects.

You will, within 2 years of approval, repeat the trial in a group of subjects with moderately impaired hepatic function, comparing them to normals in the same trial.

Final Protocol Submission:
Study Start Date:
Trial Completion Date:
Final Report Submission: by ———

b(4)

4. Long-Term Efficacy Trial

You have agreed to conduct and submit the results of a randomized withdrawal clinical trial to address longer-term efficacy for your drug at appropriate doses.

Protocol Submission: by ———
Trial Start Date: by ———
Trial Completion Date:
Final Report Submission: by ———

b(4)

Please respond by noon on Thursday, April 16, 2009.

Best regards,

Kim

Kimberly Updegraff, RPh, MS
Regulatory Project Manager
Division of Psychiatry Products
Center for Drug Evaluation and Research, FDA
Office of Drug Evaluation
Phone: (301)796-2201

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/s/

Kimberly Updegraff
4/24/2009 03:08:48 PM
CSO

Updegraff, Kimberly

From: Greeley, George
Sent: Wednesday, February 11, 2009 3:01 PM
To: Updegraff, Kimberly
Cc: Mathis, Lisa; Laughren, Thomas P; Mathis, Mitchell
Subject: NDA 22-192 Iloperidone

Importance: High

Hi Kim,

The Iloperidone partial waiver/deferral/plan was reviewed by the PeRC PREA Subcommittee on February 11, 2009. The Division recommended a partial waiver because too few children with disease/condition to study and a deferral because the product is ready for approval in adults. The PeRC agreed with the Division to grant a partial waiver for 0-12 years and a deferral for 13-17 years for this product.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-192

PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE

Vanda Pharmaceuticals, Inc.
Attention: John Feeney, M.D.
Acting Chief Medical Officer
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Dear Dr. Feeney:

Please refer to your New Drug Application (NDA 22-192) dated September 27, 2007, received September 27, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iloperidone tablets 1 mg, 2 mg , 4 mg , 6 mg , 8 mg, 10 mg , and 12 mg.

We also refer to your November 19, 2008, correspondence, received November 19, 2008, requesting review of your proposed proprietary name, Fanapt. We have completed our review of Fanapt and have concluded that it is acceptable.

The proprietary name, Fanapt will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 19, 2008 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Project Manager, at (301) 796-4264.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of New Drugs
Center for Drug Evaluation and Research

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

/s/

Thomas Laughren
2/13/2009 01:34:13 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-192

Vanda Pharmaceuticals, Inc.
Attention: Paolo Baroldi, M.D., Ph.D.
Chief Medical Officer
9605 Medical Center Drive Suite 300
Rockville, Maryland 20850

Dear Dr. Baroldi:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for iloperidone oral tablets.

We also refer to the meeting between representatives of your firm and the FDA on September 10, 2008. The purpose of the meeting was to discuss issues related to the Not Approvable action letter issued on July 25, 2008.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING
NDA 22-192 Iloperidone Tablets
Vanda Pharmaceuticals, Inc
September 10, 2008

Participants –

FDA

Ellis Unger, MD	Deputy Director, Office of Medical Policy
Thomas Laughren, MD	Director, Division of Psychiatry Products
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Team Leader
Phillip Kronstein, MD	Medical Reviewer (Observer)
Peiling Yang, PhD	Statistics Team Leader
Phillip Dinh, PhD	Statistics Reviewer
Raman Baweja	Clinical Pharmacology Team Leader
Andre Jackson	Clinical Pharmacology/Biopharmaceutics Reviewer
Ann Sohn, PharmD	Regulatory Project Manager (Observer)
ShinYe Chang, PharmD	Regulatory Project Manager (Observer)
Kimberly Updegraff, MS	Regulatory Project Manager

Sponsor

Paolo Baroldi, MD	Chief Medical Officer
Argeris Karabelas, PhD	Chairman Board of Directors
Mihael Ploymeropoulos, MD	Chief Executive Officer
Curt Wolfgang, PhD	Vice President of Therapeutic Area

b(4)

Jennifer Hamilton, MS	Clinical Research Scientist

Background:

Iloperidone is an atypical antipsychotic (5HT2 and D2 receptor antagonist). It is an immediate release formulation for bid administration. The NDA 22-192 sought a claim for both the acute and maintenance treatment of schizophrenia, in a total dose range of 12 to 24 mg/day. Iloperidone was developed under IND 36,827. This IND had 3 sponsors, including HMR, Novartis and currently, Vanda. The Division of Psychiatry Products held a number of meetings with the sponsors of this IND during the development of the drug. Key meetings with Vanda included two EOP2 meetings (9-7-05 and 9-12-06) and

Study 3000

FDA analysis: Table 1 summarizes the FDA's analysis focusing on the schizophrenia sample. The primary contrast is between iloperidone 8mg and 12mg combined against placebo. The primary contrast did not separate from placebo (p=0.148), and therefore, no additional comparisons are permitted. Haloperidol is highly statistically significantly superior to placebo (p=0.005) and shows a numerical advantage over all three doses of iloperidone. Haloperidol is also numerically superior to iloperidone 8mg and 12mg combined, although this contrast just misses statistical significance (p=0.063).

Table 1. Study ILP3000ST: FDA's efficacy results: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample (excluding schizoaffective patients)

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal 15mg	Placebo
Sample size	83	78	82	160	70	78
LS Means	9.2	4.8	10.1		12.9	3.5
Difference from placebo	5.7	1.4	6.7	4.0	9.4	
Unadjusted p-values	0.072	0.666	0.037	0.148	0.005	
Difference from haloperidol	-3.7	-8.1	-2.8	-5.4		-9.4
Unadjusted p-values	0.261	0.016	0.402	0.063		0.005

(Source: Vanda's Meeting Package, Table 12, Page 27 and FDA's results)

Protocol-specified primary analysis: Table 2 summarizes the protocol-specified primary analysis that includes all randomized patients. The primary contrast is between iloperidone 8mg and 12mg combined against placebo. The primary contrast did not separate from placebo (p=0.065), and therefore, no additional comparisons are permitted. Haloperidol is highly statistically significantly superior to placebo (p<0.001) and shows a numerical advantage over all three doses of iloperidone. Haloperidol is also numerically superior to iloperidone 8mg and 12mg combined, and this contrast is now statistically significant (p=0.027).

Table 2. Study ILP3000ST: sponsor's primary efficacy results: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal 15 mg	Placebo
Sample size	113	114	115	229	115	117
LS Means	9.0	7.8	9.9		13.9	4.6
Difference from placebo	4.4	3.2	5.2	4.2	9.3	
Unadjusted p-values	0.097	0.228	0.047	0.065	<0.001	
Difference from Haloperidol	-4.9	-6.1	-4.0	-5.1		-9.3
Unadjusted p-values	0.066	0.022	0.126	0.027		<0.001

(Source: Vanda's Meeting Package, Table 14, Page 28 and FDA's results)

Comment: Thus, either approach to defining the sample for this study yields a negative result for iloperidone. With your preferred analysis including all randomized patients, the superiority of haloperidol over the primary iloperidone group (8 + 12 mg) is statistically significant. This study, therefore, provides no support for iloperidone but does suggest the statistically significant superiority of haloperidol over iloperidone.

Study 3004

FDA analysis:
Table 3 summarizes an analysis excluding schizoaffective patients. A sequential testing approach was employed. First, a comparison was carried out between the 10-16 mg/d group and the placebo group. Subsequently, iloperidone 4-8 mg/d was tested against placebo. The results suggest that both iloperidone groups did not separate from placebo. The results also suggest that risperidone was highly significant against placebo (p=0.001). A comparison between the two iloperidone dose groups against risperidone suggests that risperidone was superior to both iloperidone dose groups (p-value = 0.006 against iloperidone 4-8 mg/d and p-value = 0.021 against iloperidone 10-16 mg/d).

Table 3. Study ILP3004ST: FDA's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp 4-8 mg	Placebo
Sample size	115	121	110	116
LS Means	5.8	6.5	10.3	4.9
Difference from placebo	0.9	1.7	5.5	
Unadjusted p-values	0.581	0.306	0.001	
Difference from risperidone	-4.5	-3.8		-5.5
Unadjusted p-values	0.006	0.021		0.001

(Source: Vanda's Meeting Package, Table 9, Page 23)

Protocol-specified analysis: Table 4 summarizes the protocol-specified analysis that includes all patients (schizophrenia and schizoaffective). Again, a sequential testing approach was employed. The comparison carried out between the 10-16 mg/d group and the placebo group was statistically significant (p-value = 0.001) in favor of iloperidone 10-16 mg/d. Subsequently, iloperidone 4-8 mg/d was tested against placebo and was statistically significant (p-value = 0.012). A comparison between the two iloperidone dose groups against risperidone suggests that risperidone was superior to both iloperidone dose groups (p-value = 0.007 against iloperidone 4-8 mg/d and p-value = 0.034 against iloperidone 10-16 mg/d).

Table 4. Study ILP3004ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp 4-8 mg	Placebo
Sample size	143	149	146	152
LS Means	6.2	7.2	10.3	2.5
Difference from placebo	3.8	4.7	7.8	
Unadjusted p-values	0.012	0.001	<0.001	
Difference from risperidone	-4.0	-3.1		-7.8
Unadjusted p-values	0.007	0.034		<0.001

(Source: Reproduced from ILP3004st-legacy Report; Table 9.1-2, page 543 and FDA's results)

Comment: Although the all-patients analysis yields a positive result vs placebo for both iloperidone dose groups, both analyses suggest clear inferiority of iloperidone at these doses to a standard dose range for risperidone. Thus, either approach to defining the sample for this study yields a result that favors a standard control agent over iloperidone.

