

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-743

Administrative/Correspondence

PATENT CERTIFICATION

Explanatory Note To The Patent Certification:

OSI Pharmaceuticals Inc. and Pfizer Inc. are co-owners of U.S. Pat. No. 5,747,498 titled "Alkynyl and Azido-Substituted 4-Anilinoquinazolines". At the time of this NDA Filing, Pfizer Inc. is preparing assignment documents to evidence each parties' 50% ownership in the patent in accordance with the terms of a contract between Pfizer and OSI Pharmaceuticals.

**APPEARS THIS WAY
ON ORIGINAL**

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

021-743

NAME OF APPLICANT / NDA HOLDER

OSI Pharmaceuticals Inc.

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

TRADE NAME (OR PROPOSED TRADE NAME)

Tarceva™

ACTIVE INGREDIENT(S)

Erlotinib hydrochloride

STRENGTH(S)

25 mg, 100 mg and 150 mg

DOSAGE FORM

Film coated tablet

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

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

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

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

a. United States Patent Number

5,747,498

b. Issue Date of Patent

5/5/1998

c. Expiration Date of Patent

3/30/2015

d. Name of Patent Owner

Pfizer Inc.

Address (of Patent Owner)

235 East 42 Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

(212) 573-7851

Telephone Number

(212) 733-2323

E-Mail Address (if available)

n/a

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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

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

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2	Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3	If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

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

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent Claim Number (as listed in the patent) 12, 13, 14, 22, 23, 27, 28 and 29	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
4.2a	If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Use: (Submit indication or method of use information as identified specifically in the approved labeling.) 2 nd /3 rd -line Non-Small Cell Lung Cancer (NSCLC)			

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

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

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

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed
January 20, 2004



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

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Shu M. Lee

Address
58 South Service Road, Suite 110

City/State
Melville, NY

ZIP Code
11747

Telephone Number
(631) 962-2056

FAX Number (if available)
(631) 752-3880

E-Mail Address (if available)
slee@osip.com

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

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

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

PATENT INFORMATION

The following patent information is presented:

- 1) International Patent: WO 96-30347
- 2) US Patent Number: 5,747,498

Note: There is a discrepancy between the erlotinib hydrochloride \square used in the patent information and that presented in Modules 2 and 3 of this NDA. The latter is based on the convention of adopting \square In the patent this is named as \square

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 21-743 SUPPL # _____

Trade Name Tarceva Generic Name erlotinib hydrochloride

Applicant Name OSI Pharmaceuticals Inc. HFD-150__

Approval Date If Known _____

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 question 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

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

YES / / NO / /

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

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

d) Did the applicant request exclusivity?

YES / / NO / /

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

_____ 5 years _____

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

YES /___/ NO /_✓_/

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

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

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

YES /___/ NO /_✓_/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /_✓_/

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

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____

NDA# _____

NDA# _____

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

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /___/ Explain _____ ! NO /___/ Explain _____
! !

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ 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: _____

Signature _____ Date _____
Title:
Paul Zimmerman, Project Manager

Signature of Office/ _____ Date _____
Division Director
Richard Pazdur, M.D.

Form OGD-011347 Revised 05/10/2004

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

/s/

Richard Pazdur
10/21/04 09:14:10 AM

30 pages redacted from this section of
the approval package consisted of draft labeling

DEBARMENT CERTIFICATION

Re: Tarceva NDA#021-743

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

Sincerely,



Christine Boisclair

Senior Director, Global Regulatory Affairs

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: NDA 21-743 Supplement Type (e.g. SE5): NA Supplement Number: NA

Stamp Date: July 30, 2004 Action Date:

HFD 150 Trade and generic names/dosage form: Tarceva (erlotinib hydrochloride) tablets, 25 mg, 100 mg and 150 mg

Applicant: OSI Pharmaceuticals Inc. Therapeutic Class: Kinase inhibitor

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: 2nd / 3rd - line Non-Small Cell Lung Cancer (NSCLC).

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

NDA 21-743

Page 2

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Paul Zimmerman (HFD-150)

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-743
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

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

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

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.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA [REDACTED]
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Paul Zimmerman
9/24/04 01:27:44 PM

CACY SUPPLEMENT ACTION PACKAGE

NDA 21-743	Efficacy Supplement Type SE-	Supplement Number	<div style="text-align: right; font-size: 2em; font-weight: bold;">/S/</div> <div style="text-align: right; font-size: 1.2em;">12/07/04</div> <div style="text-align: right; font-size: 1.2em;">52407</div>
Drug: Tarceva (erlotinib hydrochloride) tablets		Applicant: OSI Pharmaceuticals Inc.	
RPM: Paul Zimmerman, R.Ph.		HFD- 150	Phone # 301-594-5775
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:			
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority	
• Chem class (NDAs only)		5010500 1	
• Other (e.g., orphan, OTC)			
❖ User Fee Goal Dates		January 30, 2005	
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2	
❖ User Fee Information			
• User Fee		<input checked="" type="checkbox"/> Paid	
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)			
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
• Exception for review (Center Director's memo)			
• OC clearance for approval			
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		<input type="checkbox"/> Verified	
❖ Patent			
• Information: Verify that form FDA-3542a was submitted.		<input checked="" type="checkbox"/> Verified	
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified	

❖ Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
❖ Actions	
• Proposed action	(✓) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(✓) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(✓) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	12-20-00, 11-13-03
• Pre-NDA meeting (indicate date)	12-10-03, 7-11-03 (CMC)
• Pre-Approval Safety Conference (indicate date; approvals only)	9-22-04
• Other	

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	10-21-04 Med TL
❖ Clinical review(s) (indicate date for each review)	10-8-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NA
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet (NME approvals only)	NA
❖ Statistical review(s) (indicate date for each review)	10-11-04
❖ Biopharmaceutical review(s) (indicate date for each review)	10-1-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	✓
• Bioequivalence studies	
❖ CMC review(s) (indicate date for each review)	
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	9-23-04
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NA
❖ Facilities inspection (provide EER report)	Date completed: (✓) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	10-7-04
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	NA

Division Director's Memorandum

Date: November 18, 2004
NDA: 21-743
Applicant: OSI Pharmaceuticals, Inc.
Proprietary Name: Tarceva™ (erlotinib) Tablets

Regulatory History

July 15, 1997: original IND 53,728 was submitted.

