CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-117

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-117 SUPPL # 000 HFD # 130

Trade Name Saphris Sublingual Tablets

Generic Name asenapine

Applicant Name Organon USA Inc.

Approval Date, If Known August 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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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

YES ☐ NO ☒

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

N/A

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: Keith Kiedrow, PharmD, LCDR USPHS
Title: Senior Regulatory Project Manager
Date: 8/3/2009

Name of Office/Division Director signing form: Mitchell Mathis, MD
Title: Deputy Director, Division of Psychiatry Products

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22117	ORIG 1		SYCREST (ASENAPINE) TABLETS

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

/s/

KEITH J KIEDROW
08/03/2009

MITCHELL V Mathis
08/03/2009

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

NDA/BLA#: 22117 | Supplement Number: N/A | NDA Supplement Type (e.g. SE5): SE1

Division Name: Division of Psychiatry Products HFD 130 | PDUFA Goal Date: 6/30/2008(CR action) 8/13/2008 | Stamp Date: 8/30/2007

Proprietary Name: Saphris

Established/Generic Name: asenapine maleate

Dosage Form: 5 and 10mg sublingual tablets

Applicant/Sponsor: Organon USA Inc.

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): 2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: treatment of schizophrenia

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. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	12 yr. __ 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	13 yr. __ mo.	17 yr. __ mo.	☒	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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): TBD						

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 B: 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: 6/2006)

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

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: treatment of acute manic or mixed episodes associated with Bipolar I Disorder

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☒ No. Please proceed to the next question.

Q2: 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. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☒	Other	0 yr. __ mo.	2 yr. __ 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.*)

△ 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 Section 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 some or all 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	10 yr. __ mo.	17 yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ 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): _____						

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2006)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22117	ORIG 1		SYCREST (ASENAPINE) TABLETS

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

/s/

KEITH J KIEDROW
08/04/2009

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	August 7, 2009
TIME:	1:00 – 2:00 PM
LOCATION:	WO 22 RM 4270
APPLICATION:	NDA 22-117
DRUG NAME:	Saphris (asenapine) Sublingual Tablets (Organon Inc.)
TYPE OF MEETING:	Pre Approval Safety Conference (PSC)
MEETING CHAIR:	Mitchel Mathis, DPP, Deputy Division Director
MEETING RECORDER:	Keith Kiedrow, DPP, Project Manager

FDA ATTENDEES:

Ellis Unger, ODE1 Deputy Director
Mitchell Mathis, DPP, Deputy Division Director
Robert Levin, DPP, Clinical Team Leader
Ida-Lina Diak, OSE, DPV, Senior Regulatory Reviewer
Felecia Duffy, OSE, Reviewer
Abolade Adelou, OSE, DMEPA, Project Manager
Adora Ndu, OSE, Reviewer
Barry Rosloof, DPP, Supervisory Pharmacologist
George Kordzakhia, Office of Biostatistics, Reviewer
Keith Kiedrow, DPP, Project Manager

BACKGROUND:

Saphris (asenapine) is an atypical antipsychotic (5HT2 and D2 receptor antagonist). It is an immediate release sublingual formulation for twice daily administration. The NDA seeks a claim for the acute treatment of schizophrenia in adults and the acute treatment of manic or mixed episodes associated with Bipolar I Disorder in adults. The recommended dosages at this time are 5 mg twice daily for schizophrenia and 10 mg twice daily for Bipolar I Disorder. Asenapine was developed under IND 51,641. This NDA was first submitted August 31, 2007. We issued a Complete Response letter January 13, 2009. Organon submitted a complete response to our January 13, 2009 action letter on February 12, 2009. 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 asenapine.

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 asenapine.

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 with asenapine is smaller than other drugs in the class with an identifiable QT signal (2-5 msec), and as such, is not expected to be a major safety issue in postmarketing reports.

DPP explained that the metabolic effects of asenapine appear to be lower than those found with some other drugs in its class. Asenapine appears to fall in the middle among the atypical antipsychotics with regard to weight gain, It had less impact on triglycerides, cholesterol, and glucose levels in the short-term trials, compared to other drugs 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, iloperidone).

3. Labeling:

It was noted that DMEPA performed two 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 the Sponsor to ensure that the carton/container labeling was concise and clear.

DECISIONS (AGREEMENTS) REACHED:

OSE will monitor asenapine 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:

All clinical reviews, clinical team leader memos, and division director memos were distributed to meeting participants prior to the meeting.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22117	ORIG 1		SYCREST (ASENAPINE) TABLETS
NDA 22117	ORIG 1		SYCREST (ASENAPINE) TABLETS

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

/s/

KEITH J KIEDROW
08/14/2009

MITCHELL V Mathis
08/14/2009

Kiedrow, Keith

From: Paporello, Todd [todd.paporello@spcorp.com]
Sent: Wednesday, August 12, 2009 1:39 PM
To: Kiedrow, Keith
Cc: Carey, T. (Tracie)
Subject: NDA 22117 PMC Study 8 (Schizophrenia Dose Finding Study)

Keith-

As discussed, in order to determine the lowest effective dose of asenapine in schizophrenia, Schering-Plough commits to conduct an adequate well controlled 4-arm dose finding study in adults (e.g. 2.5 mg BID asenapine, 5.0 mg BID asenapine, active control and placebo).

We also commit to the following timing:

Protocol Submission Date: February 2010
Study Start Date: September 2010
Trial Completion Date: October 2013
Final Report Submission: October 2014

Please confirm receipt/agreement.

Todd

Todd Paporello, Pharm.D., MBA
Director & Regional Head, CNS
Global Regulatory Affairs
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Location: K 6 1-1135
Email: todd.paporello@spcorp.com

Schering-Plough

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Organon

Schering-Plough

CONFIDENTIAL

July 15, 2009

Electronic Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA No. 22-117
Asenapine Sublingual Tablets
Serial No. 0046
UPDATED: POST APPROVAL REQUIREMENTS & COMMITMENTS

Dear Sir or Madam:

Reference is made to the New Drug Application No. 22-117 for Asenapine Sublingual Tablets received on August 31, 2007. Reference is also made to the submission dated July 13, 2009, Serial No. 044.

Enclosed, please find an updated copy of the responses to the Division's proposed post marketing requirements and commitments. The update includes changes to the dates for Studies 1, 2, 3 and 4 and are indicated as strikeout and underline.

We consider this application and all correspondence related thereto as confidential proprietary information and hereby claim protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of the Code of Federal Regulations.

Should you have any questions or comments regarding this submission, please contact Dr. Tracie Carey at (908) 740-2719 or tracie.carey@spcorp.com or Dr. Todd Paporello at (908) 740-4252 or todd.paporello@spcorp.com.

Sincerely,

for Tracie A. Carey, Pharm.D.
Senior Manager and Liaison, Global Regulatory Affairs

Attachment – Form FDA 356h

Submitted via FedEx

Organon International
56 Livingston Avenue
Roseland, NJ 07068
USA

T 1 973 325 4000
F 1 973 325 4007

www.organon.com

Required Pediatric Assessment - Study 1

1. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study to obtain pharmacokinetic data and provide information pertinent to dosing of asenapine sublingual tablets in the relevant pediatric population.

Protocol Submission Date:	by May 2010	
Study Start Date:	by February 2011	
Trial Completion Date:	by December 2015	b(4)
Final Report Submission:	by December 2016	

Response Study 1

We have proposed dates above for this study. We will likely propose a single pharmacokinetic study in adolescent patients aged 10 to 17 with schizophrenia or bipolar disorder in order to fulfill required pediatric assessments 1 and 3.

Required Pediatric Assessment - Study 2

2. A deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients ages 13 to 17. A study of the efficacy and safety of asenapine sublingual tablets in the relevant pediatric population.

Protocol Submission Date:	by May 2010	
Study Start Date:	by November 2010	
Trial Completion Date:	by December 2015	
Final Report Submission:	by December 2016	b(4)

Response Study 2

We have proposed dates above for this study. These dates correspond to those previously submitted May 15, 2009 (Serial No. 0042).

Required Pediatric Assessment - Study 3

3. A deferred pediatric study under PREA for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder ages 10 to 17. A study to obtain pharmacokinetic data and provide information pertinent to dosing of asenapine sublingual tablets in the relevant pediatric population.

Protocol Submission Date:	by May 2010	
Study Start Date:	by February 2011	
Trial Completion Date:	by December 2015	b(4)
Final Report Submission:	by December 2016	

Response Study 3

We have proposed dates above for this study. We will likely propose a single pharmacokinetic study in adolescent patients aged 10 to 17 with schizophrenia or bipolar disorder in order to fulfill required pediatric assessments 1 and 3.

Required Pediatric Assessment - Study 4

4. A deferred pediatric study under PREA for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder ages 10 to 17. A study of the efficacy and safety of asenapine sublingual tablets in the relevant pediatric population.

Protocol Submission Date:	by	September 2010	b(4)
Study Start Date:	by	February 2011	
Trial Completion Date:	by	December 2015	
Final Report Submission:	by	December 2016	

Response Study 4

We have proposed dates above for this study. These dates correspond to those previously submitted May 15, 2009 (Serial No. 0042).

Postmarketing Requirement – Study 5

5. Drug substance impurity has been present in the drug substance commercial size clinical/stability batches at <0.05%. However, you proposed to set a specification limit for this impurity in asenapine drug substance at thus above the ICH Q3A(R) qualification limit of The content of in relevant asenapine batches used in the preclinical program was below the limit of detection. A non-GLP pilot segment II study in rabbits was performed with this impurity; however, this study is considered inadequate for several reasons, including the following: (1) only a single dose of was employed which did not result in any maternal toxicity; (2) the number of animals per group was less than the recommended 16 per group, with only 34 fetuses examined in the group; (3) relatively high post-implantation loss was observed in the control group; (4) no information on drug analysis was provided; (5) no toxicokinetic data were obtained; (6) was administered orally, although asenapine is being administered by the sublingual route; and (7) unclear terminology was used to describe fetal findings. Moreover, a 9-fold increase in the incidence of malformations, and signs of embryotoxicity demonstrated as a 2-fold increase in post-implantation loss, were observed in fetuses of female rabbits dosed with at 80 mg/kg/day during the period of organogenesis in this non-GLP pilot study. The NOAEL has not been identified for these effects. Therefore, you should perform an embryofetal development study with in the rabbit to qualify this impurity during phase IV or reduce the specification of ICH Q3A(R) qualification limit of b(4) b(4)

Protocol Submission Date:	by	
Study Start Date:	by	

Trial Completion Date: by
Final Report Submission: by

Response Study 5

We have already fulfilled this requirement as an embryofetal development study has been conducted with ——— in the rabbit. The nonclinical study report was submitted to IND 51,641 on July 10, 2009 (Serial No. 385).

b(4)

In summary, intravenous administration of 0, 0.1, 0.3 or 1.0 mg/kg ——— from day 6 of gestation up to and including day 18 of gestation resulted in very slight maternal toxicity at all dose levels as confirmed by a dose related increase in incidence of clinical signs and a slight decrease in body weight gain and food intake during the dosing period. No signs of embryotoxicity or teratogenicity were observed and therefore the no observed adverse effect level is 1.0 mg/kg for embryotoxicity and < 0.1 mg/kg for maternal toxicity.

Postmarketing Commitment – Study 6

6. To address the longer-term efficacy and safety of asenapine in the treatment of adults with schizophrenia, we request that you conduct, post-approval, an adequate and well controlled long-term maintenance study.

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

Response Study 6

Protocol A7501012 entitled "A randomized, placebo-controlled, double-blind trial of asenapine in the prevention of relapse after long-term treatment of schizophrenia" was submitted to IND 51,641 on April 4, 2005 (Serial No. 179). The core clinical trial report was submitted to the IND on May 6, 2009 (Serial No. 382).