Study 3005

FDA analysis: Table 6 summarizes an analysis excluding the schizoaffective patients. For this study, a sequential testing procedure was employed. Iloperidone 12-16 mg/d was tested first at a 0.05 level. If this test was significant, then the iloperidone 20-24 mg/d would be tested. Both iloperidone dose groups were statistically significantly superior to placebo. The results also suggest that risperidone was numerically, if not statistically, superior to iloperidone at the 20-24 mg/day group (p=0.093), and both numerically and statistically significantly superior to iloperidone at the 12-16 mg/day dose (p=0.005).

Table 5. Study ILP3005ST: FDA's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	178	111	119	113
LS Means *	7.4	8.8	11.4	4.3
Difference from placebo	3.1	4.5	7.1	
Unadjusted p-values	0.033	0.005	<0.001	
Difference from risperidone	-4.0	-2.7		-7.1
Unadjusted p-values	0.005	0.093		<0.001

(Source: Vanda's Meeting Package, Table 5, page 18 and FDA's results)

Protocol-specified analysis: Table 6 summarizes the protocol-specified primary analysis including both schizophrenia and schizoaffective patients. Iloperidone 12-16 mg/day did not separate from placebo (p-value = 0.09). Consequently, iloperidone 20-24 mg/d cannot be considered. We concluded this was a negative study based on the primary analysis. Risperidone appears to be superior to both iloperidone 12-16 mg/d and 20-24 mg/d (p-values < 0.001 and 0.034, respectively).

Table 6. Study ILP3005ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	230	141	148	152
LS Means*	7.1	8.6	11.5	5.0
Difference from placebo	2.1	3.5	6.5	
Unadjusted p-values	0.090	0.010	<0.001	
Difference from risperidone	-4.4	-3.0		-6.5
Unadjusted p-values	<0.001	0.034		<0.001

(Source: Reproduced from ILP3005st-legacy Report; Table 9.1-2, page 586 and FDA's results)

Comment: For this study, the all-patients analysis yields a negative result for the 12-16 mg/day group, and, therefore, the 20-24 mg/day group cannot be considered. Furthermore, this is yet another demonstration of the apparent inferiority of iloperidone at these doses to a standard dose range for risperidone. Thus, once again, either approach to defining the sample for this study yields a result that appears to favor a standard control agent over iloperidone.

In summary, of the 4 studies of particular interest from the standpoint of efficacy (i.e., 3101, 3000, 3004, and 3005), only study 3101 provides convincing evidence of both efficacy for iloperidone and comparable efficacy to an approved antipsychotic agent.

- For study 3000, whether the analysis focuses on the schizophrenic subgroup or all patients, it does not provide evidence of efficacy for iloperidone. Furthermore, in your preferred analysis including all patients, haloperidol is clearly superior to placebo and appears to be statistically significantly superior to iloperidone.

- For study 3004, the analysis including all patients does show superiority of iloperidone over placebo, a finding that is not seen for the analysis including only schizophrenic patients. In both instances, however, risperidone appears to be statistically significantly superior to iloperidone.
- For study 3005, only the analysis focused on the schizophrenic subgroup shows superiority of iloperidone over placebo. In your preferred analysis, iloperidone fails to show superiority to placebo and, at the same time, risperidone appears to be statistically significantly superior to iloperidone.

Questions:

Question 1

We have now attempted to assess the relative effectiveness of iloperidone vs. risperidone in Study 3005, and after accounting for one significant confounding factor, we have demonstrated that both iloperidone doses examined in this study (12-16 and 20-24 mg) as well as risperidone (6-8 mg) are superior to placebo and that both iloperidone dose groups are similarly effective and their effect is similar to that of risperidone in this study.

Does the Agency agree with this assessment?

Preliminary Comments: Your primary focus in trying to fix study 3005 is on differential dropouts. In order to address the different durations that iloperidone and risperidone patients remain in the trial, you propose to include length of stay as a covariate in the model. Using this approach, you claim to have shown that all 3 active treatment arms (2 iloperidone and 1 risperidone arm) are superior to placebo, and there is comparable efficacy among the 3 active treatment arms. You have also acknowledged, however, an obvious problem with including as a covariate in the model a variable that is itself an observed outcome. In fact, how long patients are able to stay on assigned medication in a schizophrenia trial might be considered a reasonable primary endpoint (this was the primary endpoint in the CATIE trial). Thus, we are not persuaded by this exploratory analysis. Your other major concern about study 3005 seemed to be the potential for unblinding resulting from patient and clinician familiarity with the adverse event profile of risperidone. If true, however, this bias would entirely invalidate the trial.

Discussion at Meeting: Given FDA's willingness to consider analyses including all randomized patients in the 3 Novartis studies (3000, 3004, and 3005), Vanda has focused again on study 3004 as the one positive study among these 3 studies. Thus, they now seem to concede that study 3005 is not a positive study overall. Nevertheless, they continue to view the significant contrast between the iloperidone 20-24 mg/day arm vs placebo as supportive evidence. They do, however, object to the CATIE trial as an illustration of the dropout problem they faced in their trials with iloperidone. They argue that their dropouts were within the first two weeks, due to lack of effect resulting from difficulty in getting patients up to an effective exposure level, compared to the dropouts occurring after weeks and months of therapy in the

CATIE trial. The sponsor continues to feel that the exploratory analyses they have done with study 3005, including both the analysis using length-of-stay as a covariate and the analysis including only patients who were able to complete 2 weeks of treatment, along with the observed cases analysis for this study, provide reassurance that iloperidone is an effective therapy in patients who can be brought up to an effective exposure level and not inferior to alternative therapies once this level is achieved.

Question 2

We have now assessed the impact of diagnosis on efficacy outcomes in Study 3004. After accounting for the treatment by diagnosis (schizophrenia and schizoaffective) interaction, we have demonstrated that the original finding of a positive study remains. That is that both doses of iloperidone (4-8 mg and 10-16 mg) are superior to placebo and under the new analysis the 10-16 mg dose appears to have an effect similar to that of risperidone (4-8 mg) in this study.

Does the Agency agree with this assessment?

Preliminary Comments: As revealed in our introductory note, we are now willing to consider an analysis of all patients randomized for study 3004, since this was the planned analysis for that study. Although an analysis of all patients for study 3004 does suggest superiority for iloperidone over placebo, the problem remains that, in either case (schizophrenic subgroup alone or all patients randomized), risperidone appears to be statistically significantly superior to iloperidone. Thus, there is no reason to conduct the exploratory analysis you have proposed. Nevertheless, we will comment on your proposed analysis because we feel there are problems that invalidate it.

Table 7 below provides the results from your analysis that included a treat-by-diagnosis term in the model. Diagnosis is dichotomized to schizophrenia or schizoaffective.

Table 7. Study ILP3004ST: BPRS adjusted mean change from baseline and p-values, LOCF analysis, all patients using treatment-by-diagnosis in model

Treatment	LS means change from week 6 to baseline	Pairwise comparisons (p-values)		
		Ilo 4-8mg/d	Ilo 10-16mg/d	Risp 4-8mg/d
Ilo 4-8mg/d	7.0	--		
Ilo 10-16mg/d	9.3	0.234	--	
Risp 4-8mg/d	10.5	0.058	0.500	--
Placebo	0.4	<0.001	<0.001	<0.001

(Source: Vanda's Meeting Package, Table 11. page 25)

Your interpretation of the treatment benefit for all patients based on Table 7 is problematic, in our view. The significance of the treatment-by-diagnosis interaction, if true, suggests, as you have noted, that the treatment benefit is

different between the schizophrenia and schizoaffective patients. Indeed, this treatment-by-diagnosis interaction appears qualitative for this study. Thus, it is difficult to infer that the treatment effects for iloperidone seen in Table 7 represent the treatment effects overall. The results broken down by diagnosis (schizophrenia and schizoaffective) further strengthen our belief (Table 8). There is no difference between iloperidone 4-8 mg/d and 10-16 mg/d and placebo (p-values 0.417 and 0.415, respectively) among schizophrenia patients. The results also suggest that iloperidone 4-8 mg/d and 10-16 mg/d are different from risperidone 4-8 mg/d (p-values 0.009 and 0.008, respectively). The apparent effectiveness seen in Table 7 seems to come entirely from the schizoaffective patients (p-values < 0.001 for both iloperidone dose groups).

Table 8. Study ILP3004ST: BPRS adjusted mean change from baseline and p-values, LOCF analysis, broken down by diagnosis, using treatment-by-diagnosis in model

Treatment	Diagnosis	LS means change from week 6 to baseline	Ilo 4-8mg/d		Ilo 10-16mg/d		Risp 4-8mg/d		Placebo	
			Schizo-phrenia	Schizo-affective	Schizo-phrenia	Schizo-affective	Schizo-phrenia	Schizo-affective	Schizo-phrenia	Schizo-affective
Ilo 4-8mg/d	Schizophrenia	5.7	--							
Ilo 4-8mg/d	Schizoaffective	8.3	0.347	--						
Ilo 10-16mg/d	Schizophrenia	5.7	0.993	0.340	--					
Ilo 10-16mg/d	Schizoaffective	12.9	0.009	0.190	0.010	--				
Risp 4-8mg/d	Schizophrenia	10.1	0.009	0.522	0.008	0.315	--			
Risp 4-8mg/d	Schizoaffective	10.9	0.039	0.432	0.037	0.541	0.758	--		
Placebo	Schizophrenia	4.4	0.417	0.150	0.415	0.002	0.001	0.009	--	
Placebo	Schizoaffective	-3.6	<0,001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	--

(Source: FDA's results)

These findings tend to argue that it would not be appropriate to pool and analyze the efficacy data for the schizophrenia and schizoaffective subgroups in this trial. It may be that this is an anomaly, but pooling the data for analysis doesn't fix this problem.