August 29, 2002: Product received Fast Track designation for second-line or third-line treatment of patients with incurable stage IIIb/IV non-small cell lung cancer (NSCLC) who have failed standard therapy for advanced or metastatic disease.

January 20, 2004: OSI submitted first piece of rolling NDA (CMC and non-clinical).

June 24, 2004: NDA accepted for Continuous Marketing Application (CMA) Pilot 1 program.

July 30, 2004: Division received the last piece of the rolling NDA (clinical).

January 30, 2005: PDUFA goal date for this priority review.

Indication

For treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Available Therapies

Docetaxel (Taxotere® for Injection Concentrate, Aventis), gefitinib tablets (Iressa®, AstraZeneca), and pemetrexed for injection (Alimta®, Eli Lilly) are all approved for this patient population.

Clinical (see Drs. Cohen and Johnson's reviews)

Study Description: The application is supported by a phase 3 double-blind, placebo-controlled, multi-center international study (BR.21) in patients with stage IIIB or IV NSCLC who had failed one or two prior chemotherapy regimens for locally advanced or metastatic disease. A total of 731 patients, from 86 study centers in 17 countries, were randomized in a 2:1 ratio between 150 mg oral Tarceva daily (N=488) or placebo (N=243). Patients were stratified at enrollment by center, number of prior regimens, prior platinum therapy, best response to prior therapy, and Eastern Cooperative Oncology Group performance status (ECOG PS). Treatment continued until disease progression or unacceptable toxicity. Crossover was not permitted.

Efficacy Endpoints: The primary endpoint was overall survival. Secondary endpoints were tumor response, tumor response duration, progression-free survival (PFS), quality of life (assessed by patient reported symptoms on the EORTC QLQ-C30 and QLQ LC-13 questionnaires) and to correlate the expression of epidermal growth factor receptor (EGFR) levels at diagnosis with outcomes and response to treatment.

Patient Characteristics Pretreatment: Patient pre-treatment characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male and approximately one-third had a baseline ECOG PS of 2, and 9% had a baseline ECOG PS of 3. Fifty percent of the patients had received only one prior regimen of chemotherapy.

Efficacy Results: Efficacy results are summarized in the following table.

	Tarceva	Placebo	HR ³	p-value
Survival	Med 6.7 mo.	Med 4.7 mo.	0.73	<0.001 ¹
1-year Survival	31.2 %	21.5%		
PFS	Med 9.9 wks.	Med 7.9 wks.	0.59	<0.001 ¹
Tumor Resp.	8.9%	0.9%		<0.001 ²
Response Duration	Med 34.3 wks.	Med 15.9 wks.		

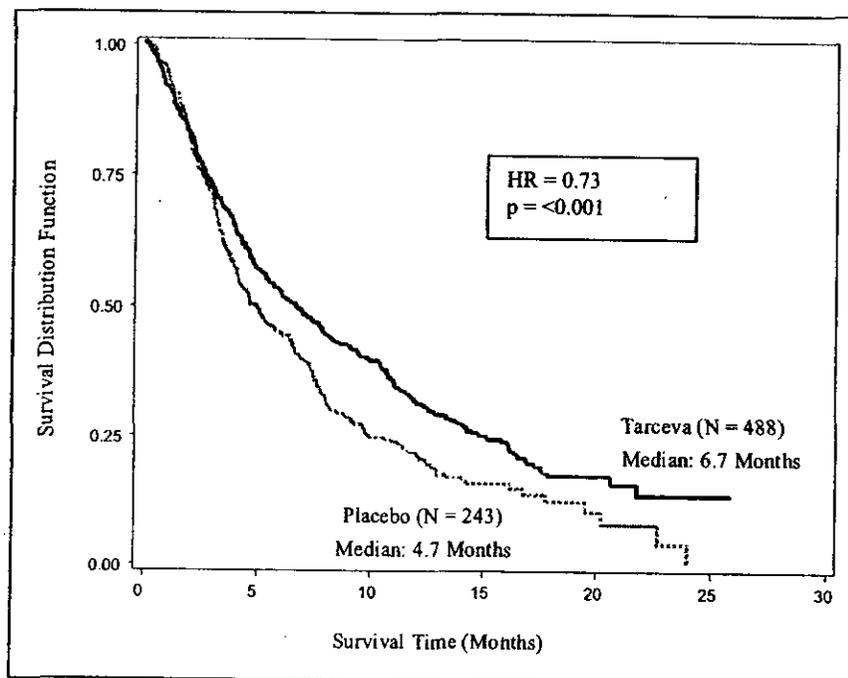
¹ Two-sided Log-Rank Test, stratified by ECOG PS, number of prior regimens, prior platinum and response to prior chemotherapy.

² Two-sided Fishers Exact Test.

³ Cox regression model with the following covariates: ECOG PS, number of prior regimens, prior platinum and response to prior chemotherapy.

Survival was evaluated in the intent-to-treat (ITT) population. The following figure depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were adjusted for the stratification factors used for randomization (ECOG PS, best response to prior therapy, number of prior chemotherapy regimens, and exposure to prior platinum).

Kaplan-Meier Curve for Overall Survival of Patients by Treatment Group



Relation of Results to EGFR Status: EGFR expression status was determined by ζ $\bar{1}$ using the DAKO EGFR pharmDx™ kit, without knowledge of treatment assignment. Scoring was performed according to the recommendations in the manufacturer's instructions. A positive EGFR expression was defined as having at least 10% of cells staining for EGFR.