The objectives of this trial were as follows:

> The primary objective of this trial was to determine the efficacy of asenapine compared with placebo with respect to the time to relapse or an impending relapse in schizophrenia subjects who received treatment with asenapine for 26 weeks. Secondary objectives included evaluating the effects of treatment with asenapine compared with placebo for up to 26 weeks in schizophrenia subjects previously treated with asenapine for 26 weeks with respect to the 5 dimensions of schizophrenia (positive symptoms, negative symptoms, disorganized thought, hostility/excitement, anxiety/depression); overall clinical impression of severity and improvement; depressive symptoms; suicidal thinking; cognitive function, as assessed with a computerized cognitive battery; and safety and tolerability.

Additionally, the overall trial conclusions are as follows:

> Asenapine was statistically significantly more effective than placebo in prolonging the time to relapse or impending relapse, which was the primary endpoint of this trial. Asenapine was also shown to be more effective than placebo in prolonging the time to early termination for any reason and the time to relapse or impending relapse based on the IERB opinion. Furthermore, statistically significant differences in favor of asenapine were observed in the change from baseline of the double-blind period to endpoint of the double-blind period for PANSS total score, PANSS Marder Factor scores, CGI-S, CDS total score, CogFu global assessment of cognitive functioning, and the CNS Vital Signs Attention/Vigilance domain. No statistically significant differences were observed between the asenapine and placebo groups during the double-blind period for ISST Modified total score or any other domains on the CNS Vital Signs cognitive battery.
>
> The safety profile from both the open-label and double-blind periods of this study indicated that asenapine at doses of 5 and 10 mg BID was generally safe and well tolerated in these subjects with schizophrenia. It was not possible to distinguish between AEs or symptomatology related to lack of treatment for the disease under study and potential withdrawal effects within 42 days post-randomization.

This long-term maintenance study will be included in a supplemental NDA.

Postmarketing Commitment – Study 7

7. To address the longer-term efficacy and safety of asenapine in the treatment of adults with acute manic or mixed episodes associated with bipolar I disorder, we request that you conduct, post-approval, an adequate and well controlled long-term maintenance study. For bipolar disorder, the maintenance study should be appropriately designed to assess the efficacy of asenapine in preventing all types of mood episodes associated with bipolar disorder (depression, mania, and mixed episodes).

Protocol Submission Date:	by February 2010
Study Start Date:	by September 2010
Trial Completion Date:	by October 2013
Final Report Submission:	by October 2014

Response Study 7

We have proposed dates above for this study.

Postmarketing Commitment – Study 8

8. It is not apparent from the studies you have conducted in schizophrenia that the lowest effective dose of asenapine has been identified. We request that you further characterize the utilization of asenapine in the treatment of adults with schizophrenia with a dose lower than 5 mg twice daily (e.g. 2.5 mg twice daily) through an adequate and well controlled trial.

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

Response Study 8

It is our position that the minimal effective dose for schizophrenia has been established in a sequence of well powered phase 2 studies in which the efficacy of doses ranging from 0.2 mg twice daily (BID) to 5 mg BID were assessed. The results showed that the 5 mg twice daily dose, but none of the lower doses, was superior to placebo. We have provided brief summaries of the studies below:

Short-term trial 041002

A double-blind, five armed, fixed-dose, active- and placebo-controlled dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia

This trial was conducted at 20 sites in the USA. Subjects were randomized to placebo, asenapine 0.2 mg BID, asenapine 0.4 mg BID, asenapine 0.800 mg BID, or risperidone 3 mg BID. Subjects in the asenapine 0.4 and 0.8 mg BID treatment groups were titrated up to their final dose over a 2-to-4-day period. Subjects in the risperidone group were titrated up to their final dose over a 2-day period. All 302 randomized subjects received double-blind trial medication: placebo, 61 subjects; asenapine 0.2 mg BID, 60 subjects; asenapine 0.4 mg BID, 59 subjects; asenapine 0.8 mg BID, 61 subjects; risperidone 3 mg BID, 61 subjects. A total of 283 subjects were included in the ITT group: placebo, 54 subjects; asenapine 0.2 mg BID, 58 subjects; asenapine 0.4 mg BID, 55 subjects; asenapine 0.8 mg BID, 59 subjects; risperidone 3 mg BID, 57 subjects.

Treatment with asenapine at the 0.2 mg BID, 0.4 mg BID, and 0.8 mg BID dose levels was no different from placebo in the changes from baseline in the PANSS total score, the primary efficacy endpoint. The mean changes from baseline were 1.0, -4.29, -3.17, and -4.35 for 0.2 mg BID, 0.4 mg BID, 0.8 mg BID, and placebo, respectively. Treatment with asenapine at the doses tested was also not different from placebo in the changes from baseline in the PANSS positive, negative, or general psychopathology subscale scores; CGI-S score; or the CGI-I score (LOCF, ITT analysis). Risperidone 3 mg BID treatment resulted in significantly greater reductions than placebo in the PANSS total score at Days 28, 35, and 42/endpoint (mean change from baseline at endpoint was -11.44).

Conclusion
Asenapine 0.2 mg BID, 0.4 mg BID, and 0.8 mg BID were not statistically different compared to placebo in treating symptoms of schizophrenia.

Short-term trial 041013

A double-blind, three-armed, fixed-dose, placebo-controlled, dose-finding study with sublingual Org 5222 in subjects with acute phase schizophrenia

This trial was conducted at 20 sites in the USA. Subjects were treated with placebo, asenapine 1.6 mg BID, or asenapine 2.4 mg BID. Subjects treated with asenapine 1.6 mg BID were titrated up to their final dose over a 5-day period; subjects treated with asenapine 2.4 mg BID were titrated up to their final dose over a 6-day period. Of 183 randomized subjects, 182 subjects were treated: placebo, 64 subjects; asenapine 1.6 mg BID, 57 subjects; and asenapine 2.4 mg BID, 61 subjects.

No statistically significant differences were observed between asenapine 1.6 mg BID and placebo or between asenapine 2.4 mg BID and placebo group in the mean changes from baseline to endpoint in the PANSS total score. The mean changes from baseline were -8.67, -5.81 and -3.68 for 1.6 mg BID, 2.4 mg BID, and placebo, respectively. In addition, no statistically significant differences were observed between the asenapine groups and placebo in the mean changes from baseline to endpoint in the PANSS positive, negative, or general psychopathology subscale scores; or the CGI-S score (LOCF, ITT analysis). There were no statistically significant differences between either of the asenapine treatment groups and the placebo treatment group in mean CGI-I scores.

Conclusion
Asenapine 1.6 mg BID and 2.4 mg BID were not statistically significantly different from placebo in treating symptoms of schizophrenia.

Short-term trial 041004

An assessment of the efficacy and safety of a sublingual dose of Org 5222 in subjects with schizophrenia (in an acutely exacerbated state) compared to risperidone and placebo in a randomized double blind, fixed-dose 6-week trial

Trial 041004 was conducted at 21 sites in the USA. Subjects were randomized to receive placebo, asenapine 5 mg BID, or risperidone 3 mg BID. Subjects who received asenapine 5 mg BID were titrated up to their final dose over a 5-day period. Subjects who received risperidone were titrated up to their final dose over a 3-day period. Of 182 subjects randomized to treatment, 180 subjects received at least one dose of trial medication: placebo, 62 subjects; asenapine 5 mg BID, 59 subjects; and risperidone 3 mg BID, 59 subjects. The ITT group included 174 subjects: placebo, 60 subjects; asenapine 5 mg BID, 58 subjects; and risperidone 3 mg BID, 56 subjects.

Subject demographics, history of schizophrenic illness, and extent of disease at trial entry appeared to be similar across treatment groups.

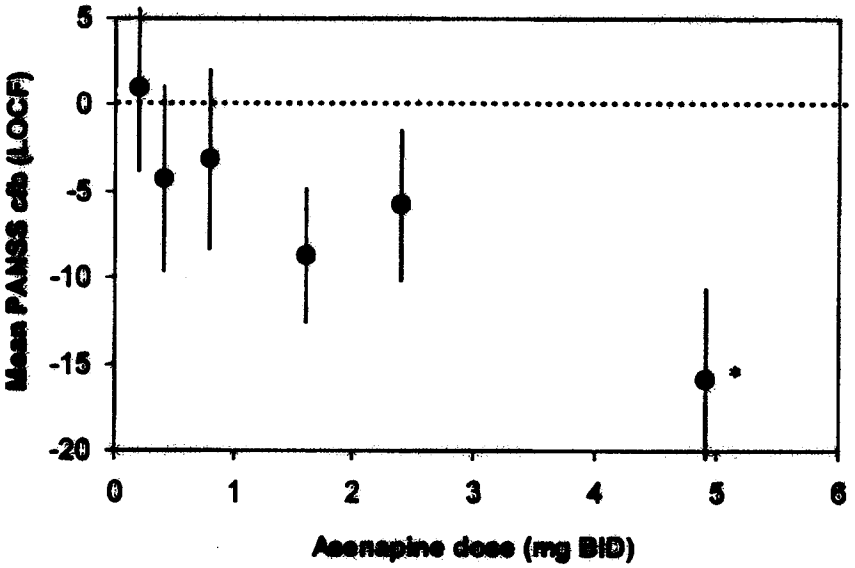
Asenapine 5 mg BID was statistically significantly ($p \leq 0.05$) more effective than placebo in reducing the symptoms of schizophrenia, as measured by the mean change from baseline to Day 42/endpoint in the PANSS total score (primary endpoint, LOCF, ITT). Sustained, statistically significant ($p \leq 0.05$) improvement in the PANSS total score compared with placebo was observed for asenapine 5 mg BID starting at Day 14. Treatment with asenapine 5 mg BID also resulted in statistically significantly ($p \leq 0.05$) greater improvement from baseline to Days 21, 28, 35, and 42/endpoint in the PANSS positive and negative subscale scores, and from baseline to Days 14, 21, 28, 35, and 42/endpoint in the general psychopathology subscale score. Additionally, a statistically significant treatment effect was apparent at Endpoint for the PANSS Marder positive, negative, and disorganized thoughts factors. CGI-S and CGI-I results were consistent with the primary efficacy results and results of secondary PANSS analyses.

Risperidone 3 mg BID was not shown to be statistically superior to placebo on the primary endpoint. However, risperidone 3 mg BID was statistically significantly more effective than placebo in treating positive symptoms of schizophrenia, as measured by changes from baseline to Days 7, 21, 35, and 42/endpoint in the PANSS positive subscale score. Risperidone 3 mg BID was also significantly more effective than placebo on the CGI-S at Days 7, 28, 35, and 42/endpoint and on the CGI-I at Days 21, 35, 42/endpoint.

Conclusion

Short-term treatment with asenapine 5 mg BID was effective in the treatment of subjects with schizophrenia in the 041004 trial on the primary endpoint.

Dose response for asenapine on Total PANSS score, phase 2 placebo controlled short-term fixed-dose efficacy studies



Source: Module 2.7.3S Table 11,Inferential analysis of change from baseline in PANSS total score (LOCF, ITT group): phase 2 and phase 3 short-term Trials

Markers represent mean Total PANSS change from baseline at endpoint (LOCF) – bars represent 95% confidence interval of the mean

* = statistically significantly different from placebo

BID = twice daily; cfb = change from baseline; ITT = intent-to treat; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale

These data were discussed with FDA during our November 20, 2002 End of Phase 2 meeting. During the meeting the agency concurred that the minimal effective dose had been established (see Clinical, Question #2 in SN0000, Module 1.6.3 – FDA MoM 20 Nov 2002 EOP2).