Discussion at Meeting: As noted in the discussion comments for question 1, the sponsor now views study 3004, as originally analyzed (i.e., without the treatment-by-diagnosis term in the model), as one of two positive studies in support of their efficacy claim for iloperidone. We had criticized the alternative model because, upon closer inspection, it is clear that the positive effect is coming entirely from the schizoaffective subgroup, and almost none from the schizophrenic subgroup. Thus, we viewed the model as inappropriate.

Post-Meeting Note: Of course, what becomes apparent in closely examining results from this study is that the original model applied to the all-randomized population has the same problem, i.e., the positive findings are coming almost entirely from the schizoaffective subgroup, and this is the analysis that one would need to rely on to view this as a positive study.

Question 3

With the analysis described in the prior two questions, the data from Study 3101 where iloperidone (24 mg) was shown to be similar to ziprasidone (160 mg) and the supporting evidence from Study 3000 where iloperidone 12 mg was shown to be effective and not significantly different than haloperidol, we conclude that iloperidone is effective at doses of 4-24 mg for the acute treatment of schizophrenia with a target of 10-16 mg (see proposed labeling, Appendix F).

Does the Agency agree with this assessment?

> ***Preliminary Comments:*** For all the reasons discussed in detail in our introductory comments and in responses to questions 1 and 2, we disagree. We agree that study 3101 provides evidence of efficacy for iloperidone at a dose of 24 mg/day, and comparable efficacy to ziprasidone at a dose of 160 mg/day. The data from the remaining trials (3000, 3004, and 3005) are problematic, and, at most, consistently suggest that iloperidone at the doses studied may be inferior to available antipsychotic agents, in particular, risperidone and haloperidol. As indicated in our 7-25-08 approvable letter, we continue to feel that an additional adequate and well-controlled efficacy trial would be required, and would need to include an active control arm.
>
> ***Discussion at Meeting:*** As noted, the sponsor is now arguing that studies 3101 (at a dose of 24 mg/day) and study 3004 (at doses of both 4-8 mg/day and 10-16 mg/day) provide the primary support for the efficacy of iloperidone. They also feel that the positive contrasts for iloperidone 12 mg/day in study 3000 and 20-24 mg/day in study 3005 should be considered at least supportive of iloperidone's efficacy. They also argue that their pk-pd modeling for studies 3000, 3005, and 3101 tend to support 12 mg/day as a reasonable threshold dose to target.
>
> The sponsor proposes three arguments against considering the contrasts of the iloperidone arms and comparator drug arms as evidence of the inferiority of iloperidone to the comparator drugs, risperidone and haloperidol.
>
> -One argument is a strength of evidence argument. They argue that, if we are going to consider these contrasts in our decision-making for this drug, it is essential that we correct for multiple comparisons, just as we did this in the primary comparisons of interest, i.e., vs placebo. Using a Bonferroni approach, of the 7 contrasts on interest, only 2 remain statistically significant.
>
>> **Post-Meeting Note:** It could be argued that a more rational approach to considering comparisons of the active comparator and iloperidone would be a sequential approach, beginning with the highest iloperidone dose and moving to lower doses only if significance was achieved at the highest dose. No adjustment would be needed for this approach. Using this approach, study 3000 would no longer provide support for superiority of an active comparator (in this case haloperidol 15 mg/day), because the contrast for the highest iloperidone dose of 12 mg/day is not significant (p=0.126). However, for study 3004, the contrast for risperidone 4-8

mg/day vs iloperidone 10-16 mg/day is significant (p=0.034). Similarly, for study 3005, the contrast for risperidone 6-8 mg/day vs iloperidone 20-24 mg/day is significant (p=0.034). Thus, in 2 of the 3 studies, the active comparator appears to be superior to the highest dose of iloperidone studied.

-A second argument is that we should not consider the apparent inferiority of iloperidone to risperidone and haloperidol as a risk to this population sufficient to justify not approving this product. They argue that the apparent inferiority can be attributed to dropouts within the first 2 weeks due to lack of efficacy, resulting from the necessarily slow titration with this drug. They contend that a similar pattern is seen with other drugs we have approved, i.e., ziprasidone and quetiapine, and that these drugs are widely used in treating schizophrenia in the US and widely perceived to be effective. They point out that our decision not to approve iloperidone rests on the assumption that this apparent inferiority of iloperidone to risperidone and haloperidol represents a significant risk to patients. They argue that this risk has not been demonstrated and is not real. They challenge us to show that there is an increased risk of suicidality resulting from a somewhat reduced efficacy for iloperidone in the first 2 weeks of treatment. They argue that clinicians always have the option of switching patients to another treatment if the patient is not improving rapidly enough and that an increased risk of suicide in this initial phase of treatment has not been shown.

-The third argument is that we are ignoring potential safety advantages of iloperidone compared to other antipsychotic agents. They provided brief summary data suggesting advantages with respect to 5 safety issues: akathisia, EPS, prolactin, weight gain, and lipids.

Question 4

We have demonstrated that iloperidone is effective at doses of 4-24 mg in Studies, 3000, 3004, 3005 and 3101. We also have demonstrated that iloperidone (10-16 mg) is non inferior to haloperidol (15mg) in time to discontinuation in 52-week studies. We have accumulated a safety database at 10-16mg that meets the ICH guidelines at the targeted dose.

Does the Agency agree with this assessment and that our current safety database is adequate?

Preliminary Comments: As noted in response to question 3, we do not feel that you have provided reliable evidence of efficacy for iloperidone in the dose range of 10 to 16 mg/day. Consequently, we continue to view your safety database as inadequate for the dose range where iloperidone may have efficacy, i.e., 20-24 mg/day.

Discussion at Meeting: The sponsor argued that they have demonstrated that iloperidone is effective in a dose range of 12 to 24 mg/day, and that they have sufficient safety data in this dose range to support approval.

Post-Meeting Note: It would be necessary to re-examine the extent of safety experience in this dose range, but in advance of such an exploration, we would first need to agree that iloperidone has been shown to be effective in the 12 to 24 mg/day dose range. This is more problematic, because the increased focus on study 3004 raises a significant concern that the all-randomized patients analysis for this study is valid, given the qualitative difference in outcomes for the schizophrenic and schizoaffective subgroups.

Question 5

Regarding the Agency's concern with Hepatic Study CILO522A0103, Vanda requests that this study be done as a post-marketing commitment. Vanda feels that labeling can address the lack of the additional information and propose the following text.

b(4)

Does the Agency agree with this approach?

Preliminary Comments: We can discuss this issue at the meeting.

Discussion at Meeting: We noted our concern that the study described in their proposed labeling statement is not interpretable, and therefore, the advice to clinicians is confusing. We noted that, if the study were to be done during phase 4, we would want labeling to state, in the meantime, that the drug should not be used in patients with any degree of hepatic impairment. In their response to the action letter, the sponsor will propose an approach and rationale for addressing this concern, including the conduct of a hepatic study.

Question 6

Regarding the Agency's request for investigating the possible in vitro interaction of iloperidone and P-Gp, Vanda understands the scientific rationale for this request and agrees to perform this in vitro interaction study. However, because this information would not instruct dosing recommendations and henceforth labeling, Vanda respectfully requests that this study be performed as a post-marketing commitment.

Does the Agency agree with this approach?

> ***Preliminary Comments:*** We can discuss this issue at the meeting.
>
> ***Discussion at Meeting:*** We indicated that we accepted the sponsor's proposal to conduct this study as a phase 4 commitment.

Question 7

We have attempted to assess the impact of location (USA vs. Non-USA) on efficacy outcomes in the iloperidone development program. We observed that neither iloperidone nor risperidone were superior to placebo in Study 3005 among the USA subpopulation. In addition, evaluation of efficacy of iloperidone in the USA subpopulation in Studies 3000, 3004 and 3101 support the efficacy of iloperidone in this subpopulation.

Does the Agency agree with this assessment?

> ***Preliminary Comments:*** Given that your preferred analysis for study 3005 is the all patients analysis, this is a negative study. Thus, while we agree that the data coming from US sites is not suggestive of any drug effect for either iloperidone or risperidone, this fact is of little consequence given the overall results of the trial. Study 3004 is a problematic trial for all the reasons discussed above, as is study 3000. Therefore, in our view, study 3101 remains the only reliable source of evidence for the efficacy of iloperidone, and we acknowledge that this study was conducted mostly in the US. If you do decide to conduct a second efficacy study, we recommend that it include a substantial number of US patients.
>
> ***Discussion at Meeting:*** If study 3004 could be considered one of 2 studies supporting the efficacy of iloperidone, this concern about an apparent disparity between results in US and non-US sites would no longer be an issue, since this difference was not observed in study 3004. As noted, however, we consider study 3004 to be problematic.

Post-Meeting Summary Comments to Sponsor:

-We feel that you have made several plausible arguments that we can consider regarding the apparent inferiority of iloperidone to risperidone and haloperidol: (1) your contention that the apparent inferiority of iloperidone to the active comparators risperidone and haloperidol is only temporary due to differences in the time it takes to get patients to effective exposures for iloperidone, (2) your contention that this early difference does not represent a significant risk to patients, and (3) there are other safety advantages that

iloperidone has over other antipsychotic drugs in the class that tend to mitigate this early disadvantage in efficacy.

-We think that the argument about the need for multiplicity adjustments for the comparisons of active control drugs to iloperidone is weak. Using a sequential approach, there still remain 2 illustrations of an apparent disadvantage for iloperidone in efficacy. As we've noted, we think it would be best to acknowledge this disadvantage and strengthen the argument that this is only an early difference and does not represent a significant risk for patients.