EGFR status was determined in 238 (33%) of patients. The table below shows the effect of Tarceva in patients with positive and negative EGFR. Survival was prolonged in the Tarceva-treated patients in the EGFR positive subgroup (HR=0.65), but there was no apparent Tarceva survival effect in the EGFR negative subgroup (HR=1.01). The confidence interval for the EGFR negative subgroup is wide and does not rule out a possible survival effect in the EGFR negative subgroup. The Tarceva response rates in the EGFR positive and negative groups were 12% and 3%, respectively.

EGFR status was not a randomization stratification factor. EGFR status was ascertained where baseline patient sample was available. The effect on survival in the subgroup with known EGFR status (N=238, HR = 0.77, 95% CI: 0.58, 1.04) was very similar to the overall population. Multivariate analyses adjusting for all prognostic factors that were unbalanced between the receptor positive and negative subgroups gave similar results to the univariate analyses shown in the following table.

Treatment Results by EGFR Status

	Tarceva		Placebo		HR	p-value
Survival EGFR +	N=78	Med 10.7 mo.	N=49	Med 3.8 mo.	0.65	0.033 ¹
Survival EGFR -	N=74	Med 5.4 mo.	N=37	Med 7.5 mo.	1.01	0.985 ¹
Survival EGFR Unknown	N=336	Med 6.1 mo.	N=157	Med 5.1 mo.	0.76	0.008 ¹
PFS EGFR +	N=64	Med 16.1 mo.	N=41	Med 7.9 mo.	0.49	0.0003 ¹
PFS EGFR -	N=74	Med 8.1 mo.	N=37	Med 8.1 mo.	0.91	0.66 ¹
RR EGFR +	N=69	12%				0.077 ²
RR EGFR -	N=62	3%				

¹ Two-sided unstratified Log-Rank Test. P-values for these exploratory analyses were unadjusted for multiple comparisons.

² Two-sided Fisher's Exact test.

	N	HR (Tarceva/placebo)	p value
Overall	731	0.73 (0.61-0.86)	0.001
EGFR+	127	0.65 (0.43-0.97)	
EGFR-	111	1.01 (0.65-1.57)	
Smokers	545	0.86 (0.71-1.05)	0.14
EGFR+	76	0.87 (0.5-1.4)	0.56
EGFR-	85	1.02 (0.63-1.6)	0.93
Non-Smokers	146	0.42 (0.28-0.65)	0.0001
EGFR+	30	0.27 (0.11-0.67)	0.0025
EGFR-	24	1.4 (0.45-6.3)	0.14

Quality of Life (QoL): QoL findings were reviewed by and discussed with Laurie Burke (Senior Regulatory Officer, Study Endpoints and Label Development Team, Office of New Drugs). Reasons for excluding QoL claims in the labeling include:

1. The measures used in this NDA for evaluating cough, dyspnea and pain are not consistent with the Agency's previous experience and advice for patient-reported outcomes.
2. The EORTC QoL instruments are developed and validated to be used in totality. There is no development and validation of the instruments to support conclusions about individual concepts (e.g., pain, dyspnea and cough) based on the use of single items from the instruments. The validity of the instrument subscales to measure these specific concepts is questionable.
3. The physical functional domain and global QoL scale analysis suggest that the Tarceva-treated group was worse than the placebo group (HR of 1.5 and 1.2, respectively). These are not consistent with the reported results for dyspnea and pain.
4. Although dyspnea as measured in QLQ-C30 single question was significant per applicant analysis, the dyspnea domain (3 questions) as measured in QLQ-C13 was not significant (p-value = 0.3452).

Safety: Dose reduction to 100 mg occurred in 15% of erlotinib patients and further reduction to 50 mg in 4% of patients, compared with 1% and < 1% in placebo patients. Discontinuation due to protocol toxicity occurred in 5% in the erlotinib group and 2% in the placebo group.

The overall incidence per patient of AEs regardless of causality was similar between the treatment arms (99% erlotinib vs. 96% placebo). Severe events (NCI CTC Grade 3 or 4) occurred in 62% and 58% of patients in the erlotinib and placebo group, respectively. AEs considered treatment-related occurred in 85% of patients in the erlotinib group and 51% in the placebo group.

Rash (75% vs. 17%) and diarrhea (54% vs. 18%) in the erlotinib and placebo group, respectively, were the most common AEs regardless of causality. Most were Grade 1 and 2 in severity and manageable without intervention. Severe rash occurred in 9% and severe diarrhea occurred in 6% of erlotinib-treated patients and each resulted in study discontinuation in 1%. Dose reductions were required for 10% of patients with rash and 4% of patients with diarrhea.

The incidence of ILS was 0.8% in both the erlotinib and placebo groups.

There was no apparent hematological toxicity associated with erlotinib therapy. The possibility of an interaction between erlotinib and warfarin was monitored in patients on such anticoagulants. Patients on warfarin frequently showed INR values outside therapeutical range. INR shifts from baseline to values that are associated with increased risk for bleeding complication (ie, INR \geq 4) were seen in 26% vs. 21% of warfarin-treated patients in the erlotinib and placebo groups, respectively. Whether patients received warfarin or not, reports of clinically recognized bleeding occurred in 24% of erlotinib-treated patients compared to 17% with placebo. Most were inconsequential Grade 1 episodes of hemoptysis and epistaxis. Severe bleeding cases include 8 erlotinib patients (2%) with serious gastrointestinal

hemorrhage and no placebo patients. Concurrent warfarin administration was present in 2 of these 8 patients and other medications (ie, NSAID) contributed as well.

Eye disorders were more frequent in the erlotinib arm (27% vs. 9%). Most were conjunctivitis and keratoconjunctivitis sicca (dry eyes) experienced by 12% each of the erlotinib patients compared with 2% and 3%, respectively, in the placebo patients. The worst severity was Grade 3 occurring in < 1% in each arm. Keratitis was reported in 3% of erlotinib patients compared with 1% of placebo patients. All except one case was less than Grade 2, and none were reported as medically significant or resulting in discontinuation of protocol therapy. Concomitant ophthalmological preparations such as artificial tears were administered to 11% and 1% of erlotinib and placebo patients, respectively.