In addition, these clinical study results have been corroborated by the dopamine D_2 receptor PET data for asenapine. Based on a pooled analysis of public domain pharmacokinetic, D_2 occupancy and clinical efficacy data for several antipsychotics (olanzapine, risperidone, ziprasidone and haloperidol), a generic quantitative relationship between dopamine D_2 occupancy and short-term clinical efficacy in schizophrenia (as measured by PANSS total score) was characterized (see SN0000, Module INT00039258). Based on this relationship, the level of D_2 occupancy at an asenapine dose of 2.4 mg BID

was found to be insufficient to provide good efficacy in the treatment of schizophrenia (expected mean change in PANSS from placebo at 6 weeks for 2.4 mg BID was -6.8 as compared to -10.2 for 5 mg BID).

In conclusion, the available data indicate that the likelihood of establishing efficacy with asenapine at a dose of 2.5 mg BID is low. Given this knowledge, the potential benefit of utilizing 2.5 mg BID as a dose regimen in the treatment of adult subjects with schizophrenia is unclear. We maintain that 5 mg BID has been established as the minimal effective dose of asenapine in this indication and that the study requested is not warranted.

Postmarketing Commitment – Study 9

9. It is not apparent from the studies you have conducted in bipolar mania that the lowest effective dose of asenapine has been identified. We request that you further characterize the utilization of asenapine in the treatment of adults with acute manic or mixed episodes associated with bipolar I disorder with a dose lower than 10 mg twice daily (e.g. 5 mg twice daily) through an adequate and well controlled trial.

Protocol Submission Date:	by February 2010
Study Start Date:	by September 2010
Trial Completion Date:	by October 2013
Final Report Submission:	by October 2014

Response Study 9

We have proposed dates above for this study.

Postmarketing Commitment – Item 10

10. The Division of Psychiatry Products is evaluating the effects of atypical antipsychotic drugs on metabolic parameters (e.g., weight, lipids, and glucose). We request analyses, post-approval, from your clinical development program.

Subject Groups to Be Evaluated

In Table 1 below, we outline the subject groups for which we request information. For each analysis discussed subsequently, we request evaluation related to each of the groupings in Table 1 (9 total), unless otherwise noted.

Table 1. Subject Groups to Be Evaluated

I. All Adult Subjects
   1. Adult Subjects in Placebo-Controlled Trials
   2. Adult Subjects in Comparator-Controlled Trials §
   3. All Adult Asenapine-treated Subject Data, Controlled and Uncontrolled

II. Pediatric and Adolescent Subjects (Age <18 at Time of Enrollment) †

1. Pediatric and Adolescent Subjects in Placebo-Controlled Trials
2. Pediatric and Adolescent Subjects in Comparator-Controlled Trials §
3. All Pediatric and Adolescent Asenapine-treated Subject Data, Controlled and Uncontrolled

III. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects*
1. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Placebo-Controlled Trials
2. Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects in Comparator-Controlled Trials §
3. All Data for Asenapine-treated Subjects with First Episode Psychosis and Antipsychotic-Naïve Subjects, Controlled and Uncontrolled

§ For evaluations of comparator-controlled trials, we request separate evaluations for each comparator with data for more than 50 subjects.

† Include all pediatric and adolescent subjects, including subjects in trials that do not enroll only pediatric or adolescent subjects.

* This subject group is comprised of two categories of subjects: subjects with first episode psychosis and antipsychotic-naïve subjects. This group includes subjects from trials with psychiatric indications only and includes adult and pediatric subjects. Include all subjects with first episode psychosis and all antipsychotic-naïve subjects, including subjects in trials that did not enroll these types of subjects exclusively. We define antipsychotic-naïve subjects as those who have received antipsychotic therapy for four months or less prior to study enrollment.

Subject Exclusion Criteria

We request the exclusion of subjects from trials that meet the following criteria:

- Studies without a source drug monotherapy arm
- Studies with duration under 7 days
- Studies with a relapse-prevention study design, in which subjects had source drug exposure prior to randomization
- Studies evaluating the source drug using routes of drug delivery other than oral drug delivery (e.g., intramuscular, intravenous)

Tables Summarizing Clinical Trials for Each Subject Group

We request tables with summary information on clinical trials with metabolic data. For each subject group in Table 1 (9 total) provide a data table with the 18 columns summarized in Table 2. Each row should contain information on a single clinical trial.

Table 2. Clinical Trial Information

Column Number	Column Name	Description	Notes
1	Study	Clinical Trial Name	
2	Indication	Trial Indication	
3	Asenapine N	Number of subjects in the clinical trial who received the source drug	
4	Asenapine Dose Range	Range of source drug doses used in the clinical trial	
5	Placebo N	Number of subjects in the clinical trial who received placebo. If no subjects received placebo, leave the column blank.	
6	Comparator	Name of the comparator(s) used in the trial. Multiple comparators may be listed.	
7	Comparator N	Number of subjects in the trial who received the comparator. If there are multiple comparators, list comparator N adjacent to the comparator (see example).	Comparator / Comparator N Comp 1 / 43 Comp 2 / 55
8	Total Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
9	HDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
10	LDL Cholesterol	If not measured, leave blank. Otherwise, enter one of the	

		following: R (random) NF (non-fasting) F (fasting	
11	Triglycerides	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
12	Glucose	If not measured, leave blank. Otherwise, enter one of the following: R (random) NF (non-fasting) F (fasting	
13	HbA1c	Hemoglobin A1c. If not measured, leave blank. If measured, enter Y for yes.	
14	UA glucose	Urine glucose. If not measured, leave blank. If measured, enter Y for yes.	
15	Weight	If not measured, leave blank. If measured, enter Y for yes.	
16	Duration Controlled	Enter the duration controlled in weeks.	
17	Duration Uncontrolled	Enter the Duration Uncontrolled in Weeks	
18	Notes	Any additional notes about the study (optional).	

Tables Summarizing Subject Demographic Information

We request demographic tables for each of the nine subject groups described in Table 1 with the following information:

- Mean Age
- Gender
- Race
- Treatment Indication
- Mean Modal Dose Received
- Median Time of Exposure to Treatment
- Number of Years Since First Antipsychotic Medication Prescribed (if available)
- Percent Discontinued due to Lack of Efficacy
- Percent Discontinued to Side Effect
- Percent Discontinued Due to Metabolic Side Effect
- Mean Baseline Weight
- Mean Baseline BMI

Tables Summarizing Subject Metabolic Data

Each data table should clearly list:

- The studies from which analyses were derived
- The mean modal dose of treatment received by each subject group
- The median, range, and interquartile range of treatment exposure time for each subject group

We have the following specific requests regarding the analysis plan for weight, lipids, and glucose:

I. Weight

I. A. Weight: Mean Change Analyses

- We request analyses of simple mean changes in weight and in body mass index (BMI) from baseline to last observation carried forward (LOCF) endpoint for all patients in each subject group; we also request similar mean change analyses of subgroups divided according to World Health

Organization categories of baseline BMI: Underweight (BMI<18.5), Normal Weight (18.5≤BMI<25), Overweight (25≤BMI<30), and Obese (BMI≥30). We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups.

- We request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean weight change should be reported for all patients who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

I. B. Weight: Categorical Analyses

To assess for weight gain outliers in each subject group, stratifying by treatment exposure time, we request analyses similar in format to the table below:

Table 3. Combined Weight Data

	6 weeks		6 months		12 months		24 months		36 months	
Weight change (kg)	n	%	n	%	n	%	n	%	n	%
Wt change ≤0	500	10								
0<Wt change≤5	500	10								
5<Wt change≤10	500	10								
10<Wt change≤15	500	10								
15<Wt change≤20	500	10								
20<Wt change≤25	500	10								
25<Wt change≤30	500	10								
30<Wt change≤35	500	10								
35<Wt change≤40	500	10								
Wt change>40	500	10								
Total for time point	5000	100		100		100		100		100

- Using this format, we request analyses for all subject groups in Table 1.
- Since changes in weight are sometimes difficult to interpret in pediatric populations, we request additional tables displaying change in BMI. The format is similar to Table 3, except that it substitutes "BMI Change" for "Weight Change." The BMI change categories should be as follows: BMI change ≤0, 0<BMI change≤1, 1<BMI change≤2, 2<BMI change≤3, 3<BMI change≤4, 4<BMI change≤5, 5<BMI change≤6, 6<BMI change≤9, 9<BMI change≤12, 12<BMI change≤15, and BMI change>15.
- Please ensure that analyses have not included individual subjects more than once.

II. Lipids

II. A. Lipids: Mean Change Analyses

- Assess simple mean changes in the following lipid parameters: total cholesterol (combined fasting and non-fasting), fasting triglycerides, non-fasting triglycerides, HDL cholesterol (combined fasting and non-lasting), and fasting LDL cholesterol. We request that treatment effect be assessed based on an analysis of variance (ANOVA) model with terms for protocol and treatment. It is not necessary to perform this analysis on the combined controlled and uncontrolled subject groups. Otherwise, we request analyses for the placebo-controlled and comparator-controlled subject groups in Table 1.
- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.
- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information on clinical trials included in calculations, drug exposure time, and dose requested earlier in this document.
- Report the mean baseline lipid value, post-treatment lipid value, and magnitude of change.

II. B. Lipids: Categorical Analyses

II. B. 1. Lipid Categorical Analyses: Adult Subjects

- We request analyses of all subject groups listed in Table 1. Because exposure time is essential to interpreting lipid results, we request for each subject group in Table 1 separate analyses of: 1.) All subjects and 2.) Subjects with at least 12 weeks of exposure 3.) Subjects with at least 24 weeks of exposure.

- We request that median exposure at time of lipid measurement also be listed with each table related to lipids. This is in addition to information previously requested on studies included, dose, and treatment exposure time.
- In tables of categorical lipid analyses, report the mean or median baseline, post-baseline, and change in lipid values for each analysis.
- We request the following analyses of treatment-emergent significant changes in lipids listed in Tables 4 and 5.

Table 4. Treatment-Emergent Significant Changes in Lipids: Based on NCEP-based Classifications for Adults*

	Baseline	Postbaseline
Total Cholesterol (Fasting and Non-Fasting)*		
Normal to High	<200 mg/dL	≥240 mg/dL
Borderline to High	≥200 and <240 mg/dL	≥240 mg/dL
Normal/Borderline to High	<240 mg/dL	≥240 mg/dL
Normal to Borderline/High	<200 mg/dL	≥200 mg/dL
LDL Cholesterol (Fasting)		
Normal to High	<100 mg/dL	≥160 mg/dL
Borderline to High	≥100 and <160 mg/dL	≥160 mg/dL
Normal/Borderline to High	<160 mg/dL	≥160 mg/dL
Normal to Borderline/High	<100 mg/dL	≥100 mg/dL
HDL Cholesterol (Fasting and Non-fasting)*		
Normal to Low	≥40 mg/dL	<40 mg/dL
Triglycerides (Fasting)		
Normal to High	<150 mg/dL	≥200 mg/dL
Normal to Very High	<150 mg/dL	≥500 mg/dL
Borderline to High	≥150 and <200 mg/dL	≥200 mg/dL
Borderline to Very High	≥150 and <200 mg/dL	≥500 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Normal/Borderline to Very High	<200 mg/dL	≥500 mg/dL
Normal to Boederline/High/Very High	<150 mg/dL	≥150 mg/dL

* The National Cholesterol Education Program (NCEP) Adult Treatment Program Classifications of lipids refer to fasting lipid measurements. However, given that total cholesterol and HDL cholesterol measurements are not significantly changed by fasting status and that the majority of clinical trial lipid data is non-fasting, we elect to include fasting and non-fasting values for total cholesterol and HDL cholesterol in combined analyses.