-There remains a concern, however, about the primary source of evidence for the efficacy of iloperidone.

-**Study 3101** is still the only unambiguously positive study, in our view.

-**Study 3004** As we have noted, we consider the all-randomized patients analysis of study 3004 problematic because of the qualitative differences in outcomes for the schizophrenic and schizoaffective subgroups, and the analysis focusing only on the schizophrenic subgroup is not positive. [Note: Have you done similar analyses to those you provided for study 3005 illustrating that the weakness in the data for the schizophrenic subgroup is a result of early dropouts for lack of efficacy, and that patients who remain on drug catch up and are effectively treated?]

-**Study 3000** is negative overall.

-**Study 3005** That leaves study 3005 as the only remaining primary source of support. As noted, we consider the analysis focusing on the schizophrenic patients as positive overall, however, we remain concerned about the geographic disparity in results. The positive findings are coming almost entirely from nonUS sites. Thus, you would need to make a convincing argument that this disparity should not be a concern. In addition, of course, relying on study 3005 as a second primary source of support would mean that the effective target dose range is 20-24 mg/day, and there are not sufficient safety data, in our view, to support this target dose.

Conclusions:

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Vanda Pharmaceuticals, Inc. is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Kimberly Updegraff, R.Ph., M.S.
Regulatory Project Manager

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/s/

Thomas Laughren
9/22/2008 12:40:16 PM

no significant effect for iloperidone, while risperidone 4-8 mg showed a highly significant effect. Study 3000 included fixed doses of 4, 8, and 12 mg iloperidone, as well as haloperidol and placebo, and showed a marginal effect of 12 mg (the study was nominally negative as the primary endpoint was the combined 8/12 mg group effect, and this was in fact NS).

2.1 Study 3101

Study 3101 was a straightforward, predominately US, some India, 4 week comparison of iloperidone 24 mg and ziprasidone 160 mg. The effect on the PANSS is shown in the table, using an MMRM analysis, rather than more common (in the past) LOCF.

Study 3101					
	n	Baseline PANSS	Mean Change	Diff from Plbo	p value
Ilo 24 mg	283	92.7	- 12.0	4.9	p = 0.007
Zip 160 mg	144	90.9	- 12.3	5.2	p = 0.012
Placebo	140	90.3	- 7.1	---	

[The lower p-value for iloperidone reflects the truly huge sample size]. This is a clearly positive study and the effect of iloperidone does not seem to be unduly small. I note Dr. Laughren's disagreement with the primary reviewer's desire to comment in labeling on one study site's weaknesses and I agree with him. If we believe this study is positive despite the unreliability of one site, which is apparently everyone's view, I see little reason to undermine the study in labeling. I note that the study had 50% African-Americans, 35% Caucasian, and 8% Asians, and that 84.5% of patients were paranoid schizophrenics.

2.2 Study 3005

This was a 6 week study, conducted in 67 sites in the US, Canada, S. Africa, Israel, and Eastern Europe comparing iloperidone 12-16 mg, iloperidone 20-24 mg, risperidone 6-8 mg, and placebo in a mixed population of schizophrenic and schizo-affective patients. The study posed a variety of analytic issues but, in the end, our analysis was sensible. We considered the schizophrenic subset only (75-80% of the total), not the schizo-

affective patients, and did an MMRM analysis in addition to the planned LOCF, a very good idea as only 58% of patients completed the 6 weeks. The LOCF results are shown in the table below. A MMRM analysis (Dinh) gives similar results.

Study 3005					
	n	Baseline BPRS	Mean Change	Diff Placebo	p-value
Ilo 12-16	178	54.4	- 7.4	3.1	p=0.033
Ilo 20-24	111	55.0	- 8.8	4.5	p=0.005
Risp 6-8	119	55.1	- 11.4	7.1	p=<0.001
Placebo	113	55.3	- 4.3	--	

[I note that the analytic plan was for a sequential analysis of the whole population, (schizophronics and schizo-affective patients), with the 12-16 mg group needing to be significant, before going on to other analyses. The study failed because the p value was 0.09 for the 12-16 mg analysis, even though nominal p value for 20-24 mg was 0.01. Had they used a Bonferroni, each at 0.025, they'd have "won." Why they made the sample size larger for the 12-16 mg group, and used the planned sequential analysis is not known to us but is certainly odd].

There are two further problems with study 3005, particularly pertinent to the question of whether it represents a second study supporting effectiveness, which Dr. Khin thinks it does and Drs. Chuen and Laughren think it does not (at least not quite): 1) effect size vs risperidone, 2) effect in the US population.

2.2.1 1) Effect size

The effect of risperidone is substantially greater than iloperidone 20-24, and this is an issue, even though the nominal p-value for the comparison of risperidone with 20-24 mg is p=0.093 (p=0.005 vs 12-16 mg). We have in the last year : b(4)

b(4)

2.2.2 2) Effect in US

As Dr. Laughren points out (p 9), Dr. Dinh has examined the data in study 3005 by region, finding that the non-US sites, representing about 55-60% of patients, drive the favorable result, with an effect vs placebo of 1.21 points on the BPRS in the US vs 7.11 for non-US sites. Although it is true, as Dr. Laughren notes, that we have seen such findings more often than one might expect, as study 3005 is the only other study that provides any support for the 20-24 mg dose, the absence of any suggestion of an effect in the US is a problem and is an important component of my view that iloperidone should not be approved.

3.0 Safety

Apart from the size of the 20-24 mg safety database, there are 2 other issues: QT prolongation and dose-response of adverse effects, both relevant to the need for more study of the larger dose.

3.1 QT

Iloperidone plainly has a significant QT effect, with a positive hERG at a pretty low concentration (0.1 microM and above). The TQT study carried out had no placebo, a limitation, but I am less dissatisfied with it than the QT team. The QT review was also critical of lack of blinding, and there are some grounds for concern, but ECG's were blindly read and the lack of blinding might be a greater concern had the study been negative, which it was not. The QT review also said that assay sensitivity was not confirmed because no clear quetiapine effect (apparently 10 msec was expected based on asenapine and peliperidone studies) was seen, but in fact the study did show a ziprasidone effect of roughly expected size (perhaps somewhat smaller) and an effect of iloperidone that was larger, and that increased with maneuvers that inhibited iloperidone metabolism (3A4, 2D6 inhibition), so there is clearly evidence that the study detected QT effects and found them to be of roughly the expected size.

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The effects with no inhibitor (period 1) a 2D6 inhibitor (period 2) and both 3A4 and 2D6 inhibitors (period 3, paroxetine and ketoconazole) were:

	Ilo 8	Ilo 12	Ilo 24	Zip	Quet
Period 1 Least Sq Mean	+ 9.1	+ 9.7	+14.6	+ 9.7	+ 1.3
Period 2	+ 11.9	+ 11.9	+ 16.0	+ 15.4	+ 2.1
Period 3	+ 15.8	+18.5	+ 17.6	__	__

The paroxetine (period 2) and paroxetine/ketocanozole (period 3) increased the peak concentration of the iloperidone 24 by 30% and 54% respectively, with greater effects at lower doses of iloperidone. Concentrations of iloperidone after doses of 12 and 24 mg were not very different from each other in the inhibited state, especially in period 3.

All in all, and despite the lack of discernable TdP or clear pro-arrhythmic effects in trials, iloperidone plainly has a QT effect at least as large as ziprasidone (actually, probably somewhat larger) and would need labeling similar to ziprasidone (consider alternatives). The increase in QTc with metabolic inhibition was modest but so was the effect on Cmax. This would not necessarily bar study of higher doses than 24 mg but there would need to be good reason to go higher. I agree with Drs. Laughren and Khin that none of the deaths are notably suspicious for TdP. I note also that in the clinical database there was a roughly 10 msec increase in QTcF compared to placebo at iloperidone 20-24 mg, but no major change in outliers.

3.2 Dose-related ADRs

As a peripheral alpha-adrenergic blocker, iloperidone requires daily titration doing the first week to avoid orthostatic hypotension and syncope. This would be a major burden to any user. Drs. Laughren and Khin have gone through the major other toxicity concerns (seizures, priapism, weight gain, suicidality, hyperglycemia, lipid effects, anemia, and CPK elevations) and I have little to add.

In Dr. Chuen's Table 7.1.5.3.1 (p 64) there are very few dose related adverse effects.

	Placebo	Ilo 10-16	Ilo 20-24
Tachycardia	0.9%	2.5%	7.7%
Dizziness	7.0%	10.4%	19.7%

These are both presumably alpha-blocker effects and they occurred despite the careful titration. I did not see other ADR's that seemed dose limiting.

4.0 Action

I agree with Dr. Laughren's NA plan, and have suggested wording for the NA letter.

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/s/

Robert Temple
7/25/2008 06:36:24 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 16, 2008

TO: Kimberly Updegraff, Regulatory Project Manager
Mitchell Mathis, M.D., Medical Officer

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-192

APPLICANT: Vanda Pharmaceuticals, Inc.

DRUG: Trade name – to be determined (generic name - iloperidone)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Treatment of schizophrenia

PDUFA DATE: July 27, 2008

I. BACKGROUND: Iloperidone is a psychotropic agent belonging to the chemical class which shares the binding characteristics of other developed psychotropic agents. The clinical development of iloperidone was initiated by Hoechst Marion Roussel in 1990. Novartis licensed iloperidone in 1998 and continued clinical development until 2004, at which time Vanda licensed iloperidone and completed clinical development of iloperidone tablets for the treatment of schizophrenia. Vanda submitted a New Drug Application (NDA 22-192) for iloperidone on September 27, 2007 for the treatment of schizophrenia. The Division of

Medical Errors and Technical Support is conducting a trade name review of the proposed trade names for iloperidone: Fiapta (first choice) and Fanapta (second choice).