Phase 4 commitments: OSI agreed to assess the relation of EGFR status to efficacy in future studies.

1. A double-blind randomized phase 3 study to evaluate the efficacy of Tarceva or placebo following 4 cycles of platinum-based chemotherapy in patients with histologically documented or advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (stage IV) NSCLC who have not experienced disease progression or unacceptable toxicity during chemotherapy. The primary endpoint will be PFS. The study will also be sized to detect a realistic difference in survival. For eligibility all patients must have EGFR expression status determined by Dako Kit prior to randomization. Analyses of results will include assessment of treatment effect in the subgroup with EGFR expression status positive and the subgroup with EGFR expression status negative.
 - **Protocol submission date:** March 2005
 - **Study Start:** June 2005
 - **Final Report Submission:** December 2008

2. A double-blind randomized phase 3 study to evaluate the efficacy of Tarceva or chemotherapy (Alimta or Taxotere) following 4 cycles of platinum-based chemotherapy in patients with histologically documented or advanced or recurrent (stage IIIB and not amenable for combined modality treatment) or metastatic (stage IV) NSCLC who have experienced disease progression or unacceptable toxicity during chemotherapy. The primary endpoint will be overall survival (subject to FDA agreement during SPA review). For eligibility all patients must have EGFR expression status determined by Dako Kit prior to randomization. Analyses of results will include assessment of treatment effect in the subgroup with EGFR expression status positive and the subgroup with EGFR expression status negative.
 - **Protocol submission date:** March 2005
 - **Study Start:** June 2005
 - **Final Report Submission:** December 2008

Biostatistical (see Drs. Chen & Sridhara's review)

There was a statistically significant difference between the two treatment arms with respect to overall survival in the ITT population (log-rank test, p-value = 0.002, stratified log-rank test, p-

value = < 0.001), with a median survival of 6.7 months and 4.7 months for Tarceva and placebo, respectively (HR adjusted for stratification factors = 0.73, 95% CI: 0.61, 0.86).

Because the mechanism of action of erlotinib is through direct inhibition of the EGFR tyrosine kinase, the relationship between EGFR status and treatment effect was further examined. Among the patients whose EGFR status was evaluated (238/731 patients), there were 127 patients who were EGFR positive and 111 patients who were EGFR negative, with a positive EGFR expression defined as having at least 10% of cells staining for EGFR. The results of the exploratory analyses in the subgroups suggest a significant survival benefit in the EGFR positive patients with a median survival of 10.7 months vs. 3.8 months, for Tarceva and placebo, respectively (log-rank p-value = 0.0333, HR = 0.65, 95% C.I.: 0.43, 0.97). An erlotinib survival benefit in the EGFR negative population is not observed with this limited data and exploratory analysis, although benefit in this subgroup can not be ruled out (median survival: 5.2 months vs. 7.5 months for Tarceva and placebo, respectively, log-rank p-value = 0.9581, HR = 1.01, 95% C.I.: 0.65, 1.57).

The secondary endpoints of the study included PFS and objective response rate. The results with respect to PFS were similar to overall survival in the overall population (median PFS: 9.9 weeks vs. 7.9 weeks, in Tarceva and placebo, respectively; log-rank p-value < 0.001 , HR = 0.59, 95% CI: 0.50, 0.70) and in the subgroups of patients who were EGFR positive (median PFS: 16.1 weeks vs. 7.9 weeks, in Tarceva and placebo, respectively, log-rank p-value = 0.0003, HR = 0.49, 95% CI: 0.33, 0.72) or EGFR negative (median PFS: 8.1 weeks in both Tarceva and placebo, log-rank p-value = 0.6570, HR = 0.91, 95% CI: 0.59, 1.39).

The objective response rate in the Tarceva group was 8.9% (95% CI: 6.4 to 12.0%), and the median duration of response was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. Two responses (0.9%, 95% CI: 0.1 to 3.4) were reported in the placebo group. A higher response rate was observed in females (22/173 or 12.7%, 95% CI: 8.1, 18.6%) compared to males (17/315 or 5.4%, 95% CI: 3.2, 8.5%). Similarly, a higher response rate was observed in oriental patients (10/63 or 15.9%, 95% CI: 7.9, 27.3%) compared to white patients (25/379 or 6.6%, 95% CI: 4.3, 9.6%). Response rate among smokers was 12/358 (3.4%, 95% CI: 1.7, 5.8%) and among non-smokers response rate was 24/104 (23.1%, 95% CI: 15.4, 32.4%). Response rate in EGFR positive patients was 8/69 (11.6%, 95% CI: 5.1, 21.6%) and response rate in EGFR negative patients was 2/62 (3.2%, 0.4, 11.2%).

Chemistry, Manufacturing and Controls (see Drs. Hsieh & Chidambaram's reviews)

Tarceva is formulated as immediate release tablets, and are available in three strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg or 164 mg) equivalent to 25 mg, 100 mg or 150 mg of erlotinib and inactive ingredients lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The 100mg and 150 mg tablets have a common composition where the substance: — In order to ensure a suitable size for the 25 mg tablet, additional lactose monohydrate and microcrystalline cellulose are used as tablet — resulting in a drug substance: — All tablets are round, biconvex face, straight sides, white, film-coated and are distinguished by size and color of the imprint, (— , orange for 25 mg; — , gray for 100 mg; and — , maroon for 150 mg), of the printed tablet strength identifiers. Tarceva is supplied in bottles of 30 tablets. It is stored at

25°C (77°F); excursion permitted to 15°-30°C (59°-86°F). The primary and supportive stability data supports the proposed expiry-dating period of 24 months.