Table 5. Treatment-Emergent Significant Changes in Lipids: Additional Analyses

	Baseline	Post-baseline
Treatment- emergent very high triglycerides (fasting)	Fasting triglycerides <500 mg/dL	Fasting triglycerides ≥500 mg/dL
Treatment-emergent very high triglycerides (non-fasting and random)	Non-fasting and random triglycerides <500 mg/dL	Non-fasting and random triglycerides ≥500 mg/dL
Treatment-emergent triglycerides >1000 mg/dL (All cases—fasting, non-fasting, and random)	Triglycerides <1000 mg/dL	Triglycerides ≥1000 mg/dL
Change in fasting or non-fasting total cholesterol ≥40 mg/dL at any time post-baseline[1]	Any value	Increased fasting or non-fasting total cholesterol ≥40 mg/dL
Change in fasting LDL cholesterol ≥ 30 mg/dL at any time post-baseline[2]	Any value	Increased fasting LDL cholesterol ≥ 30 mg/dL
Change in fasting or non-fasting HDL cholesterol ≥20 mg/dL at any time post-baseline[3]	Any value	Decreased fasting or non-fasting HDL cholesterol ≥20 mg/dL
Change in fasting triglycerides ≥50 mg/dL at any time post-baseline[4]	Any value	Increased fasting triglycerides ≥50 mg/dL

[1] We also request subgroup analyses based on the following categories of baseline fasting or nonfasting total cholesterol for adults: Normal (<200 mg/dL), Borderline (≥200 and <240 mg/dL), and High (≥240 mg/dL). For pediatric subjects use the total cholesterol categories listed in Table 6.

[2] We also request subgroup analyses based on the following categories of baseline fasting LDL cholesterol for adults: Normal (<100 mg/dL), Borderline (≥100 and <160 mg/dL), and High (≥160 mg/dL). For pediatric subjects use the fasting LDL cholesterol categories listed in Table 6.

[3] We also request subgroup analyses based on the following categories of baseline fasting or non-fasting HDL cholesterol: Normal (≥40 mg/dL) and Low (<40 mg/dL).

[4] We also request subgroup analyses based on the following categories of baseline fasting triglycerides: Normal (<150 mg/dL), Borderline (≥150 and <200 mg/dL), High (≥200 and <500 mg/dL), and Very High (≥500 mg/dL).

II. B. 2. Lipid Categorical Analyses: Pediatric Subjects

Because the National Cholesterol Education Program (NCEP) defines borderline and high cut-off values for LDL cholesterol and total cholesterol differently in pediatric subjects, we request using these criteria in pediatric subject analyses. The LDL cholesterol criteria apply to fasting lipid measurements, and the total cholesterol criteria apply to fasting and non-fasting lipid measurements.

Since NCEP has designated specific pediatric cut-off values for neither HDL cholesterol nor triglycerides, we request using identical categories for clinically significant changes in HDL cholesterol and triglycerides in adult and pediatric subjects (see Tables 4 and 5 above).

Regarding the pediatric and adolescent subject groups only, we request the following categorical lipid analyses (Tables 7) based on the NCEP criteria (Table 6).

Table 6. Criteria for Abnormal Metabolic Values in Pediatric Subjects

Criterion	Abnormal Value in Pediatric Subjects
Normal Fasting LDL Cholesterol Level	<110 mg/dL
Borderline Fasting LDL Cholesterol Level	110-129 mg/dL
High Fasting LDL Cholesterol Level	≥130 mg/dL
Normal Total Cholesterol Level	<170 mg/dL
Borderline Total Cholesterol Level	170-199 mg/dL
High Total Cholesterol Level	≥200 mg/dL

Table 7. Pediatric Categorical Analyses: Treatment-Emergent Significant Changes in Lipids

	Baseline	Post-baseline
Normal to borderline total cholesterol level (fasting and non-fasting values)	<170 mg/dL	170-199 mg/dL
Normal to high total cholesterol level (fasting and non-fasting values)	<170 mg/dL	≥200 mg/dL
Borderline to high total cholesterol levels	170-199 mg/dL	≥200 mg/dL
Normal to borderline fasting LDL cholesterol level	<110 mg/dL	110-129 mg/dL
Normal to high fasting LDL cholesterol level	<110 mg/dL	≥130 mg/dL

Borderline to high fasting LDL cholesterol level	110-129 mg/dL	≥130 mg/dL

III. Glucose

III. A. Glucose: Mean Change Analyses

III. A. 1. Glucose: Overall Mean Change Analyses

We request analysis of mean and median changes in serum glucose levels from baseline to endpoint (separate analyses for fasting and non-fasting data). We also request mean and median changes in serum glucose levels from baseline to highest measurement (separate analyses for fasting and non-fasting data).

We also request observed case analyses of mean change for the following specified exposure durations: 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks. For these analyses, mean change in serum glucose from baseline to highest post-baseline measurement should be reported for all subjects who completed the study time up to the time point specified for that analysis. Comparison between treatment groups should be conducted and p-values reported. We request information on all subject groups in Table 1 for this analysis.

III.A. 2. Glucose: Mean Change Analyses by Baseline Values

We request that each of the mean change analyses (baseline to endpoint and baseline to highest measurement for fasting and non-fasting data) described in section III.A.1 also be performed with stratification according to baseline serum glucose measurement for each of the six categories in Table 8, as follows:

Table 8. Categorization of Serum Glucose Levels (Based on American Diabetes Association Criteria)

Fasting Serum Glucose	
Normal	<100 mg/dL
Impaired Fasting Glucose	100-125 mg/dL
Diabetes (High)	≥126 mg/dL
Non-fasting Serum Glucose	
Normal	<140 mg/dL
Borderline	140-199 mg/dL
High	≥200 mg/dL

III. B. Glucose: Categorical Analyses

We request analyses of proportions of subjects with treatment-emergent changes of interest at any time post-baseline as described in Table 9 below. We request that you compare the proportions of subjects with clinically significant changes using Fisher's exact test.

Table 9. Serum Glucose: Criteria for Clinically Significant Changes

	Baseline	Post-Treatment
Fasting Serum Glucose		
Normal to High	<100 mg/dL	≥126 mg/dL
Impaired Fasting Glucose to High	100-125 mg/dL	≥126 mg/dL
Normal/Impaired Fasting Glucose to High	<126 mg/dL	≥126 mg/dL
Change in fasting serum glucose ≥10 mg/dL at any time post-baseline*	Any value	Fasting glucose increased ≥10 mg/dL
Non-Fasting Serum Glucose		
Normal to High	<140 mg/dL	≥200 mg/dL
Borderline to High	140-199 mg/dL	≥200 mg/dL
Normal to Borderline/High	<140 mg/dL	≥140 mg/dL
Normal/Borderline to High	<200 mg/dL	≥200 mg/dL
Change in non-fasting serum glucose ≥20 mg/dL at any time post-baseline*	Any value	Non-fasting glucose increased ≥20 mg/dL

* For these two analyses, we request additional subgroup analyses divided according to baseline glucose levels. Please use the categorizations of fasting serum glucose and non-fasting serum glucose listed in Table 8 to define the subgroups.

In addition to the analyses listed in Table 9, we request similar analyses using the following additional serum glucose cut-off values:

- For fasting serum glucose, we request analyses of the proportion of subjects with post-treatment levels of 140 mg/dL, 200 mg/dL, and 300 mg/dL.
- For non-fasting glucose, we request analyses of the proportion of subjects with post-treatment level of 300 mg/dL.

We request analyses of the proportion of subjects with post-baseline hemoglobin A1c ≥ 6.1%, 8%, 10%, and 12% among patients with baseline hemoglobin A1c values below 6.1%.

We also request analyses of the proportion of subjects with treatment-emergent glycosuria (defined as any glucose in the urine) for each subject database listed in Table 1.

Time Frame for Submission to the Division of Psychiatry Products

Responses to this information request may be submitted in stages. Specifically, information from placebo-controlled trials (all subject groups), comparator-controlled trials (all subjects groups), and combined controlled and uncontrolled data (all subjects),

may be submitted separately, as they are completed. We expect that the response to all components of this request will be submitted by February 28, 2010.

Response Item 10

We believe we can fulfill this request by February 28, 2010.

Kiedrow, Keith

From: Greeley, George
Sent: Friday, December 12, 2008 3:21 PM
To: Kiedrow, Keith
Cc: Mathis, Lisa
Subject: NDA 22-117 Saphris (asenapine maleate)

Importance: High

Hi Keith,

The Saphris (asenapine maleate) partial waiver/deferral/plan was reviewed by the PeRC PREA Subcommittee on December 10, 2008. The Division recommended a partial waiver because disease/condition does not exist in children and a deferral because the product is ready for approval in adults. The PeRC agrees with the Division to grant a partial waiver for this product. However, the PeRC will require the Protocol Submission Date, Study Start Date and the Final Report Submission Date before the deferral/plan for this product can be approved.

The PeRC has noted that the Division will take a Complete Response action for the product at this time.

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

Please consider the environment before printing this e-mail.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-117

Organon USA Inc.
Attention: Todd Paporello, Pharm.D., MBA
Associate Director & Liaison, Regulatory Affairs
56 Livingston Ave.
Roseland, NJ 07068

Dear Dr. Paporello:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for asenapine maleate sublingual tablets.

We also refer to your submission dated April 10, 2008, which utilized the proposed tradename Saphris.

With the aid of the Division of Medication Errors and Technical Support of the Office of Surveillance and Epidemiology we have completed the review of your submission and have the following comments.

Proprietary name

The Division of Medication Error Prevention has no objections to the use of the proprietary name Saphris for this product provided that a proposed (but not yet approved) proprietary name, associated with a different application, is not approved before this application. In the event that the other application is awarded approval first, we recommend that the second product to be approved seek an alternate name.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and recommend that the name be resubmitted for review. If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation.

Established name

Additionally, we note the established name (asenapine) of the proposed name, Saphris, may be prone to potential confusion because of its similarity to the currently marketed product, olanzapine. Because established names are not regulated by FDA, we recommend the Applicant discuss this issue with USAN/INN (International Nonproprietary Name) and petition for a new established name, if they feel this is a significant safety concern with their product.
Below is a summary of our concerns:
The main concerns with olanzapine are with its potential for confusion with the proposed product's established name, asenapine. The three main factors contributing to our concern with

the established name for Saphris (asenapine) includes orthographic similarity, overlapping product characteristics with olanzapine. Our concerns are described below.
Olanzapine and asenapine share a similar orthographic prefix ('olan-' vs. 'asen-') see example below. Both names also the letter 'a' in the middle of the name, and they also share the same ending ('-pine'). Adding to our concern regarding potential confusion between olanzapine and asenapine are overlapping product characteristics in addition to their orthographic similarities. These products share several overlapping product characteristics such as indication (schizophrenia and bipolar I disorder), strength (5 mg and 10 mg), dose (5 mg to 10 mg), dosage form (solid oral: sublingual tablet/tablet), and route of administration (oral) see Table 1 on page 18.

Olanzapine
Asenapine

Table 1. Comparison of Asenapine and Olanzapine

	Saphris	Zyprexa	Orthographic similarity ('Asen-' and 'Olan-' may look similar; both contain middle vowel 'a'; same ending '-pine'). Overlapping indication (schizophrenia, bipolar disorder), strength (5mg, 10 mg), dose (5 mg to 10 mg), dosage form (tab), route of administration (oral)
[illegible]	Organon	Lilly	
[illegible]	1. Schizophrenia 2. Bipolar disorder (acute manic or mixed episodes associated with bipolar I disorder)	1. Schizophrenia 2. Bipolar disorder (acute mixed or manic episodes associated with bipolar I disorder)	
[illegible]	5 mg and 10 mg	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg	
[illegible] Supplied	Box of 60 (6 Blisters x 10 tabs each) Box of 100 (10 Blisters x 10 tabs each)- hosp. UD	Bottles of 30 Blisters of 100 Bottles of 1000	
[illegible] Dose and [illegible]	Schizophrenia: 5 mg BID Bipolar disorder: 10 mg BID	Schizophrenia: 5 mg to 10 mg QD Bipolar disorder: 5 mg to 20 mg QD (pts on 10 mg could overlap w/ Syprexa)	
[illegible] of [illegible]	Twice daily	Once daily	
[illegible] of [illegible]	Oral	Oral	
[illegible] Form	Sublingual tablet	Tablet Sublingual tablet	

Labels and Labeling

The Label and Labeling Risk Assessment findings indicate that the presentation of information of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The Division of Medication Error Prevention believes the risks we have identified on the container labels and carton labeling can be addressed and mitigated prior to drug approval, and provides recommendations below that aim at reducing the risk of medication errors.