Clinical data from studies conducted by all 3 sponsors are included in this NDA. Iloperidone efficacy and safety data are based on 10 controlled clinical trials. Of these 10 trials, 5 placebo-controlled trials provided data for the assessment of short-term efficacy. Long-term efficacy was assessed in 3 active-controlled trials. In addition to the 10 controlled clinical trials, 17 Phase 1 trials in healthy volunteers provide data on the clinical pharmacology of iloperidone. Furthermore, nine additional Phase 1 and Phase 2 trials in patients with schizophrenia and one trial in elderly patients with dementia were conducted.

Clinical investigator sites participating in the following two protocols were chosen for audit based on high enrollment:

Protocol VP-VYV-683-3101: A randomized, double-blind, placebo- and ziprasidone-controlled, multicenter study to evaluate the efficacy, safety and tolerability of a 24 mg/day dose iloperidone given b.i.d. for 28 days to schizophrenic patients in acute exacerbation followed by a long-term treatment phase

This is a prospective, randomized, placebo- and ziprasidone-controlled, double-blind, parallel-group, multicenter study to evaluate the efficacy and safety of fixed doses of iloperidone and ziprasidone in adults age 18-65 with schizophrenia. The primary objective of the short-term, double-blind phase was to evaluate the efficacy of a 24 mg/day iloperidone dose compared with placebo, administered bid over 28 days to schizophrenic patients. After a pre-randomization phase, the dosage of study medication was gradually increased over a period of 7 days using a fixed-titration regimen, whereby the doses were increased gradually from iloperidone 2 to 24 mg/day and ziprasidone 40 to 160 mg/day (dose titration period: Days 1 to 7). During the maintenance period (Days 8 to 28), a fixed maintenance dosage of study medication was administered (iloperidone 24 mg/day and ziprasidone 160 mg/day). The primary efficacy variable was the change from baseline to endpoint (Day 28 or early termination) in the PANSS-T (Positive and Negative Syndrome Scale total) score in the modified ITT population. The primary analysis was the comparison of iloperidone to placebo using the MMRM (Mixed Model Repeated Measures) model with baseline as covariate. After completion of the 4-week, double-blind phase, patients were given the option to continue iloperidone treatment in a long-term, open-label phase for an additional 175 days. The long-term, open-label phase consisted of a 7-day fixed titration period and a 24-week flexible maintenance period.

Protocol ILO522 3005: A randomized, double-blind, placebo- and risperidone-controlled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given bid for 42 days to schizophrenic patients, followed by a long-term treatment phase with iloperidone given qd.

This is a randomized, double-blind, placebo- and risperidone-controlled, multicenter study to evaluate the safety and efficacy of two dose ranges of iloperidone, followed by a long-term treatment phase in subject 18-65 years of age with schizophrenia or schizoaffective disorder.

The primary objective of the study is to determine the efficacy and safety of iloperidone 12-16 mg/day (administered as 6 or 8 mg bid) and 20-24 mg/day (10 or 12 bid) and risperidone 6-8 mg bid (3 or 4 mg bid) compared with placebo over 42 days in patients with schizophrenia or schizoaffective disorder. After a single-blind placebo run-in period (Days -2 to 0), subjects entered a double-blind treatment phase (6 weeks), consisting of a seven-day fixed titration period followed by a flexible-dosage maintenance period. Subjects were assigned to one of four treatment groups: iloperidone 12-16 mg/day, iloperidone 20-24 mg/day, risperidone 6-8 mg/day, and placebo. Initially, patients were randomized in a ratio of 2:1:1 to receive bid treatment with iloperidone 12-16 mg/day, risperidone 6-8 mg/day, or placebo. After the results of Study ILP3004 indicted that patients might benefit from a higher iloperidone dosage than 16 mg/day, randomization to iloperidone 20-24 mg/day was initiated; at that time approximately one-half of the anticipated enrollment had been completed. Patients were subsequently randomized in a ratio of 1:2:1:1 to receive treatment with iloperidone 12-16 mg/day, iloperidone 20-24 mg/day, risperidone 6-8 mg/day, and placebo. The primary efficacy variable was the adjusted mean change from baseline to the 6-week endpoint on the Brief Psychiatric Rating Scale (BPRS). Treatment comparison was between each of the iloperidone treatment groups and placebo. The primary treatment comparison was between the iloperidone 12-16 mg/day group and the placebo group. If this comparison was significant, the 20-24 mg/day group was to be compared to placebo. Patients were switched to open-label treatment on Day 50, the first day of the long-term maintenance period. On Day 43, all patients were switched from the bid dosing regimen to a once daily regimen. Patients who received iloperidone during the short-term double-blind phase had their study medication restarted at a dose of 8 mg/day. Patients who received either resperidone or placebo during the short term, double-blind phase were changed to iloperidone at a starting dose of 2 mg/day. Titration of all subject doses could be performed from Day 50 onwards. The maintenance treatment could consist of iloperidone 4, 8, 12, 16, or 24 mg/day.

Protocol CILO522 0108: An Open Label, One Sequence Crossover Study in Healthy Subjects to Evaluate the Pharmacokinetics of Iloperidone and Fluoxetine Administered Separately and in Combination"

This pharmacokinetics study was audited by HFD-48 GLP/Bioequivalence simultaneously with the HFD-47 Sponsor audit for NDA 22-192.

II. RESULTS (by Site):

Name of CI, or Sponsor City, State or Country	Indication: Protocol # and # of Subjects	Insp. Date	Interim Classification NAI/VAI/OAI	Final Classification NAI/VAI/OAI/ Pending
John Gilliam	Protocol VP-VYV-683-3101	Not Done, deceased	----	-----
Rick Mofsen	Protocol ILO5223005: pending Protocol VP-VYV-683-3101: pending	Pending	NAI	Pending

Tram Tran-Johnson	Protocol ILO5223005: 50 enrolled, 25 audited Protocol VP-VYV-683-3101: 30 enrolled, 15 audited	3/4 – 3/7/08;3/10 , 3/12, 3/20, 3/21, and 3/28/08	VAI	VAI
Miro Jakovljevic	Protocol ILO5223005: 13 enrolled, 9 audited	4/21/08 – 4/25/08	VAI	Pending
Vera Folnegovic-Smalc	Protocol ILO5223005: 30 enrolled, 7 audited	4/13/2008-4/18/2008	VAI	Pending
Saibal Nandy	Protocol ILO5223005: 8 enrolled	4/28/2008 – 5/1/2008	VAI	Pending
Vanda	Protocol ILO5223005, Protocol VP-VYV-683-3101, and Study CILO522 0108	4/16/08 – 4/24/08	VAI	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. John Gilliam, M.D.
International Clinical Research Associates
1601 Rolling Hills Dr., Suite 210
Richmond, VA 23229-5011

Although Dr. Gilliam's site was included in the original assignment, DSI and the Division of Psychiatry decided not to pursue this inspection due to Dr. Gilliam's legal issues and subsequent death.

2. Rick Mofson, D.O.
Clinical Research, Inc.
St Louis, MO 63118

a. **What was inspected**: Inspection was conducted in accordance with Compliance Program 7348.811. For study ILO5223005, 34 subjects were screened and 23 subjects were enrolled. For Study VP-VYV-683-3101, 38 subjects were screened, 24 were enrolled, and 15 completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: No Form FDA 483 was issued to the investigator.

c. **Assessment of data integrity:** The data from Dr. Mofson's site appear acceptable for use in support of the NDA.

3. **Tram K. Tran-Johnson, Pharm.D.**
9466 Black Mountain Rd Ste 100
San Diego, CA 92126-4550

a. **What was inspected:** This inspection was conducted in accordance with Compliance Program 7348.811 on 9 days between March 4 and March 28, 2008. For study ILO5223005, 74 subjects were screened, 50 subjects were enrolled, and 21 subjects went on to participate in the long term phase. For study VP-VYV-683-3101, a total of 49 subjects were screened, 30 subjects started and completed at least some of the short term phase, and 3 subjects went on to participate in the long term phase. Complete files were reviewed for the subjects audited. All informed consent documents were verified, and data points were verified for those subjects audited. Written informed consent was obtained from all subjects prior to their entrance into the study. The data in the clinical investigator's records were compared to the case report files and the data supplied by the sponsor to FDA in support of its NDA, including primary objectives, secondary objectives, adverse events, subject randomization, subject discontinuations, and concomitant medications. Institutional Review Board correspondence and drug accountability records were also reviewed. There were no limitations to the inspection.

b. **General observations/commentary:** Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. In general, the inspection revealed that subjects were informed appropriately; the study proceeded following IRB authorization; and information pertaining to concomitant medications and discontinuations was reported in a timely manner (adverse events were not, and these are described below). The recordkeeping system appeared adequate for tracking study medications, and the source documents were well-organized and complete. Subject records were consistent with the diagnosis and description provided in the NDA.

However, the inspection documented that Dr. Tran-Johnson did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b) and did not adhere to the investigational plan, in violation of 21 CFR 312.60.

<u>Recordkeeping Violations [21 CFR 312.62(b)]</u>
Various physician sub-investigators conducted tests and made evaluations regarding subjects on the study before they had been placed on a signed Form FDA 1572 as follows, all for study ILO522 3005:

i. Sub-investigator made the initial diagnosis of subject 1006 on 5/9/00; the first date of his inclusion on a Form FDA 1572 was 7/17/00. b(4)

b(4)

ii. Sub-investigator [redacted] evaluated ECG's for subject 1006 on 5/26/00 and 6/6/00; the first date of his inclusion on a Form FDA 1572 was 7/17/00. The ECGs were performed on 5/22/00 and 5/26/00, respectively.

iii. Sub-investigator [redacted] evaluated 2 laboratory reports and 2 ECG's for subject 1006, a physical examination for subject 1018, and an ECG for subject 1020 between 6/9/00 and 7/14/00; the first date of his inclusion on a Form FDA 1572 was 7/17/00.

iv. Sub-investigator [redacted] evaluated the initial diagnosis of subject 1018 on 6/23/00; the first date of his inclusion on a Form FDA 1572 was 7/17/00.