Erlotinib hydrochloride is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. It is a white to pale yellow/pale beige solid. J

Its molecular formula is $C_{22}H_{23}N_3O_4 \cdot HCl$ and the molecular weight is 429.90. Erlotinib hydrochloride has a pKa of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water. Aqueous solubility is pH dependent with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2. Adequate controls are provided to assure its quality. The primary and supportive stability data supports the proposed retest period of 12 months.

Nonclinical (see Drs. Benson & Leighton's reviews)

Erlotinib is a small molecule EGFR inhibitor for the treatment of patients with NSCLC. The applicant conducted a complete battery of toxicology studies, including safety pharmacology, genetic toxicology (ICH battery), general toxicology studies in rats and dogs, and reproductive toxicology (Segments I-III). Based on erlotinib's mechanism of action and findings (abortifacient, etc.) for similar products previously reviewed and approved by the Division, the team recommended Pregnancy Category "D" for this product. Carcinogenicity studies have not been conducted and are not required for this indication, as per CDER practice and ICH guidance.

The pharmacology studies conducted by the applicant are limited in breadth and scope. Specificity of erlotinib as an EGFR inhibitor could not be ascertained due to the limited evaluation for inhibition of related tyrosine kinases. These and other pharmacology studies would have been informative to the nonclinical safety assessment, but they generally do not impact on the approvable decision. No additional pharmacology studies by the sponsor are required as a condition of approval.

An impurity in the manufacturing process J was present in approximately half the batches used in toxicology testing, including the long-term studies. This impurity was not present in any batches used for genetic toxicity testing of erlotinib, but was separately tested in the Ames mutagenesis assay. If the applicant pursues approval of indications for which carcinogenesis studies are necessary, then they should fully assess the genetic toxicity and carcinogenic potential of this impurity, if warranted by ICH guidance on impurities in new drug substances (Q3A).

Clinical Pharmacology and Biopharmaceutics (see Drs. Williams & Booth's reviews)

Erlotinib's putative mechanism of action is inhibition of the Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase. A 150 mg daily dose was determined as the MTD in cancer patients. The average trough concentration on Day 24 - 29 was 918 ng/mL, which is well above the concentration required for erlotinib activity in various nonclinical assays, even when erlotinib's *in vitro* protein binding value of 95% is considered. Based on these considerations, it was concluded that the 150 mg/day dose would be sufficient to provide a high anti-neoplastic effect with a tolerable and manageable safety profile. In a population pharmacokinetic analysis performed using data from 708 patients (62% female)

in 6 studies clearance was 4.29 L/h for females and 4.70 L/h for male patients. The majority of volunteers and patients included in the clinical program were Caucasian, with only small numbers of other races participating in individual studies. Race was not found to be a significant variable, but too few non-Caucasian patients were enrolled to make a conclusive determination.

Erlotinib is metabolized in human liver primarily by the cytochrome P450 isoform CYP3A4, but also by CYP1A2 and, to a minor extent, by CYP2C8. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumor tissue may contribute to the metabolic clearance of erlotinib. Studies with human liver microsomes identified a strong inhibition of the formation of erlotinib metabolites by ketoconazole, a potent CYP3A4 inhibitor. The predominant metabolism via CYP3A4 also raised the question of the role of enzyme inducing agents such as rifampicin. Clinical studies to address interaction with ketoconazole and rifampicin have been conducted. No hepatic impairment studies have been conducted.

In vitro studies examining erlotinib's activity as a CYP inhibitor revealed some potential for erlotinib to inhibit CYP 2C8 and 2C9. The applicant has an ongoing clinical study to determine the effect of erlotinib on the pharmacokinetics of the CYP3A4 substrate midazolam. Current smokers had a 24% greater clearance than patients who were not current smokers. The mechanistic reason for the change could be due to an increase in erlotinib metabolism by CYP1A in smokers.

Coadministration of erlotinib with ketoconazole, a potent inhibitor of CYP3A4, resulted in a significant (67%) increase in erlotinib exposure. Due to inter-subject variability and the differential inhibitory potency of various CYP3A4 inhibitors, specific recommendations for dose reduction are judged inappropriate. The CYP3A4 inducer rifampicin has been demonstrated to reduce erlotinib AUC by 64%. These data suggest that for patients taking potent CYP3A4 inducers, erlotinib exposure could be sub-optimal or ineffective for the period of co-administration. The proposed labeling suggests that alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible. In addition, the applicant should study the appropriate dose adjustments of erlotinib in patients who take CYP3A4 enzyme-inducing drugs.

Phase 4 commitments: OSI agreed to the following phase 4 commitments on October 26, 2004.

1. Conduct a study to determine the pharmacokinetics of erlotinib in hepatically-impaired cancer patients.
2. Conduct a study to assess the ability of dose adjustment to compensate for the large decrease in erlotinib AUC seen when Tarceva is co-administered with a strong enzyme inducer.
3. Complete the ongoing midazolam drug interaction study.
4. Explore the contribution of non-CYP routes to the metabolism of erlotinib.

Tradename and Labeling Consultation (see DMETS & DDMAC reviews)

The Division of Medication Errors and Tech Support (DMETS) had no objection to the use of the proprietary name, Tarceva. Additionally, DMETS provided label & labeling recommendations in their reviews.

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the proprietary name acceptable from a promotional perspective. DDMAC reviewer Joseph Grillo reviewed and commented on the draft labeling submitted in the application.

Data Integrity Issues (see Dr. Gan's Clinical Inspection Summary)

Only foreign data was submitted to support the application. The Division of Scientific Investigation (DSI) inspected two Canada sites (Montreal and Toronto). DSI found the data for these sites acceptable. A final review is not yet available in Division File System (DFS).

Pediatric Considerations

Non-small cell lung cancer does not exist in children so the Division granted a full waiver to the applicant regarding conduct of pediatric studies.