Container labels and Carton labeling

1. For consistency purposes use the same colored band on the upper, lower, right and left portions of the carton and container labels (e.g. 5 mg strength contain — bands, 10 mg strength contain bands). b(4)
2. Increase the prominence of 'sublingual tablets' and relocate it so it appears in conjunction with the established name (asenapine). The dosage form should appear with the same prominence as the established name per 21 CFR 201.10(g)(2).
3. In order to improve readability, relocate the product strength so it appears closer in proximity to the proprietary name and established name. This can be either beneath the established name or next to the proprietary and established name. After relocating the product strength, ensure the net quantity is not in close proximity to the strength.
4. In order to avoid interference with the readability of the proprietary name, established name, and product strength, ensure this information is not bisected by the colored triangles on the carton and container labels.
5. Due to the poor bioavailability if Saphris is swallowed, include a statement on the principle display panel of the carton labeling and container label instructing the user not to crush, chew, or swallow the tablet.
6. On the carton labeling, relocate the statement, "Fragile: Do not push tablets through tablet pack" from the side panel on the carton labeling to the principle display panel. We recommend you consider displaying this information using color, bolding, or some other means.
7. On the container label, relocate the statement, "Fragile: Do not push tablets through tablet pack" from the last statement to the first statement on the label (above the "Each sublingual tablet contains..." statement). Increase the prominence of this statement by color, bolding or some other means.
8. Increase the prominence of the middle portion of the NDC numbers by presenting the middle portion in bolded, tall man format (e.g., 0052- 0118- 06).
9. Since only the 10 mg blister label was provided for review, ensure the 5 mg and 10 mg blister labels are adequately differentiated by boxing, color, or some other means, in order to avoid confusion and errors.
10. Indicate on the blister label that the user should peel the blue tab to remove the sublingual tablet. This could be accomplished through graphics (e.g., shaded area, arrows) if space does not allow, and may help to avoid patients pushing the sublingual tablets through the back of the blister.
11. Remove — from the blister labels. b(4)

Insert labeling

1. In the highlights section of the insert bold the statement "Do not swallow tablet" and relocate it to appear as the first sentence in the "administration" subsection in the dosage and administration section of the insert.
2. Replace the abbreviation BID, with twice daily.
3. Delete the bolded statement in sections 2.1 and 2.2 of the package insert "Patients should be told the following."
4. Reorganize the first paragraph under "Important" in sections 2.1 and 2.2 so it instructs the user what not to do, and then what to do. For example: Do not remove a tablet until ready to administer. Do not push tablet through tablet pack. Do not cut or tear tablet pack. Do not crush tablet. Use dry hands when handling tablet. Firmly press and hold thumb button while pulling out tablet pack. Peel back colored tab. Gently remove tablet.
5. In section 12 of the package insert (Clinical Pharmacology) include information about the low bioavailability of asenapine when swallowed.
6. After the statement "Do not swallow tablet" in sections 2.1 and 2.2 in the package insert, refer the reader to the Clinical Pharmacology section to provide the rationale for not swallowing the tablets.
7. Provide instructions for patient and providers on what to do in the event that the sublingual tablet is swallowed. For example, patients may be instructed to consult with their healthcare provider if they swallow the sublingual tablet; and healthcare providers should be given provided with guidelines on whether a patient should immediately administer another sublingual tablet in the appropriate manner (sublingually), or whether a patient should wait until their next scheduled dose to administer the sublingual tablet.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Project Manager, at 301-796-1924.

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

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
6/16/2008 08:55:06 PM

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 3, 2008

TO: Keith Kiedrow, Regulatory Project Manager
Robert Levin, M.D., Medical Officer

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-117

APPLICANT: Organon USA, Inc.

DRUG: Asenapine

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard review

INDICATIONS: Treatment of acute exacerbation of schizophrenia

CONSULTATION REQUEST DATE: November 14, 2007

DIVISION ACTION GOAL DATE: April 30, 2008

PDUFA DATE: June 30, 2008

I. BACKGROUND

The trial was a double-blind, fixed-dose, placebo- and positive-controlled, multicenter, randomized efficacy trial in subjects with a DSM-IV-TRTM (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision 2000) diagnosis of schizophrenia who are acutely exacerbated at the time of admission to the trial. This trial consisted of screening, a 2-day taper period (eligible severely ill patients may be randomized immediately upon screening at the discretion of the investigator), and a 6-week active treatment period. Subjects were hospitalized for the first 2 weeks of the 6-week active treatment period. Hospitalization beyond 2 weeks had to be accompanied by adequate justification and approval from the sponsor. For the remainder of the trial, subjects continued as outpatients.

Protocols and Site Selection

Protocol: 041023 A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia.

Protocol A7501004 A Phase III, Randomized, Placebo- Controlled, Double-Blind Trial Evaluating the Safety and Efficacy of Sublingual Asenapine vs. Olanzapine and Placebo in In-Patients with an Acute Manic Episode.

A total of five clinical sites were selected for inspection based on enrollment of large numbers of study subjects. Three foreign sites were selected in addition to two domestic sites since domestic data were insufficient; efficacy results were driven by foreign data. The study protocols, clinical sites, and inspection results are summarized below.

II. RESULTS

	Name of CI City and State/Country	Protocol Subjects	Inspection Dates	Classification	
				Inspec.	Final
1	Drs. Daniel Zimbroff/Joachim Rasse Riverside, CA 92506	Protocol 41023 41 subjects	1/2/08- 1/10/08	NAI	NAI
2	Dr. Richard Louis Jaffe Philadelphia, PA 19131	Protocol 41023 18 subjects	1/10/08- 1/16/08	NAI	NAI
3	Dr. Mikhail Popov St. Petersburg 197341, Russia	Protocol 41023 40 subjects	2/11/08- 2/25/08	NAI	NAI
4	Dr. Ramasubbu Sathiyanathan Chennai, Tamilnadu 600003, India	Protocol A7501004 15 subjects	2/18/08- 2/22/08	VAI	VAI
5	Dr. Padma Sudhakar Tirupati, Tamilnadu 517507, India	Protocol A7501004 15 subjects	2/25/08- 2/28/08	VAI	VAI

Key to Classifications

NAI = No action indicated; no deviations from regulations
VAI = Voluntary action indicated; no significant deviations from regulations
OAI = Official action indicated; significant deviations from regulations

1. Dr. Daniel Zimbroff (Investigator deceased)
Dr. Joachim Raese (current PI): Site 319, Study 41023, 41 subjects

Riverside Center for Behavioral Medicine (in-patient unit); 5900 Brockton Avenue
Unit III (out-patient facility); 5945 Brockton Avenue
Riverside, CA 92506

Dr. Raese appears to not have participated in the trial but took over the trial in late 2007 after Dr. Zimbroff's death. We found only evidence that in very late 2007 he signed a document attesting that a CD of eCRFs was received from the CRO/Sponsor. Dr. Raese is not with the firm, [redacted] which Dr. Zimbroff used as the umbrella organization for research. b(4)

Of the 44 subjects screened, 41 enrolled and 40 completed the study. An in-depth audit was performed for 21 subjects. There were no deficiencies warranting an FDA 483. The trial appeared to have been conducted per protocol with a high degree of organization and documentation.

Recommendation: Data from this site are reliable.

2. Dr. Richard Louis Jaffe: Site 313, Study 41023, 18 subjects

Belmont Center for Comprehensive Treatment
4200 Monument Road
Philadelphia, PA 19131

Of the 28 (313001-313028) subjects screened, 22 were randomized and 7 (313002, 313006, 313009, 313010, 313012, 313018, 313022) completed the study. Subject records for all 28 subjects were reviewed. Data listings were verified against CRFs and source documents. No deficiencies were observed and no FDA-483 was issued.

Recommendation: Data from this site are reliable.

3. Dr. Mikhail Popov: Site 362, Study 41023, 40 subjects

City Psychiatric Hospital #3 of Skvortsov-Stepanov
Fernskoye Shosse, 36
St. Petersburg 197341, Russia

Of the 42 subjects screened, 40 were randomized and 32 completed the study. An in-depth audit was performed for 21 subjects. No deviations from regulations/good clinical practice were noted and no FDA 483 was issued.

Recommendation: Data from this site are reliable.

4. Dr. Ramanathan Sathianathan: Site 4103, Study A7501004, 15 subjects

Madras Medical College and Government General Hospital
Department of Psychiatry
EVR Periyar Salai
Chennai, Tamilnadu 600003, India

Of the 18 subjects screened, 14 were randomized, 1 was lost to follow-up, 5 withdrew, and 8 completed the study. An in-depth audit was performed for 10 subjects. An FDA Form 483 was issued for the following deficiencies:

(1) In obtaining informed consent from subject 41031012, the subject's full signature (and date) was not obtained until several days after obtaining the consent.

(2) In subject 41031008, the investigational drug assignment records contain conflicting information. The kit assignment number documented on the source records appeared to be incorrect, and the kit assignment number documented on the drug assignment confirmation report appeared to be correct.

(3) The performance of protocol-specified cognitive testing was cancelled prior to the receipt of official written communication from the sponsor authorizing the cancellation.

Recommendation: In general, the data from this site are reliable. It is unlikely that the isolated deficiencies would affect data reliability.

5. Dr. Padma Sudhakar: Site 4125, Study A7501004, 15 subjects

Sri Venkateshwara Medical College
Department of Psychiatry
Tirupati, Tamilnadu 517507, India

Of the 16 subjects screened, 15 were randomized and 13 completed the study. An in-depth audit of was completed for 15 subjects. An FDA Form 483 was issued for the following deficiencies:

(1) There is no documentatin in the study records to demonstrate that 3 female subjects (41251004, 41251013, 41251003) used an acceptable method of birth control as defined in the protocol.

(2) In subject 41251001, the baseline measure for the primary efficacy endpoint (mania score) was incorrect.

Recommendation: In general, the data from this site are reliable. It is unlikely that the isolated deficiencies would affect data reliability.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of two US and three foreign (India, Russia) clinical sites. The deficiencies noted at two foreign sites (both in India) appeared to be isolated occurrences.

- At site 4103, the deficiencies were administrative errors in record keeping.
- At site 4125, although the deficiencies carried significant potential to compromise patient safety (inclusion of women not observing adequate contraception) or data integrity (incorrect assessment of baseline mania score), the findings are limited to a few subjects and are unlikely to affect the outcome of the study.

The inspectional findings limited to a few, apparently isolated deficiencies support validity of data as reported by the sponsor under this NDA.

{See appended electronic signature page}

John Lee, MD
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

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/s/

John Lee
6/4/2008 02:09:52 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
6/4/2008 02:22:43 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-117

Organon USA Inc.
Attention: Todd Paporello, PharmD, MBA
Associate Director & Liaison, Global Regulatory Affairs
56 Livingston Ave.
Roseland. NJ 07068

Dear Dr. Paporello:

Please refer to your August 30, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for asenapine maleate sublingual tablets.

The following comments/requests come from the Pharmacology/Toxicology group and the Office of New Drug Quality Assessment.

Pharmacology/Toxicology

We have completed our review of your carcinogenicity studies, entitled "104 week subcutaneous administration oncogenicity study with Org 5222 in the rat" and "104 week subcutaneous administration oncogenicity study with Org 5222 in the mouse", and have concluded that further information is needed as discussed below.