In a April 23, 2008 written response to FDA, Dr. Tran-Johnson stated that these sub-investigators "did not perform any direct study related procedures before they were added to the 1572 form", since these elements of psychiatric evaluation and medical management would have been performed regardless of the clinical trial. The protocol does not specifically allow use of data from routine hospital procedures (e.g. physical examinations, ECGs, etc.) performed prior to enrollment in a clinical trial to be used for required study procedures. However, we agree with Dr. Tran-Johnson's contention that these procedures (and their professional evaluation) would have been performed regardless of subject participation in the clinical trial, and the results are appropriately included despite being performed prior to sub-investigator inclusion on Form FDA 1572. We find this explanation for the failure to complete Form FDA 1572 for these sub-investigators prior to their performance of study procedures unacceptable.

Protocol Violations [21 CFR 312.62(b)]

1. A psychiatric evaluation of Subject 1018 in study ILO522 3005 dated 6/23/00 indicates that she attempted suicide most recently in October, 1999. The protocol states that patients "who have a history of suicide attempt within the past year" should be excluded. This subject was randomized to the study on 6/27/00. Dr. Tran-Johnson's explanation for the inappropriate inclusion of a subject with a history of a suicide attempt within the past year in this study is unacceptable: although she recalled that the patient was not in fact suicidal, there is no documentation to support this contention.

2. Reporting of adverse events – The protocol states that "Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF". None of the adverse events presented here were serious adverse events.

   i. Adverse event reports were not always completed properly and/or promptly in Study ILO522 3005; all of these adverse events were suspected to be related to study drug. Examples include:
      - Subject 1010 experienced nausea on 6/2/00, which was first written up as an adverse event on 7/29/00, and dizziness upon standing on 6/2/00, first written up on 6/26/00.
      - Subject 1042 experienced chest pressure on 9/9/00, which was first written up as an adverse event on 11/16/00.
      - Subject 1018 experienced vomiting on 6/27/00, which was first written up as an adverse event on 7/18/00.

   ii. Adverse events received by the site, and written up on an "Adverse Event Documentation Form" were not always promptly evaluated by a medical sub-

investigator in Study ILO522 3005; all were suspected to be related to study drug. This is of special concern, since Dr. Tran-Johnson is a Pharm.D., not a physician. Examples include:

- Subject 101 experienced vomiting on 6/27/00, which was first documented as being evaluated by a medical sub-investigator on 7/21/00.
- Subject 1055 experienced abdominal distress on 10/4/00 and vomiting on 10/7/00 which were evaluated by a medical sub-investigator on 11/3/00 and abdominal cramping on 10/20/00 with medical sub-investigator evaluation on 11/15/00.

iii. Adverse event reports were not always dated as to when they were evaluated by the medical sub-investigator in study ILO522 3005. This occurred for subject 1006 with an adverse event of runny nose dated 6/5/00 and for subject 1018 with adverse events of constipation dated 7/1/00 and URI on 6/25/00. The evaluating sub-investigator did not date any of these adverse events evaluations.

iv. Adverse event reports were not always closed out properly in that they did not always include information such as "recovered without sequelae", "recovery with sequelae", etc. in Study ILO522 3005. Examples of adverse events without follow-up information include:

- Subject 1042 – adverse events of dyspepsia and chest pressure were reported on 8/27/00 and 9/9/00, respectively
- Subject 1055 – adverse events of abdominal distress and vomiting were reported on 10/4/00 and 10/7/00, respectively.
- Subject 1018 – adverse events of heart palpitation and dizziness were reported on 8/9/00.

v. Adverse events reported in patient progress notes were not always documented as study adverse events promptly in Study VP-VYV-683-3101. Subject 0008 had grogginess (12/26/05) and inability to focus (12/30/05) documented in the progress notes, but the evaluation by the medical sub-investigator was dated 7/6/06. Subject 0007 had a severe headache (1/16/06) documented in the progress notes, but the evaluation by the medical sub-investigator was dated 3/21/06.

vi. The CPK serum level for subject 0039 was found to be 1223 U/L on 5/3/06 (normal range 0-235) (Study day 14) and was judged to be clinically significant by the investigator on 5/8/06. The protocol states that clinically significant laboratory abnormalities should be reported as adverse events. There was no record that this laboratory finding had ever been reported as an adverse event. A repeat CPK determination was not done until 5/18/06 at which time it was 908. This result was interpreted as not clinically significant by the investigator on 5/24/06. It is not clear why the elevated repeat value of 908 was not considered clinically significant.

Dr. Tran-Johnson's written response of April 23, 2008 noted that her site's practice is not to generate adverse event reports until retesting occurs. This explanation for the handling of an adverse event report regarding an elevated CPK is unacceptable. The initially elevated CPK (1223) was deemed significant by the investigator, but it was not repeated until 15 days later. In this instance, a repeat value obtained 15 days later will not assist in assessing the significance of the original elevation, and an adverse event report should have been generated. The retest value remained elevated at 908, although on this occasion, the investigator deemed the finding not significant.

vii. Adverse events were not always written up promptly in accordance with the onset time in Study VP-VYV-683-3101; all were deemed possibly related to study drug. Examples include:

- Subject 0018 – the onset of the adverse events of sedation on 1/28/06 and gastric distress on 2/2/06 were first written up by the site on 8/8/06.

- Subject 0007 – the onset of severe headache on 1/16/06 was first written up by the site on 3/20/06.

Dr. Tran-Johnson's explanation for the failure to report adverse events properly and/or promptly is unacceptable. Even if adverse events are "transient and non-serious adverse events", the protocol states that "information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF".

Additional Findings not Documented on the FDA 483

1. Study Personnel Signature Form for Study ILO522 3005– It was noted during the inspection that this form (which was also being used as a delegation log) did not include information as to which sub-investigator was assigned specific functions for the study. Some of the sub-investigators had performed functions on the study before they had been authorized by the Principal Investigator to do them by way of the delegation form. An example:
   i. [redacted] M.D. evaluated ECG's from Subject 1006 on 5/26/00 and 6/6/00, but was not approved to perform study functions by the investigator until 9/9/00.

2. Site Personnel Signature/Delegation Log for Study VP-VYV-683-3101 - The first subject was randomized on 11/24/05. Although the study log states that "PI to sign & date prior to first subject screened", Dr. Tran-Johnson did not sign the log until 1/4/06. Therefore, sub-investigators performed functions prior to approval by Dr. Tran-Johnson. An example: (4)
   i. [redacted], M.D. performed physical examinations on Subject 001 on 11/18/05 and 12/21/05, prior to Dr. Tran-Johnson's approval signature on 1/4/06.

3. Brief expiration period for [redacted] IRB approval – Study ILO522 3005 was initially approved by the [redacted] IRB on 6/8/00 with a one-year expiration date of 6/8/01. The study was not re-approved by the IRB until 6/14/01. No subjects were enrolled or seen during this 6 day gap.

4. Adverse event documents were signed by Dr. Tran-Johnson before the medical sub-investigator had signed the document.

c. Assessment of data integrity: Although recordkeeping and protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of schizophrenia.

4. Miro Jakovljevic, M.D.
Kilinicki bolnicki centerZagreb,
Psihija Medicinskog fakulteta Kispatieceva 12-Re
Zagreb, Croatia

a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 on 9 days between April 21 and April 25, 2008. For study ILO5223005, 13 subjects were screened, 13 subjects were enrolled, and 9 subject records were reviewed during the inspection. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. **General observations/commentary:**

Recordkeeping Violations [21 CFR 312.62(b)]

The clinical investigator did not maintain adequate and accurate case histories that record all observations and data pertinent to the investigation. Specifically:

i. There was no identified caregiver to ensure compliance in any record audited, as required by the protocol
ii. All audited CRFs showed that the protocol-required 16 element physical examinations had been performed, but the medical record (source documentation) did not indicate that all 16 elements had been performed.
iii. The number of study drug doses dispensed to Patient 1 (34) did not correspond to the number of days of the dispensing period (31).
iv. Diary cards and instructions for completion were to be provided to subjects prior to visits for pharmacokinetic sampling. The inspector found no documentation that diary cards were dispensed to subjects or returned and no documentation as to the identity of the person making the diary entries. The Study Nurse and a Sub-Investigator completed parts of Patient 2's diary, and time entries for Patients 2 and 13 were unclear.
v. The usual procedure for recording inpatient medication dispensation is on a "TEMPERATUNI LIST". There is no documentation that Patient 2 received medication from 10/8 through 10/18/00, although he/she was an inpatient. (In the absence of the Exhibits and the EIR, it cannot be documented that the medication was actually received).
vi. The source documents did not indicate that the required ophthalmologic examination at screening for Patient 3 or a physical examination for Patient 13 were performed.
vii. The source documents for Patient 1 indicate that the ESRS questionnaire was performed on December 15, 2000, while the ESRS questionnaire itself was dated December 14, 2000.
viii. The protocol required that the IVRS system be phoned at specific visits, with a subsequent automatic fax-back confirmation. The fax-back confirmation was missing from the medical record for one or more visits for Patients 1, 3, 4, 10, and 13.
ix. There were multiple changes in the entries in the drug accountability forms made by writing over the original entries.