Conclusions

Survival benefit was demonstrated in a single trial. The Division has accepted survival as evidence of clinical benefit in similar disease settings. Tarceva treatment was also associated with an improvement in 1-year survival, progression-free survival and response rates. An exploratory subgroup analysis suggested a significant prolongation in survival of patients who were EGFR positive and unmeasured, but did not appear to have an effect on the survival in the EGFR negative subgroup. The confidence intervals for the EGFR positive, negative, and unmeasured subgroups are wide and overlap; hence, a survival benefit due to Tarceva in the EGFR negative subgroup cannot be excluded. The Tarceva labeling, after extensive discussions within the Division, with the Office, and with the applicant, describes evidence of benefit in the EGFR positive population — especially, in non-smokers with EGFR positive tumors. Although these analyses are exploratory, the EGFR subgroup is based on the proposed mechanism of drug action providing a biological/clinical rationale for selection of this analysis. The applicant has agreed to prospectively examine the relationship of EGFR status and survival in two clinical trials. In addition, the applicant committed to conduct post-marketing clinical pharmacology and biopharmaceutic studies as outlined above.

Recommendation: Regular Approval

Richard Pazdur, MD
Director, Division of Oncology Drug Products

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this page is the manifestation of the electronic signature.**

/s/

Dianne Spillman
11/22/04 05:03:35 PM
CSO

Richard Pazdur
11/22/04 05:14:33 PM
MEDICAL OFFICER

RECORD OF TELEPHONE CONVERSATION

DATE: November 18, 2004

NDA: 21-743

DRUG: Tarceva

BETWEEN: Richard Pazdur and Paul Zimmerman, FDA

AND: Robert Simon, OSI.

Dr. Pazdur and Robert Simon agreed to the following changes to the package insert text for Tarceva. Dr. Pazdur and Robert Simon agreed that these changes will be incorporated at the next printing of the package insert as the previously-agreed to version of the package insert text is already printed, to allow for a rapid product launch. In addition the changes are considered to be minor editorial changes.

Line 37: removal of [] .

Line 142: Addition of text "and the effects of TARCEVA were". The sentence will therefore read.. "However, the survival in the EGFR tested population and the effects of TARCEVA were almost identical to that in the entire study population, suggesting that the tested population was a representative sample".

Line 147: remove " [] from the start of the sentence and add (Figure 3), (Figure 4) or (Figure 5) after each set of parentheses containing the respective data.

Line 155: Insertion of a paragraph break before the statement on patients who never smoked. In the first sentence of this new paragraph, the word "also" will be added after "EGFR status". The sentence will therefore read "For the subgroup of patients who never smoked, EGFR status also appeared to be predictive of TARCEVA survival benefit".

Line 191: Change RANDOMIZED to lower case and remove "phase 3".

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

/s/

Paul Zimmerman
11/23/04 08:07:52 AM
CSO

Paul Zimmerman
11/23/04 08:09:32 AM
CSO

NDA ACTION LETTER ROUTING RECORD

NDA#: 21-743

Date Received: 11/15/04

Drug: Tarcera

Division: HFD- 150

Type of Letter: (AP) AE NA

Drug Classification: IP

REVIEWER

RECEIPT

ACTION

1. Colleen LoCicero Associate Director for Regulatory Affairs
 Date 11/15/04 Initials /S/ Date 11/16 Initials /S/
 Press Office notification. Press release planned.
 Financial Disclosure info reviewed - P.12 MOR. Labeling & letter (PMC) language
 Comments: User fee goal date - still under negotiation.
2. Chemistry Review
 Date 10/28 Initials /S/ Date 10/29 Initials /S/
 Comments: There are no pending EMC issues. EER is acceptable. EA is a categorical exclusion. The labeling is adequate and acceptable. There are no micro issues. Recommend approval from the EMC standpoint. Methods validation is pending. Please include the standard paragraph in the letter.
3. Pharmacology & Toxicology Review
 Date _____ Initials _____ Date _____ Initials _____
 Comments: See attached.
3. R Behrman, M.D. Dep Director, ODEI
 Date _____ Initials _____ Date _____ Initials _____
 Comments:
4. R. Temple, M.D. Director, Office of Drug Evaluation I
 Date 11/15/04 Initials /S/ Date 11/15/04 Initials _____
 Returned to Division for Corrections _____ Forwarded _____
 Letter Signed /S/
 Comments:

Withheld

2

**page(s) of trade
secret
and/or confidential
commercial
information**

(b4)

20 pages redacted from this section of
the approval package consisted of draft labeling

OSI Pharmaceuticals, Inc.
58 South Service Road, Suite 110
Melville, NY 11747
T 631.962.2000 F 631.752.3880
www.osip.com

(osi) pharmaceuticals

November 03, 2004

Richard Pazdur, M.D.
Director, Division of Oncology Products
Center for Drug Evaluation and Research HFD-150
Office of Drug Evaluation I
1451 Rockville Pike Woodmont Building II
Rockville, MD 20852

Dear Dr. Pazdur:

RE: NDA # 21-743

Tarceva™ (erlotinib)
New Drug Application
Response To FDA Request Regarding Dissolution Specification

Reference is made to an email from Paul Zimmerman, dated October 12, 2004, regarding the Agency's request regarding the dissolution specification.

Our response to this request is provided with this letter.

If there are any questions in connection with this application I can be contacted at (631)-962-2156 (phone) or (631)-962-2076 (fax).

Yours sincerely,



for Christine Boisclair
Senior Director, Global Regulatory Affairs

(osi)[™] pharmaceuticals

ORIGINAL NDA 021-743

RESPONSE TO FDA REQUEST

DATE REQUEST RECEIVED: OCT 12 2004

DATE RESPONSE SUBMITTED: NOV 03 2004

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1 FDA REQUEST RECEIVED OCTOBER 12 2004 3
2 RESPONSE TO FDA REQUEST 3

**APPEARS THIS WAY
ON ORIGINAL**

1 FDA REQUEST RECEIVED OCTOBER 12 2004

We recommend a dissolution specification of Q = @ 45 minutes, —
Apparatus 2 (Paddle) @ ~ RPM,

2 RESPONSE TO FDA REQUEST

OSI agrees to utilize a dissolution specification of Q = @ 45 minutes, —
Apparatus 2 (Paddle) @ ~ RPM, — This will be implemented November
2004.