Rat carcinogenicity study:

The MTD (maximum tolerated dose) was clearly exceeded in this study in males at all dose levels and in females at the high dose based on significant and dose-dependent decreases in body weight gain and body weight. The incidence of preneoplastic changes and tumors (total number of tumors and tumor-bearing animals) was decreased at the high dose when compared to the vehicle controls. The low dose and medium dose groups were not routinely examined. Since it is known that a significant decrease in body weight can lead to a decrease in tumor development, you should conduct a full histopathologic examination of the low and mid dose males and females.

Mouse carcinogenicity study:

The incidence of pleomorphic malignant lymphomas and all combined lymphomas in the hemolymphoreticular system was statistically significantly increased in the female mice at the

high dose compared to the vehicle control (7/57 and 22/60 in the vehicle control and high dose group, respectively). However, the incidence of these tumors in the female mice at the high dose was similar to that in the untreated controls (22/57). The reason for this large difference between the vehicle and untreated controls is not known. The vehicle did not appear to cause a general decrease in other tumor types.

You should provide an explanation for the large difference in the incidence of lymphomas between vehicle and untreated female controls. Furthermore, full histopathology examination of the low dose and medium dose female groups should be performed. The final evaluation of the lymphomas will be made after the additional data are received.

In addition, we recommend that slides from all groups in the rat study and the female groups in the mouse study, including the slides from previously fully evaluated groups, be examined simultaneously by one study pathologist. Peer review should also be conducted for all of these groups.

Office of New Drug Quality Assessment

1. The acceptable limits for impurities should not be based on strength. Please reduce the acceptance criteria for both strengths for total degradation product and total degradation products to the levels that are more consistent with your data. b(4)

2. Please revise the acceptance limit for each unspecified individual impurity for both strengths to no more than based on maximum daily dose of 20 mg/day.

If you have any questions, contact Keith Kiedrow, PharmD, Regulatory Project Manager, at (301) 796-1924.

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
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,641 serial #294, #303
IND 70,329 serial #103

Organon USA Inc.
Attention: Tracie Carey, PhD, Regulatory Affairs Manager
56 Livingston Ave.
Roseland, NJ 07068

Dear Dr. Carie:

Please refer to the meeting between representatives of your firm and FDA on July 18, 2006. The purpose of this meeting was to discuss efficacy and safety data, and statistical issues with regard to asenapine, which is intended to be indicated for schizophrenia and acute mania associated with bipolar disorder.

The official minutes of the 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 Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

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
IND 51,641 serial #294, #303; IND 70,329 serial #103; asenapine
Organon USA Inc.
Type B, pre-NDA meeting
February 22, 2007

Participants –
FDA

Robert Temple, MD	Office of Drug Evaluation I Director
Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Division Director
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Reviewer
Peiling Yang, PhD	Statistics Team Leader
Raman Baweja, PhD	Biopharmaceutics Team Leader
Andre Jackson, PhD	Biopharmaceutics Reviewer
Doris Bates, PhD	Regulatory Project Manager
Keith Kiedrow, PharmD	Regulatory Project Manager

Attendees Representing the Sponsor

Howard Berkeley	Director Regulatory Affairs
June Bray	Vice President, Regulatory Affairs
Andre Broekmans	Senior Vice President Global Regulatory Affairs and Quality
Tracie Carey	Senior Manager, Regulatory Affairs
Rik de Greef	Group Leader Modeling & Simulation, Clinical Pharmacology
Alex Kouassi	Group Director, Biometrics
David Nicholson	Executive Vice President, Research and Development
John Panagides	Senior Director, Clinical Development
Peter Schot	Vice President, Project Team Leader
Armin Szegedi	Executive Director Global Clinical Development Neuroscience
Jun Zhao	Principal Statistician

Background:

Asenapine is an antagonist at 5HT, DA, and α-adrenergic receptors that has been developed for schizophrenia and acute mania under INDs 51,641 and 70,329, respectively, at a total daily dose of 10-20 mg/day (given on bid basis). Asenapine is available as a fast-dissolving tablet for sublingual administration. The sponsors plan to submit an NDA for both indications, and the purpose of this meeting is to gain FDA concurrence on the adequacy of the program and also the plan for the analysis and presentation of data in the planned eCTD. Dose finding studies for schizophrenia suggested that the lower end of the sublingual dose range for effectiveness was 5 mg bid. Results from one 6-week phase 3 trial (041023) and one 6-week phase 2 trial (041004) will be submitted in support of an acute efficacy claim in schizophrenia. It is noteworthy that study 004 evaluated an asenapine dose of 5 mg bid, while study 023 evaluated fixed asenapine doses of 5 mg bid and 10 mg bid. Study 023 failed to distinguish asenapine 10 mg bid from placebo. Apparently 2 other phase 3 trials were for asenapine were either negative (041021 or

failed 041022). Data from two 3-week mania studies (A7501004 and A7501005) will be submitted in support of an acute efficacy claim in mania.

The sponsors expect to have phase 2/3 safety data from approximately 1950 patients exposed to asenapine in a dose range of 5 to 10 mg bid, including sufficient longer-term exposure to meet ICH criteria. The results of a thorough QT study will be submitted as part of the NDA. Narratives will be provided for deaths, SAEs, and adverse dropouts for laboratory abnormalities. A 4-month safety update will include line-listings of new deaths and SAEs, as well as narrative summaries.

The NDA will include results of a 10-day adolescent pk and tolerability trial. Safety and efficacy data in pediatric schizophrenia and mania patients has been deferred to phase 4.
The purpose of this meeting is to discuss with the agency the adequacy of the planned NDA for filing.

Questions:

1. Efficacy Program (Schizophrenia)
   A. In view of the aggregate of studies conducted for schizophrenia, does the Division concur that pivotal studies 041004 and 041023 can adequately support the review of an NDA for asenapine for the treatment of schizophrenia?

      Preliminary Comments: ***On face, the studies planned for submission should be sufficient to support the filing of an NDA for acute efficacy in schizophrenia. However, whether or not the submitted data will be sufficient for filing the application will be determined following the submission of the NDA. The failure of the 10 mg bid dose group to be distinguished from placebo is a finding that will be closely examined.***

      Discussion at Meeting: ***We reiterated that, on face, the data they plan to submit for an acute efficacy claim in schizophrenia should be sufficient for filing.***

   B. Studies 041004 and 041023 were both positive in that asenapine 5 mg BID demonstrated efficacy on the primary endpoint, change in total PANSS score from baseline to endpoint. While the 10 mg BID dose did not demonstrate efficacy on this primary endpoint in either study 041021 or study 041023, it was numerically better than placebo and it did demonstrate statistical superiority to placebo on several secondary efficacy endpoints including the PANSS positive subscale and PANSS Marder positive factor. Based on the efficacy and PK-PD data provided, does the Division agree that there is adequate data to support a 10 mg BID dose for the treatment of schizophrenia? If not, what additional data would the Division require to support approval of a 10 mg BID dose for the treatment of schizophrenia?

      Preliminary Comments: ***On face, there are not sufficient data to support a 10 mg bid dose for the treatment of schizophrenia. You would need to provide robust data from at least one adequate and well-controlled trial supporting the efficacy of the 10 mg bid dose in schizophrenia. Even with such a finding, we would carefully evaluate the aggregate evidence pertinent to this dose before reaching a final judgment on this matter.***

Discussion at Meeting: ***The sponsor asked if the planned data would be sufficient for filing a claim for a 5 mg bid dose for acute efficacy in schizophrenia, and we indicated that, on face, it should be sufficient.***

2. Efficacy Program (Bipolar I disorder)
   A. The two pivotal 3-week acute studies (A7501004 & A7501005) were positive; 9-week extension of these two studies confirmed maintenance of the acute effect. Because our NDA submission has been delayed, we would like to re-confirm with the Division that this package adequately supports the review of an NDA for asenapine for the treatment of acute manic or mixed episodes associated with bipolar 1 disorder.

      Preliminary Comments: ***On face, the studies planned for submission should be sufficient to support the filing of an NDA for acute efficacy in acute manic and mixed episodes associated with bipolar disorder. However, whether or not the submitted data will be sufficient for filing the application will be determined following the submission of the NDA.***

      Discussion at Meeting: ***No further discussion.***

3. Safety Program (Schizophrenia & Bipolar I disorder)
   A. Does the Division concur that appropriate and adequate safety data have been collected to support the review of an NDA for asenapine?

      Preliminary Comments: ***On face, the safety data described should be sufficient for the filing of an NDA. However, whether or not the submitted data will be sufficient for filing the application will be determined following the submission of the NDA.***

      Discussion at Meeting: ***No further discussion.***

4. Suitability for Filing
   A. Based on the information presented in the Pre-NDA briefing package, is the proposed submission for asenapine for treatment of schizophrenia and for treatment of acute manic or mixed episodes associated with bipolar 1 disorder adequate for review?

      Preliminary Comments: ***On face, the clinical data described should be sufficient for the filing of an NDA for the treatment of schizophrenia and for the treatment of acute manic or mixed episodes associated with bipolar 1 disorder. However, whether or not the submitted data will be sufficient for filing the application will be determined following the submission of the NDA.***

      Discussion at Meeting: ***No further discussion.***

Discussion of Statistical Comments from Protocol A7501012 (IND 51,641 / SN 203)

Description of Asenapine Protocol A7501012 (IND 51,641)

Protocol A7501012 is a long-term maintenance trial of asenapine in schizophrenia. This is a multicenter, randomized withdrawal, placebo-controlled, double-blind efficacy trial of asenapine

exploring delay in relapse after long-term (26 weeks), open-label stabilization treatment with asenapine.

The primary objective is to determine the efficacy of asenapine compared to placebo with respect to the time to relapse or impending relapse in schizophrenia subjects who have received open-label treatment with asenapine for at least 26 weeks. The primary endpoint is defined as time to relapse or impending relapse. A relapse or impending relapse will be declared if any of the following criteria are met:

1. PANSS score increased by at least 20% from baseline of the double-blind phase and CGI-S $\geq$ 4 in at least 2 days within a 1-week period. Subjects with a PANSS total score < 50 at baseline must have an increase from baseline of at least 10 points.
2. PANSS score $\geq$ 5 on 'hostility' or 'uncooperativeness' items and CGI-S $\geq$ 4 (for at least 2 days within a 1-week period).
3. PANSS score $\geq$ 5 on 'unusual thought content,' 'conceptual disorganization,' or 'hallucinatory behavior' items (for at least 2 days within a 1-week period).
4. CGI-I score $\geq$ 5 for at least 2 days during a one-week period.
5. In the investigator's opinion, the subject's symptoms of schizophrenia have deteriorated to such an extent or the risk of violence to self or others or suicide has increased so that one or more of the following measures is necessary or has occurred:
   a) Requires at least one additional dose of lorazepam $\geq$ 2 mg (or benzodiazepine equivalent) per day as compared to the highest open-label dose during the monotherapy phase.
   b) Addition of open-label antipsychotic medication or mood stabilizer
   c) Addition or increase in the dose of antidepressant medication
   d) Increase in the level of psychiatric care (e.g., supervised living, day hospital)
   e) Hospitalization or increase in the level of hospitalization
   f) An arrest or imprisonment for objectionable behavior
   g) Electroconvulsive therapy

Question from Sponsor:

1. Does the Division concur that the statistical design and analysis, as currently planned, is acceptable?

   Preliminary Comments: ***1) Please submit your Monte Carlo simulation (detailed algorithm, program, and results) regarding statistical validity of asymptotic p-value. 2) Please also submit your Monte Carlo simulation (detailed algorithm, program, and results) regarding statistical power performance of the selected alpha-spending function based on the scenarios of the postulated effect size, and the rationale or other prior data to support the projected effect.***

   Discussion at Meeting: ***The sponsor agreed to submit these to us for review.***

Additional Comments/Questions from the Office of Clinical Pharmacology and Biopharmaceutics

1. In trial 041022, neither the positive control olanzapine nor asenapine were distinguishable from placebo. Please explain your choice of a flexible dose design to determine exposure response in this study?