Protocol Violations [21 CFR 312.62]

The clinical investigator did not adhere to the investigational plan. Specifically:

i. According to the protocol, study assessments are to be done on the day assigned during the Run-in (Study Day 0 and earlier) and Titration Phases (Study Day 1-7). However, 7 of 10 subjects did not have the Day 7 assessment performed on the correct day: Subjects 1, 9, and 13 had their assessment on Study Day 6 and Subjects 3, 5, 7, and 8 had the Day 7 assessment of Study Day 8.

ii. According to the protocol, the study drug must be "stored in accordance with the conditions specified on the drug labels". The drug label states "Do not store above 25°C (77°F)". There are no temperature logs to verify the study drug was stored in accordance with the specified temperature. This issue was discussed with Dr. Donghau Lu, the Chemistry reviewer, who felt that it is unlikely that drug product stability would be seriously affected by storage at room temperature.
iii. According to the protocol, when a subject is prematurely discontinued from the study, efficacy assessments were to be performed at the time of discontinuation or within 24 hours. Patient 4 had the study medication discontinued on September 23, 2000 for the adverse event of increased psychosis and received antipsychotic agents over the next several days. Patient 4 did not have the efficacy assessments performed until September 25, 2000 (minus one), and the concomitant medications administered after September 23 were not listed in the case report.
iv. The adverse event of hypertension was not reported for Patient 10.
v. According to the protocol, the IVRS should be phoned on day 1 for randomization to a study medication and assignment of a schedule of visits and on day 43 for subjects continuing into the open-label phase for scheduling of visits. For all patients audited at this site, the IVRS was called one day early for these two time points, resulting in a schedule 1 day off for the double-blind phase and 2 days off for the open-label phase.
vi. Patient 1 had return visits outside of the 3 day visit window for 7 of 12 visits.
vii. The protocol states that a urinalysis should be performed on study day 42 (end of the double blind phase). The urinalysis was not performed for patient 2 until day 48.
viii. The protocol states that the Extrapyramidal Symptom Rating Scale (ESRS) should be done at screening. The medical records and case report form do not indicate that the ESRS was done at screening for Patient 10.
ix. The protocol states that that a pregnancy test is to be performed at baseline on females of childbearing potential. The CRF for Patient 1 states that a pregnancy test was erroneously not performed.
x. The protocol specifies that laboratory testing (hematology, blood chemistry, and urinalysis) should be done on Study Day 273. The Form FDA 483 states that the medical records for Patient 1 dated June 6, 2001 showed that the labs were not done on Study Day 273 (which should be June 15, 2001) because the patient arrived at noon. The laboratory studies were subsequently performed on July 22, 2001 (Study Day 300).
xi. According to the Principal Investigator, there is no signed 1572 for Dr. Jakovljevic's site.

Assessment of data integrity: Although recordkeeping and protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of schizophrenia.

5. Prof.Vera Folnegovic-Smalc, M.D., ScD,
Psychiatric Hospital Vrapce Univ.,
Bolnica cesta 32
HR 10090 Zagreb, Croatia

a. **What was inspected**: Inspection was conducted in accordance with Compliance Program 7348.811 on 5 days between April 13 and April 18, 2008. For study ILO5223005, 30 subjects were screened, 30 subjects were enrolled, and 7 subject records were reviewed during the inspection.

b. General observations/commentary:

Recordkeeping Violations [21 CFR 312.62(b)]

i. There was no identified caregiver to ensure compliance in any record audited, as required by the protocol
ii. All audited CRFs showed that the protocol-required 16 element physical examinations had been performed, but the medical record (source documentation) did not indicate that all 16 elements had been performed.
iii. The CRF for Patient 19 shows that the patient was on study medication for 6 days; however, the drug accountability form indicates that the subjects received 10 days of therapy, based on doses dispensed.
iv. The drug accountability form for Patient 8 indicates noncompliance (patient took approximately 3 ½ days of study medication over 7 days), while the corresponding medical records do not indicate noncompliance, with the exception of 1 day.
v. Although the screening and baseline laboratory reports indicate that Patient 10 had confirmed levels of codeine and codeine/morphine, respectively, these drugs are not listed as concomitant medications in the CRF, and the medical record has no evaluation regarding drugs of abuse. In addition, scabs noted on the left lower arm and resolving hematomas on both legs were not noted on the screening visit records, although hospital records from the previous day record these physical findings.
vi. The early discontinuation laboratory report from Patient 19 was positive for codeine and morphine. Codeine and morphine were not reflected on the concomitant medications listing.
vii. A medication (Akineton) which Patient 10 had taken for the two months prior to study enrollment was not reflected in the corresponding case report.
viii. The medical records of Patient 5 indicate that IVRS was called on Study Day 14, as specified by the protocol; however, the faxed IVRS confirmation sheet indicates that the call occurred on Day 15.
ix. The drug accountability form was not available for review during the audit for Patient 26.

Protocol Violations [21 CFR 312.62]

The clinical investigator did not adhere to the investigational plan. Specifically,

i. According to the protocol, the study drug must be "stored in accordance with the conditions specified on the drug labels". The drug label states "Do not store above 25°C (77°F)". There are no temperature logs to verify the study drug was stored in accordance with the specified temperature. This issue was discussed with Dr. Donghau Lu, the Chemistry reviewer, who felt that it is unlikely that drug product stability would be seriously affected by storage at room temperature.
ii. A signed Form FDA 1572 is required for all sites. According to the investigator, there was no Form 1572 for this site.
iii. The protocol specifies that the study medication dose will be adjusted based on the subject's response to and tolerance of therapy. The CRF and medical records of Patient 26 indicate that the dose was changed because the site ran out of the required strength of study medication.
iv. The protocol specifies that an ophthalmology exam should be conducted in the case of premature discontinuation from the study or within 7 day of the last dose of study medication; no such exams were conducted at premature discontinuation for Patient 8 or at study completion for Patient 19.

c. **Assessment of data integrity:** Although recordkeeping and protocol violations occurred at this site, it is unlikely that these errors will impact on the final outcome

of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromise due to these inaccuracies.

6. Saibal Nandy, M.D.
631 Prospect Drvie Sw AB
Medicine Hat, Canada

a. **What was inspected**: Inspection was conducted in accordance with Compliance Program 7348.811 on 4 days between April 28 and May 1, 2008. For study ILO5223005, 9 subjects were enrolled. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**:
Failure to obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration
Specifically, the extension phase Informed Consent version Amendment 5 was not issued to and signed by Subjects 1004 and 1005 prior to the increase in dosage of study drug specified in the extension phase of the protocol.

Protocol Violations [21 CFR 312.62]
The clinical investigator did not adhere to the investigational plan. Specifically, the protocol required certification of raters for the administration of the PANSS and the ESRS. However, ESRS ratings were performed by a study nurse without documentation of the Rating Certification for Subject 1009.

c. **Assessment of data integrity**: Although informed consent and protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies.

7. Vanda Pharmaceuticals, Inc.
9605 Medical Center Drive, Suite 300
Rockville, MD 20850

a. **What was inspected**: The FDA investigators reviewed Vanda procedures and records for protocols ILO5223005 and VP-VYV-683-3101 as well as the pharmacokinetics study CILO522 0108. The inspection was conducted between April 16, 2008 and April 24, 2008. There were no limitations to the inspection.

b. **General observations/commentary**: The Form FDA 483 noted that Vanda personnel completed the clinical pharmacology report and a report amendment for this study without possession of or access to the source data for the bioanalytical portions of the study. Instead, Vanda relied on uncompleted draft reports CIL0522 0108 and DMPK (US) R99 663, and supplemental information provided by

Novartis. The Novartis draft reports and supplemental information contained errors including analytical accuracy and precisions for iloperidone and two metabolites; Vanda transcribed the Novartis draft reports and supplemental information into their own clinical pharmacology report and Amendment #1, without being able to verify the controls.

Although not cited on the Form FDA 483, the inspectors discussed with the Vanda representatives that the sponsor is responsible for collection of signed investigator statements (Form FDA 1572), which was not done. Since Vanda was not the sponsor at the time the studies were conducted, this item was not included on the Form FDA 483.

Vanda responded to the Form FDA 483 on May 2, 2008. In their response, Vanda stated that they verified the data in the study report against the original primary source collected by Novartis and submitted an amended study report. Vanda stated that a few transcriptional errors were identified, and that none of the errors had a meaningful effect on the conclusions. The adequacy of Vanda's response will be evaluated by the GLP/Bioequivalence group.

c. **Assessment of data integrity**: The data collected and maintained at the sponsor's site, as it pertains to the five clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810 are consistent with that submitted to the agency as part of and in support of NDA 22-192.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the sites of Drs. Tran-Johnson, Jakovljevic, Folnegovic-Smale, and Nandy regarding protocol, recordkeeping, and informed consent violations. There were no significant violations at Dr. Mofsen's site. In general, the studies appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

The sponsor inspection of Vanda revealed that source data generated by Novartis was not available to Vanda at the time that a clinical pharmacology report was generated, with subsequent errors in the document. The relevance to outcome will be evaluated and provided to the review division by the GLP/Bioequivalence Branch in DSI.
Follow-Up Actions:
The observations noted above for Drs. Mofsen, Jakovljevic, Nandy, and Folnegovic-Smalcare are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

/s/

Susan Thompson
6/17/2008 01:01:31 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
6/18/2008 08:25:21 AM
MEDICAL OFFICER

MEMORANDUM

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

DATE: May 14, 2008

FROM: Samuel H. Chan, Pharm.D.
Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-192
Iloperidone Oral tablets
Vanda Pharmaceutical, Inc.