**APPEARS THIS WAY
ON ORIGINAL**

OSI Pharmaceuticals, Inc.
58 South Service Road, Suite 110
Melville, NY 11747
T 631.962.2000 F 631.752.3880
www.osip.com

(osi) pharmaceuticals

November 03, 2004

Richard Pazdur, M.D.
Director, Division of Oncology Products
Center for Drug Evaluation and Research HFD-150
Office of Drug Evaluation I
1451 Rockville Pike Woodmont Building II
Rockville, MD 20852

Dear Dr. Pazdur:

RE: NDA # 21-743

Tarceva™ (erlotinib)
New Drug Application
Response To FDA Request For Submitting 15-day Alert Reports of
Grade 3 or 4 Ophthalmologic AEs

Reference is made to the Agency's:

1. Request, dated October 13, 2004, to provide Grade 3 or 4 ophthalmological AE's
2. Response, dated November 2, 2004, to our request for clarification on the reporting of ophthalmologic AEs.

In light of the Agency's response to our request for clarification, please find our response to the Agency's original request, for the submission of 15-day Alert Reports of Grade 3 or 4 Ophthalmologic AEs.

If there are any questions in connection with this application I can be contacted at (631)-962-2156 (phone) or (631)-962-2076 (fax).

Yours sincerely,



Christine Boisclair
Senior Director, Global Regulatory Affairs

(osi)[™] pharmaceuticals

ORIGINAL NDA 021-743

RESPONSE TO FDA REQUEST

DATE REQUEST RECEIVED: OCT 13 2004

DATE RESPONSE SUBMITTED: NOV 03 2004

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1 FDA REQUEST RECEIVED OCTOBER 13 2004 3
2 RESPONSE TO FDA REQUEST 3

**APPEARS THIS WAY
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1 FDA REQUEST RECEIVED OCTOBER 13 2004

"OSI: Please provide Grade 3 or 4 ophthalmological AE's as unlabeled reports, ie, 15 day report"^a

^a This request made by the Agency as part of their response to the proposed package insert for TARCEVA, dated October 13, 2004.

2 RESPONSE TO FDA REQUEST

Reference is made to:

- 1) Our request for clarification on the reporting of ophthalmologic AEs, dated October 28, 2004.
- 2) The Agency's response to our request for clarification, dated November 2, 2004 (re-presented below):

Regarding our (FDA) request for 15 day reports for Grade 3 or 4 ophthalmologic AEs, The Division and ODS agree with your proposal below.

"Therefore, in order to meet the intent of the Agency's request, OSI propose to submit 15-day Alert reports for:

- *All serious, labeled and unlabeled ADR reports (including important medical events) within the primary MedDRA SOC "Eye Disorders" from domestic spontaneous sources.*
- *All serious, drug-related events regardless of expectedness within the primary MedDRA SOC "Eye Disorders" from company-sponsored and non-sponsored clinical trials."*

OSI acknowledge the Division and ODS's agreement to our proposal and agree to submit 15-day Alert reports for Grade 3 or 4 ophthalmologic AEs in accordance with this proposal.

**APPEARS THIS WAY
ON ORIGINAL**

MEMO

To: Richard Pazdur, M.D.
Division of Oncology Drug Products, HFD-150

From: Linda M. Wisniewski, RN
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

CC: Paul Zimmerman
Project Manager, Division of Oncology Drug Products
HFD-150

Date: October 18, 2004

Re: ODS Consult 01-0132-3, Tarceva™ (Erlotinib Hydrochloride) Tablets, 25 mg (base),
100 mg (base), and 150 mg (base).
NDA 21-743

This memorandum is in response to an October 12, 2004 request from your Division for a final review of the proprietary name Tarceva. Additionally, revised container labels and carton labeling were submitted for review and comment at this time.

The proposed proprietary name was found acceptable by DMETS on June 9, 2002 (See ODS Consult 01-0132-2). Since this initial review, DMETS has identified three additional names, Luceve, Trivora, and Tacrine that have the potential for orthographic similarity to Tarceva.

- A. Luceve is a synthetic narcotic analgesic that is similar to morphine. Luceve is indicated for the relief of severe pain, temporary maintenance treatment of narcotic addiction, and for detoxification treatment of narcotic addiction. Both names begin with letters that may look similar when scripted (t vs. l). Additionally, the remaining letters (arceva vs. uceve) may also look similar when scripted (see below). Although both drugs may be dosed once daily, Luceve is most often dosed every three to four hours for pain. The daily dosing frequency is generally used only when patients cannot tolerate oral methadone detoxification. Additionally, detoxification is most often conducted in an inpatient setting. Thus, the most likely scenario for confusion is in an inpatient setting. There are differentiating product characteristics, such as dose (2.5 mg to 20 mg or higher as needed vs. 150 mg), dosage form (injection vs. tablet), strength (10 mg/mL vs. 25 mg, 100 mg, and 150 mg), route of administration (intravenous, intramuscular, or subcutaneous vs. oral), and storage location (in locked cabinet with other Schedule II injectables vs. oral solids). Luceve requires Schedule II drug distribution controls and requires documentation that would help to minimize confusion. The different product characteristics and conditions of use will help to minimize confusion involving Luceve and Tarceva.