Discussion at Meeting: ***The sponsor explained that the intent of this trial was not to show dose response. The sponsor clarified that the goal of trial 041022 was not to specifically measure exposure response. Rather, this trial will be one of six short-term schizophrenia trials utilized for creation of the exposure response model. As part of the model validation, a trial-by-trial deletion will be performed in order to confirm the validity of pooling the six trials. This should indicate if there are specific differences between the fixed and flexible dose trials that would affect the exposure response model. OCP questioned whether the number of samples obtained per trial was comparable. The sponsor indicated that in each trial 4 to 6 samples were obtained per individual.***

2. In study 041021 the PANSS scores were -
   5 mg BID PANSS=-14.5
   10 mg BID PANSS=-13.4
   This indicates a flat dose response. Have you investigated the effectiveness of doses below 5 mg?

   Discussion at Meeting: ***The sponsor did not have an explanation but believed that the lack of response for the 10 mg was due to the higher than expected placebo response at this dose.***

3. For trial 041023, you used a mixed model repeated measures analysis (MMRM), compared an LOCF analysis in the other trials. Please explain the rationale for the different primary analyses in these different trials.

   Discussion at Meeting: ***The sponsor stated that the mixed model repeated measures analysis (MMRM) was not a primary method of analysis but a secondary one. They were encouraged to further investigate the possibility of using MMRM as a primary method of analysis.***

4. Is the dosage form referred to in study A7501015 USA as 'tablets used in Phase 3 clinical trials....', a conventional immediate release oral dosage form or does it refer to a sublingual tablet? Please clarify.

   Discussion at Meeting: ***The sponsor clarified that it was the sublingual tablet dosage form.***

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

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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/s/

Thomas Laughren
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,641 serial #254
IND 70,329 serial #64

Organon USA Inc.
Attention: Tracie Carey, PhD, Regulatory Affairs Manager
56 Livingston Ave.
Roseland, NJ 07068

Dear Dr. Carie:

Please refer to the meeting between representatives of your firm and FDA on July 18, 2006. The purpose of this meeting was to discuss the anticipated NDA submission for Asenapine; indicated for schizophrenia and acute mania associated with bipolar disorder.

The official minutes of the 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 Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

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
IND 51,641 serial #254; IND 70,329 serial #64; asenapine
Organon USA Inc.
Type B, pre-NDA meeting
July 18, 2006

Participants –
FDA

Thomas Laughren, MD	Division of Psychiatry Products Director
Ni Aye Khin, MD	Medical Team Leader
Robert Levin, MD	Medical Reviewer
Jing Zhang, MD	Medical Reviewer
Peiling Yang, PhD	Statistics Team Leader
Andre Jackson, PhD	Biopharmaceutics Reviewer
Keith Kiedrow, PharmD	Regulatory Project Manager

Attendees Representing the Sponsor
Organon USA Inc.

Miriam Annett	Biometrics
Howard Berkeley	Regulatory Affairs
June Bray	Regulatory Affairs
Tracie Carey	Regulatory Affairs
Marlou van Iersel	Drug Metabolism and Kinetics
John Panagides	Clinical Development
Gerald Quirk	Clinical Documentation
Peter Schot	Project Team Leader
Edwin Spaans	Clinical Pharmacology

Pfizer Inc.

Larry Alphs	Clinical Development
Susan Anway	Safety and Risk Management
Howard Bockbrader	Clinical Pharmacology
Anthony Brown	Regulatory Submissions
Cathryn Carter	Safety and Risk Management
Scott Lancaster	Biostatistics
Larry Paglia	Regulatory Affairs
Navid Samad	Clinical Development
Stephen Sasson	Project Team Leader
Lu Zhang	Regulatory Affairs
Peggy Zorn	Regulatory Submissions

Background:

Asenapine is an antagonist at 5HT, DA, and α-adrenergic receptors that has been developed for schizophrenia and acute mania under INDs 51,641 and 70,329, respectively, at a total daily dose of 10-20 mg/day (given on bid basis). Asenapine is available as a fast-dissolving tablet for sublingual administration. The sponsors plan to submit an NDA for both indications in December, 2006. The purpose of this meeting is to gain FDA concurrence on the adequacy of the program and also the plan for the analysis and presentation of data in the planned eCTD.

Dose finding studies for schizophrenia suggested that the lower end of the sublingual dose range for effectiveness was 5 mg bid. Results from two 6-week phase 3 trials (041021 and 041022) and one 6-week phase 2 trial in schizophrenia (041004) will be submitted in support of an acute efficacy claim in schizophrenia. Data from two 3-week mania studies (A7501004 and A7501005) will be submitted in support of an acute efficacy claim in mania.

The sponsors expect to have phase 2/3 safety data from approximately 1630 patients exposed to asenapine in a dose range of 5 to 10 mg bid, including sufficient longer-term exposure to meet ICH criteria. The results of a thorough QT study will be submitted as part of the NDA. Narratives will be provided for deaths, SAEs, and adverse dropouts for laboratory abnormalities. A 4-month safety update will include line-listings of new deaths and SAEs, as well as narrative summaries.

The NDA will include results of a 10-day adolescent pk and tolerability trial. Safety and efficacy data in pediatric schizophrenia and mania patients has been deferred to phase 4.

Questions:

1. Efficacy Program and Presentation of Efficacy Data
    a. Does the Division concur that appropriate and adequate efficacy studies have been conducted to support the review of an NDA for asenapine for the treatment of schizophrenia?

    Preliminary Comments: ***On face, the studies planned for submission should be sufficient to support the intended claims of acute efficacy for schizophrenia. However, whether or not the submitted data will support this claim is a matter for review.***

    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

    b. Does the Division concur that appropriate and adequate efficacy studies have been conducted to support the review of an NDA for asenapine for the treatment of manic or mixed episodes associated with bipolar 1 disorder?

    Preliminary Comments: ***On face, the studies planned for submission should be sufficient to support the intended claims of acute efficacy for manic or mixed episodes associated with bipolar 1 disorder. However, whether or not the submitted data will support this claim is a matter for review.***

    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

    c. Does the Division concur that the proposed presentation of efficacy data for asenapine is appropriate to support the review of an NDA?

    Preliminary Comments: ***Yes.***

    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

2. Safety Program and Presentation of Safety Data
    a. Does the Division concur that appropriate and adequate safety evaluations have been conducted to support the review of an NDA for asenapine?

    Preliminary Comments: ***On face, the safety assessments included in the schizophrenia and mania programs appear sufficient to support an NDA for these indications.***

    Discussion at Meeting: ***There was no further discussion of this question at the***

meeting.

b. Does the Division concur that the proposed presentation of safety data is appropriate to support the review of an NDA?

Preliminary Comment: ***On face, the proposed presentation of safety data appears to be generally adequate. However, we ask that you clarify for which patients CRFs will be provided. In addition, we ask that you clarify what your plans are for providing information on exposure to asenapine (dose and duration).***

Discussion at Meeting: ***The sponsor clarified that, for phase 3 studies, case report tabulations (what they referred to as patient profiles) would be provided in lieu of traditional CRFs. They noted that there were electronic CRFs for these studies, and these profiles would include all information found in a traditional CRF. The sponsor would also provide a sample copy of eCRF for each of the phase 3 studies. For phase 1 and 2 studies, they will provide scanned images of CRFs for deaths, SAEs, and adverse dropouts (for AEs or lab abnormalities, but not for events considered to be extension of underlying illness) in completed studies. For ongoing studies, they would submit CRFs for deaths and SAEs. They also clarified their plans for providing dose/duration data, and in addition, will provide PEY data. We indicated that this plan is acceptable.***

c. Does the Division concur with our proposal regarding the presentation of narratives?

Preliminary Comment: ***The proposal for presenting narratives is generally acceptable. However, we ask that you provide narrative for all adverse dropouts, and not limit them to adverse dropouts for laboratory abnormalities.***

Discussion at Meeting: ***The sponsor noted that they will provide narratives for for deaths, SAEs, and adverse dropouts (for AEs or lab abnormalities, but not for events considered to be extension of underlying illness). We indicated that this plan is acceptable.***

d. Following our July 22, 2005 Type C Meeting to discuss our dedicated QTc (A7501001) study, we communicated to the Division (IND 51,641, Serial No. 215, October 26, 2005) our plan to assure that all QTc $\geq$ 500 msec observed in the Phase 3 program are captured. Following that plan, we propose to include a list of subjects whose QTc interval was reported as $\geq$500 msec in the Summary of Clinical Safety section 2.7.4.4 titled "Vital Signs, Physical Findings, and Other Observations Related to Safety". Does the Division concur with our plan for monitoring and capturing QTc$\geq$500 msec from our Phase 3 program (as described in above mentioned communication and attached in Attachment 8, herein) and the presentation of this data?

Preliminary Comment: ***The plan is generally acceptable. However, we ask that you also provide proportions of patients who experience on treatment increases of QTc $\geq$ 60 msec.***

Discussion at Meeting: ***The sponsor clarified that they will provide proportions of patients who experience on treatment increases of QTc $\geq$ 60 msec only for study 25517, because interval data were not collected for other studies. We indicated that this plan is acceptable.***

3. Pediatric Plan
    a. At our End of Phase 2 meeting we discussed and agreed upon pediatric information to be collected and submitted with our NDA. The agreed information will be submitted with the NDA.

    Preliminary Comments: ***Yes.***

    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

4. Ongoing Efficacy Studies
    a. We plan to submit a complete application for review. There will likely be two additional efficacy studies (041023 and A7501008) for which clinical trial reports will become available early in the NDA review. We would be willing to submit these reports during the review period and/or with the 4-month safety update. Provided that these reports are submitted in the earlier part of the review, would the Division accept this additional information without extending the review time?

    Preliminary Comments: ***No. The division will not commit to the review of additional efficacy trials submitted during the initial review cycle. Data from such trials should be submitted as efficacy supplements, once the NDA is approved.***

    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

5. 4-Month Safety Update
    a. Does the Division concur with the following proposals for the content of the Safety Update for asenapine?

    i. For the safety update, we propose to submit additional safety data from studies that completed following our NDA submission cut-off date and data from ongoing open-label safety studies. For ongoing blinded studies, data will be limited to deaths and serious adverse events.

    ii. Regarding data from an elderly population, our Phase 3 program did not have an upper age limit and our intent was to capture sufficient data from an elderly (>65 years of age) population. We noted that there were fewer elderly patients being enrolled into our Phase 3 program than we had anticipated. In response to this, we initiated a dedicated study in the elderly (A7501021). This study is ongoing. Our NDA will include all available data from elderly patients from completed studies i.e., data from fewer than 100 elderly patients. We will provide further data from the ongoing study (A7501021) with the 4-month safety update. We would seek the Agency's concurrence that we would be permitted to submit additional safety data from this elderly population as it becomes available during the review. Our goal is to have data from at least 100 elderly subjects. Does the Division concur with our proposal?

    Preliminary Comments: ***The plan is generally acceptable. However, we need clarification that CRFs will be provided for all deaths and adverse dropouts occurring during this additional time period (and, again, do not limit the dropouts to these few labs). In addition, we ask that you clarify the age ranges that will be included in the special population data.***

    Discussion at Meeting: ***The sponsor clarified that CRFs will be provided in the safety update according to the same principles articulated for the initial submission (see 2b). The sponsor also noted that they are conducting a study in***

approximately 120 elderly patients, and that data from this study will be submitted. We noted that this plan was acceptable.