TO: Thomas Laughren, M.D.
Division Director
Division of Psychiatry Products (HFD-130)

At the request of HFD-130, the Division of Scientific Investigations conducted an audit of the following pharmacokinetic study:

Protocol CILO5220108: An Open Label, One Sequence Crossover Study in Healthy Subjects to Evaluate the Pharmacokinetics of Iloperidone and Fluoxetine Administered Separately and in Combination

Novartis Pharmaceutical conducted Study CILO5220108 prior to licensing Iloperidone to Vanda Pharmaceuticals ("Vanda") in 2004. However, Novartis did not complete a final bioanalytical report or study report. Vanda completed the final reports for Study CILO5220108 from draft reports provided by Novartis. During review of NDA 22-197, the biopharmaceutics reviewer noted discrepancies in the bioanalytical data.

In response to FDA's request for clarifications of the bioanalytical data, Vanda obtained additional data from Novartis and submitted an amended report on March 17, 2008.

Inspection Site: Vanda Pharmaceuticals
9605 Medical Center Drive
Suite 300
Rockville, MD 20850

Following the inspection at Vanda (4/16/2008 - 4/24/2008), Form 483 was issued. DSI received Vanda's response to the Form 483 on 5/2/08, including Amendment #2. The objectionable items and our evaluation follow.

1. **Vanda personnel completed the clinical pharmacology report and a report amendment for this study, without possession of, or access to, the source data for the bioanalytical portions of the study. Instead, Vanda relied on uncompleted draft reports CILO522-0108 and DMPK(US) R99-663, and supplemental information provided by Novartis. The Novartis draft reports and supplemental information contained errors including analytical accuracy and precision for iloperidone and two metabolites; Vanda transcribed the Novartis draft reports and supplemental information into their own clinical pharmacology report and Amendment #1, without being able to verify the contents.**

It is objectionable that Vanda could not verify the accuracy of data in their study report. During the inspection, Vanda obtained the bioanalytical records and source data from Novartis. A comparison of the data in the original records, the Vanda clinical pharmacology report, and Amendment #1 revealed that no significant discrepancies in the pharmacokinetic data. However, the following discrepancies were noted between the original QC data and the QC tabulations in Amendment #1:

Plasma Iloperidone	Run Date	reported	actual
0.204 ng/mL	3/8/01	0.181	0.185
0.204 ng/mL	5/9/01	1.91	0.191
0.204 ng/mL	5/9/01	0.204	0.202
	Run Summary Statistics		
	Mean	0.329	0.197
	S.D.	0.477	0.038
	%C.V.	144.9	19.2
	%Acc.	161.2	96.5
	%Bias	61.2	3.5

Plasma Iloperidone	Run Date	reported	actual
102 ng/mL	3/14/01	104	105
	Run Summary Statistics		
	Mean	99.7	99.8
	S.D.	8.49*	4.38*
	%C.V.	8.51*	4.39*
	%Acc.	97.8	97.9
	%Bias	-2.23	-2.15

*Also calculation error in Vanda's spreadsheet

Plasma P95 Metabolite		reported	actual
0.812 ng/mL	Run Summary Statistics		
	Mean	0.737	0.737
	S.D.	0.099*	0.084
	%C.V.	13.5*	11.3

*Also calculation error in original spreadsheet

Plasma P88 Metabolite	Run date	reported	actual
202 ng/mL	5/22/01	188	190*
202 ng/mL	5/22/01	194	191*
	Run Summary Statistics		
	QC Mean	193.286	193.214*
	S.D.	8.004	7.944*
	%C.V.	4.1	4.1
	%Acc.	95.7	95.7
	%Bias	-4.31	-4.35*

*Also calculation error in spreadsheet

Urine P95 Metabolite	Run date	reported	actual
0.406 ng/mL	5/17/01	0.405	0.403
0.406 ng/mL	5/17/01	0.454	0.379
	Run Summary Statistics		
	Mean	0.409	0.396
	S.D.	0.053	0.049
	%C.V.	13.0	12.3
	%Acc.	101	97.5
	%Bias	0.62	2.55

These and some additional minor discrepancies were tabulated by Vanda in Amendment #2. The errors in reporting the QC data in Amendment #1 did not affect the 2001 run acceptance/rejection decisions, which used the actual results. However, we note that the formula errors in some cells of the Excel spreadsheets used for calculating S.D. and %C.V. in performance data for Amendment #1 were carried over into Amendment #2, and thus errors remain in the summary statistics.

In addition, we confirmed that subjects were treated with the test drugs in two cohorts, of subjects 1-18 and subjects 19-23. The biopharmaceutics reviewer should consider whether statistical adjustment for the cohort effect is appropriate in this single-sequence study.

Vanda committed to correcting the objectionable condition on Form 483 for future studies, and submitting the amended Clinical Study Report for Study No. CILO522-0108 to the NDA.

Conclusions:

Following our evaluation of the inspectional findings, DSI concludes that pharmacokinetic data from Study CILO522-0108 are acceptable for Agency review. The evaluations of QC performance for within-study accuracy and precision should use the corrected data in Amendment #2, except for the calculation errors noted above.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Samuel H. Chan, Pharm.D.

Michael F. Skelly, Ph.D.

Final Classification:
VAI - Vanda Pharmaceuticals, Rockville, MD

CC:
HFD-45/RF
HFD-45/Vaccari
HFD-48/Chan/Himaya/CF
HFD-130/Updegraff/Jackson
HFR-CE250/Shapley/Breithaupt
Draft: SHC 5/10/08
Edit: MFS 5/14/08
DSI (b) (4) O:\BE\EIRCOVER\22192Ilo.doc
FACTS (b) (4) (See also (b) (4)

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

/s/

Samuel Chan
5/15/2008 10:41:39 AM
DRUG SAFETY OFFICE REVIEWER

Please sign the Vanda EIR review for Iloperidone

Michael Skelly
5/15/2008 10:43:11 AM
PHARMACOLOGIST

Martin Yau
5/15/2008 11:14:06 AM
CSO

Department of Health and Human Services | Public Health Service
Food and Drug Administration
Rockville, MD 20857

SEP 19 2007

William D. Clark
Chief Business Officer
Vanda Pharmaceuticals Inc.
9605 Medical Center Drive, Suite 300
Rockville, MD 20850

RE: Vanda Pharmaceuticals Inc., Small Business Waiver Request 2007.049 for New Drug Application 22-192 for Iloperidone

Dear Mr. Clark;

This responds to your May 14, 2007, letter and the May 29, 2007, facsimile from Thomas Copmann of Vanda Pharmaceuticals Inc. (Vanda) requesting a waiver of user fees under the small business waiver provision, section 736(d)(1)(D)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2007.049). You request a waiver of the fiscal year (FY) 2007[2] human drug application fee for new drug application (NDA) 22-192 for iloperidone. For the reasons described below, the Food and Drug Administration (FDA) grants Vanda's request for a small business waiver of the application fee for NDA 22-192 for iloperidone.

According to your waiver request, Vanda is a small company with 49 employees and no affiliates. You state that NDA 22-192 will be your first human drug application submitted for review. You expect to file the application on or before September 28, 2007.

Under section 736(d)(3) of the Act,[3] a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate[4] submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

FDA's decision to grant Vanda's request for a small business waiver for NDA 22-192, iloperidone, is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated August 31, 2007, that Vanda is a small business and has fewer than 500 employees. SBA also determined that Vanda did not have any affiliates.

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[1] 21 U.S.C. 379h(d)(1)(D).
[2] FY 2007 = October 1, 2006, through September 30, 2007.
[3] 21 U.S.C. 379h(d)(3).
[4] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

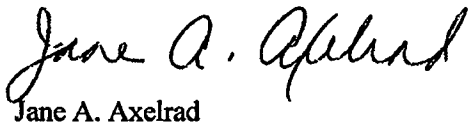
Second, according to FDA records, the marketing application for NDA 22-192 is the first human drug application, within the meaning of the Act, to be submitted to FDA by Vanda or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 22-192 for iloperidone is granted provided that FDA receives the marketing application for the NDA no later than September 30, 2007.[5]

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for Vanda's NDA 22-192 for iloperidone. FDA records show that Vanda has not yet submitted NDA 22-192. Once the full application is received, if FDA refuses to file the application or if Vanda withdraws the application before it is filed by FDA, a reevaluation of the waiver may be required should the company resubmit its marketing application. If this situation occurs, Vanda should contact this office approximately 90 days before it expects to resubmit its marketing application to determine whether it continues to qualify for a waiver.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,



Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[5] In accordance with section 509 of Public Law 107-188 Title V, Subtitle A (the Prescription Drug User Fee Amendments of 2002), sections 735 and 736 of the Act cease to be effective October 1, 2007. Applications submitted after that date are expected to comply with the requirements of new prescription drug user fee legislation (if enacted). Please contact Beverly Friedman or Michael Jones for a reevaluation of the waiver, if required.

BCC:
HFD-5 M. Jones
HFD-7 B. Friedman
HFD-7 Chron file
HFD-5 Vanda waiver file
HFD- Steve Hardeman/Paul David – Supervisory Project Managers for DPP (NDA 22-192)
HFM-110 C. Vincent/R. Eastep
HFA-103 K. Boyd (RECORD ON PAYMENT AND ARREARS LIST)
HF-20 Y. Chae
HFV-3 T. Forfa
HFV-100 D. Newkirk

Drafted: B. Friedman 8/31/2007
CDER Application Check: 8/31/2007 – no applications
CBER Application Check: C. Vincent: 8/31/2007 – no applications
Reviewed: M. Jones – 9/7/2007
Edited: S. O'Malley 9/7/2007
Reviewed: J. Axelrad

Date: 9/7/2007