6. Format of Electronic Submission
   a. Does the Division concur with the following proposals regarding the format of an electronic submission for asenapine?

      i. We are proposing to submit the full archival copy of the asenapine CTD/NDA organized in electronic format as suggested in the guidances entitled, "Providing Regulatory Submission In Electronic Format----Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications", which was issued in April 2006 and "Providing Regulatory submission in Electronic Format----General Considerations", which was issued in October 2003.

      ii. For trials where electronic data capture was used, we propose to provide subject profiles (for Phase 3 trials) or PDF representations of the eCRFs (for Phase 1 trials) in accordance with the January 1999 Guidance for Industry titled "*Providing Regulatory Submissions in Electronic Format– NDAs*".

      Preliminary Comment: ***It will be necessary to provide the clinical reviewer with a capability to generate individual patient safety profiles from the various safety data domains. Alternatively, these may be generated in advance and made easily accessible. We will provide, at the meeting, a template document in which we will be requesting that you submit materials to support a question-based review by the biopharm group.***
      Discussion at Meeting: ***The sponsor had not planned on submitting in a form that we consider to be a "patient safety profile," i.e., a time-by-variable display of important safety findings. The sponsor agreed to try to develop this capability for the NDA and will provide us sample displays for our comment.***

7. Electronic Submission – Data Components
   a. Does the Division concur with our proposed data component for the electronic submission for asenapine?
      Preliminary Comment: ***For all randomized efficacy studies, please include in your submission (a) all raw as well as derived variables in .xpt format, (b) SAS programs that produced all efficacy results, (c) SAS programs by which the derived variables were produced from the raw variables, and (d) a list of serial numbers for all protocol/SAP submissions.***
      Discussion at Meeting: ***The sponsor agreed to provide this information except in (d), where the sponsor agreed to provide the serial number of the protocol and protocol amendments, but not SAP submissions. The sponsor clarified that the protocol/amendments included detailed statistical analysis plan and any changes in the primary analysis, so SAP was never submitted to the Division.***
      We agreed with this plan. We also agreed to a separate meeting with statistical reviewers to further discuss the specifics in (a) – (c).

   b. In addition to providing individual data sets for Phase 2 and 3 studies conducted with the sublingual formulation, with the exception of those studies which utilized the oral formulation, we will be providing individual data sets for all Phase 1 studies. Does the Division concur with our proposal?

Preliminary Comments: ***Yes.***
Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

8. IND Annual Reports
    a. Per our agreement with the Division, a single Annual Report is compiled for both INDs for asenapine (Org 5222) sublingual tablets. The reporting period for this report is October 1 to September 30 of the following year, making the report due annually on November 28. If the NDA will be submitted, as planned, within sixty days of this year's Annual Report due date i.e., within sixty days of November 28, 2006, we propose to provide a letter to each IND cross-referencing them to the soon to be filed NDA. If we note that the NDA is not to be submitted within sixty days of the Annual Report due date, we would submit a full Annual Report on or prior to November 28, 2006. Does the Division agree with this proposal?
    Preliminary Comments: ***No.***
    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

9. Suitability for Filing
    a. Based on the information presented in the Pre-NDA briefing package, is the proposed submission for asenapine adequate for review?
    Preliminary Comments: ***With the exceptions noted, the planned NDA appears to be adequate, on face. However, a filing decision for any submitted NDA can be made only after examining such a document. We also remind you that it will be necessary to submit product labeling in the newly proposed PLR format.***
    Discussion at Meeting: ***There was no further discussion of this question at the meeting.***

Additional Issue: There was discussion of the Question Based Review template provided by OCP to the sponsor. The sponsor agreed to comply with this request.

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

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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/s/

Thomas Laughren
7/26/2006 08:23:56 AM

Meeting Minutes

Meeting Date:	7/22/05
Location:	WOCII - Conference Room G
IND:	51,641
Drug:	Asenapine (ORG 5222) Sublingual Tablets
Sponsor:	Organon / Pfizer
Type of Meeting:	Guidance - Phase III Cardiac Monitoring Plans
Meeting Chair:	Thomas Laughren, M.D.
Meeting Recorder:	Steven D. Hardeman, R.Ph.

Participants:

FDA

Robert Temple, M.D., Director, ODEI
Tom Laughren, M.D., Acting Director, Division of Psychiatry Products (DPP)
Steve Hardeman, R.Ph., Acting Chief, Project Management Staff, DPP
Robert Levin, M.D., Clinical Reviewer, DPP
Barry Rosloff, Ph.D., Pharm/Tox Team Leader, DPP
Sonia Tabacova, Ph.D., Pharm/Tox Reviewer, DPP
Judy Racoosin, M.D., Safety Team Leader, Division of Neurology Products (DNP)
Alice Hughes, M.D., Safety Team Reviewer, DNP

SPONSOR

George Haig, Pharm.D.	Clinical Development, Pfizer
Marilyn Agin, Ph.D.	Biostatistics and Reporting, Pfizer
Edwin Spaans, Pharm.D.	Clinical Pharmacology, Organon
Larry Alphs, M.D. Ph.D.	Clinical Development, Pfizer
Sunny Chapel, Ph.D.	Clinical PK-PD, Pfizer
Erno Krajnc, M.Sc.	Preclinical Development, Organon
Stephen Saason, Ph.D.	Project Team Leader, Pfizer
Howard Berkeley, Ph.D.	Regulatory Organon
Tracie Carey, Pharm.D.	Regulatory Organon
Peter Machado, M.Phil.	Regulatory Pfizer
Mark Ammann, PharmD	Regulatory Pfizer

Meeting Objective: The purpose of this meeting was to discuss the QTc data available to date, to seek concurrence on the plans for Phase 3 ECG monitoring, and to discuss labeling implications with regard to QTc.

Background: Asenapine is available in a sublingual form (SL), due to poor oral availability. The sponsor plans to study it at doses of 5-10 mg bid (i.e., total daily doses of 10-20 mg).

- **Nonclinical Data** (*Note*: These data were not discussed at the 7-22-05 meeting):
  - **hERG assay:** The sponsor tested both asenapine and desmethyl asenapine; the IC20 for asenapine was 30-fold greater than the estimated efficacious free concentration; similar for metabolite. However, the IC50 was 0.3 micromolar (i.e., in a range where

we think there might be a concern, and further, we usually look at total, and not free). Thus, this finding is not particularly reassuring.

- Purkinje fiber assay: There is no effect at relevant concentrations. We agree this is negative, but also, we do not think much of this assay anymore, and it is not included in the ICH S7B guidance.

- Dog studies: The sponsor characterized this as a minimal effect; however, we disagree. Rather, we find a 10-30 msec effect (using Fridericia's and Van de Water's correction formulae) in the current study provided in the briefing package, and there were earlier studies that were also positive. Thus, we view the dog data as a positive signal.

- Clinical Data:

  - Early (Phase 1-2): These data were reviewed in the briefing package, but it was agreed they are not of much value, because of the doses and ECG collection and assessment methods. They generally suggested little effect, but are not reliable.

  - Thorough QTc Study: The sponsor had also conducted a thorough QTc study (Protocol A7501001) in order to better understand the potential for QTc prolongation with asenapine: RCT; DB; pbo and quetiapine controlled; 4 groups of n=35—38 each (actually had 4 asenapine dose groups based on titration to higher doses; 10 days for first comparison, 16 days for second); triplicate ECG measures at each time point; 7 time points at BL, 10 days, and 16 days; wide range of doses (5,10,15, and 20 mg bid for asenapine; 375 mg bid for quetiapine); manual reading, central lab; optimal correction factor (Fridericia). The dose effect analysis for this study suggested about a 5-10 msec effect for asenapine at approximate tmax (the largest time-matched mean increases in QTc vs. placebo were similar), and about the same as quetiapine. However, the results were not linear, i.e., for asenapine, the largest effect appeared to be at 10 mg bid and a smaller effect at 20 mg bid (but not as low as the 5 mg bid dose). An exposure response analysis suggested a more linear exposure response relationship, with a 2-5 msec effect for asenapine and a 7-8 msec effect for quetiapine (QTcF) at Cmax. No subjects had a > 60 msec increase from BL, and none had a QTcF > 500 msec. [Note: We generally agreed that the two drugs looked about the same, but also that they were both different from placebo.]

- Plan for ECG monitoring in Phase 3:

  - The sponsor plans very limited ECG monitoring and analysis in Phase 3 placebo-controlled studies, except for outlier analyses, because they feel they have adequately addressed QTc issues with Protocol A7501001, and because they are doing a large safety study (described below).

  - For most Phase 3 trials, they plan to obtain ECGs at reasonable intervals, however, they are not planning to analyze interval data. Rather, they intend to report on proportions of patients with QTc > 500 msec.

- The exception is for study ACTAMESA, a DB safety study: n=1200; asenapine vs olanzapine; 1 year; they will measure and report QTc intervals for this study.

- **Further metabolic work planned:**

  The sponsor plans a more complete exploration of asenapine metabolism. The current understanding is that asenapine is cleared by 1A2 and 3A4, but also multiple other pathways, such that blocking single pathways is not likely to affect clearance substantially. Further, there is nonlinear pK, with less than linear accumulation as the dose is increased. Studies to determine serum levels of asenapine in the presence of metabolic inhibitors are planned.

Questions:

1. Based on summarized data from the thorough QTc study (Protocol A7501001) and previous asenapine studies, does the agency agree with our Phase 3 cardiac monitoring plans, which include electrocardiography at specified visits in all studies, interval analysis in a large safety study, and evaluation of morphological changes and monitoring and reporting cardiac adverse events in all other studies?

   Agency Comment/Response:

   - The sponsor began with a brief presentation to summarize what they have done and what they plan to do (see background). They also noted that, even though there is a very modest QTc prolongation (similar to quetiapine), there are mitigating factors that would limit the risk of having increased exposure:

     - Swallowing the SL formulation would inactivate it,
     - Even keeping an excess dose in mouth would not be an effective way of increasing exposure because of limited amounts of saliva,
     - Exposures are nonlinear, i.e., get less exposure as increase the dose,
     - There are multiple metabolic pathways that reduce risk of inhibition of any one pathway being a problem, and
     - The drug is not well tolerated as the dose is pushed, thus, limiting the risk of increased dosing

   - We voiced a concern that they would likely not be obtaining ECGs at peak concentrations in the phase 3 studies. They acknowledged that they will collect relatively random ECGs with regard to Tmax, will have only machine readings, and do not plan QTc interval analysis for these studies. As noted, they will focus on picking up outliers (>500 msec), and for those ECGs >500 msec, they will do manual reads. Further, they estimated that a fair number of these will be at peak, but of course, there is no way of knowing this with any precision.

- They further elaborated that the primary source of new ECG information for ph 3 will be from the planned large safety study (ACTAMESA). This will involve 1200 pts, including about 900 getting asenapine (3:1 randomization). They will collect periodic ECGs and plasma samples at same time; ECGs will all be read centrally; will record time of last dose and time of ECG/sampling; expect to obtain about 1400 total samples, of which they expect about 1/3 to be at Cmax.

- We gave a qualified yes to their plan, but encouraged them to do a sampling of more than just ECGs with QTc>500 msec for manual reads in the phase 3 trials, to ensure that they are not missing ECGs with QTc>500 because of misreads by the ECG machine (either looking at all those over some threshold, e.g., > 480, or simply a random sample). They will make a proposal and send it to us.

2. Could the agency provide comment on any QTc labeling implications for asenapine based on the thorough QTc study and assuming there are no unusual or significant findings in Phase 3 relative to prolonged QTc?

   Agency Comment/Response:

   We could not be definitive, however, we did acknowledge that, based on what they have presented thus far, asenapine appears to be no worse than quetiapine, which of course does not have the "ziprasidone labeling." However, as always, we indicated that this would be a matter of review, and we cannot make labeling commitments at this early timepoint, not having reviewed the complete data.

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/s/

Thomas Laugharn
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