Tauer
Luceve

- B. Trivora may look similar to Tarceva when scripted. Trivora is an oral-contraceptive indicated in the prevention of pregnancy. Both names begin with similar looking letters (tar vs. tri and vor vs. cev) and end in the same letter 'a'. Although both products are tablets that are administered once daily, there are product characteristics that may help to differentiate them, such as dose (150 mg vs. 0.03 mg; 0.04 mg; 0.03 mg; 0.05 mg; 0.125 mg ;0.075 mg), strength (25 mg, 100 mg, and 150 mg vs. 0.03 mg; 0.04 mg; 0.03 mg; 0.05 mg; 0.125 mg ;0.075 mg), and indication of use (non small-cell lung cancer vs. prevention of pregnancy). An order for either drug would have additional information, such as, strength in an order for Tarceva, and number of tablets in an order for Trivora. However, if an order for Trivora-28 were misinterpreted as Tarceva #28, the strength would need to be clarified before dispensing. Therefore, the different strengths of Tarceva will help to minimize confusion involving Trivora and Tarceva.

trivora
tarceva

- C. Tacrine may look similar to Tarceva when scripted. Tacrine is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. Both names contain letters that may look similar when scripted (tar vs. tac and rin vs. cev) (see below). There are some differentiating product characteristics, such as dose (150 mg vs. 10 mg to 40 mg), dosage form (tablet vs. capsule), strength (25 mg, 100 mg, and 150 mg vs. 10 mg, 20 mg, 30 mg, and 40 mg), frequency of administration (once daily vs. four times daily), and indication of use (non small-cell lung cancer vs. dementia of Alzheimer's). Although there is post-marketing evidence that the scripted frequencies "QD and QID" have been confused in the past, the differences in dose and strength will help to differentiate these two products.

tacrine
tarceva

Additionally, DMETS reviewed the labels and labeling submitted October 14, 2004 from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

The beige color and the contrasting white background of the 25 mg strength is difficult to read. DMETS recommends revising the font and contrasting color to provide better readability.

In summary, DMETS has no objection to the use of the proprietary name, Tarceva. Additionally, DMETS recommends implementing the label and labeling recommendation included in this review. DDMAC finds the proprietary name acceptable from a promotional perspective. We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the signature date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Denise Toyer
10/21/04 03:58:51 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/21/04 04:15:35 PM
DRUG SAFETY OFFICE REVIEWER

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, October 15, 2004 9:51 AM
To: Boisclair, Christine
Subject: NDA 21743 QoL labeling issues
Are attached as discussed.

APPEARS THIS WAY
ON ORIGINAL

Reasons for Deletion of QoL claims in the Tarceva Label:Comments on the instrument and specific questions used to evaluate the treatment effect:

1. The goal of measurement using EORTC-QLQ-C30 is to capture a patient's report of overall health and wellbeing.
2. The symptom questions used as endpoints in the NDA ask patients to average their experience over the past week. The agency in general prefers static assessments that ask patients about their current state rather than ask questions that require the patients to average their experience over a period of time.
3. The endpoint of Cough is as measured by the Question 1 of the QLQ-LC13: During the past week, how much did you cough? This question does not address the severity, productivity or its impact on functioning.
4. The endpoint of Dyspnea is as measured by Question 8 of the QLQ-C30: During the past week, were you short of breath? This question does not address the magnitude of effort and the magnitude of the task at the time of shortness of breath assessment (for example: shortness of breath occurred during strenuous activity, light activity, basic activity or at rest).
5. The endpoint of Pain is as measured by Questions 9 and 19 of the QLQ-C30: During the past week, have you had pain? And During the past week, did pain interfere with your daily activities? The first question asks whether a patient has experienced any pain without addressing the intensity of the pain. The second question asks about the impact of pain on functioning. In the endpoint determination average of these two responses are considered. A change in score could therefore be because of frequency of reported pain or impact of pain on functioning. These do not reflect the rate of deterioration in the patient's condition with respect to pain.
6. The measures used in this NDA for evaluating cough, dyspnea and pain are not consistent with the agency's previous experience and advice for patient-reported outcomes.
7. The EORTC QOL instruments are developed and validated to be used in totality. There is no development and validation of the instruments to support conclusions about individual concepts (e.g., pain, dyspnea and cough) based on the use of single items from the instruments. The validity of the instrument subscales to measure these specific concepts is questionable.

Comments regarding the submission of statistical analysis plan:

1. In the protocol (last amended on Nov 14, 2002), no specific items were identified as items of interest in the QoL measurement/analysis. It was stated that QoL will be assessed longitudinally and analysis of variance for repeated measure would be used for *domains* represented by aggregate scores.
2. The sponsor submitted a draft statistical analysis plan to the agency on October 17, 2002, which was subsequently discussed in a meeting on November 13, 2002. In this draft plan the sponsor for the first time specified that for the primary

symptom benefit analysis, dyspnea, coughing and pain will be considered the three primary lung cancer symptoms. The draft plan further stated that the analyses of these symptoms will include estimation of the incidence (with 95% confidence intervals based on binomial distributions) of the individual symptoms (by grade) at baseline and by cycle, and comparisons between the treatment groups using chi-square test. It was further stated that additional analyses would include categorization of each symptom as improved, not changed, or deteriorated by cycle, and comparisons between treatment groups using chi-square tests; a third set of analyses would define an event as the worst severity grade or the presence of a new symptom, with time-to-event analyses using log-rank tests. In this submission, improvement, stable or worsening of symptoms were not defined. In this submission, the sponsor had asked the agency "Does the agency agree with the selection of dyspnea, cough and pain as the main disease related symptoms in the clinical benefit assessment?" The Agency's response was "Yes". This question did not address the actual measure or definition of endpoint for these 3 symptoms.

3. In this registration study, first patient was entered on November 1, 2001 and the last patient was entered on January 31, 2003. The sponsor submitted their final statistical analysis plan on June 18, 2003, 6 months after the last patient was entered on the trial. In this analysis plan for the first time the endpoint for the three symptom measurements was defined as the time to worsening, worsening defined as a 10 points or more decrement in the score from baseline. The agency did not comment on the choice of criteria for worsening or the endpoint at that time, as this was considered one among many secondary endpoints.

Comments about the analyses results:

1. The statistical reviewer conducted time to deterioration analyses in the other functional and symptom domains, global QoL scale and single items (a total of 26 identified measurements by the sponsor in the EORTC QLQ-C30 and QLQ-LC13 questionnaires). These results suggest that the time to deterioration in cough, dyspnea, and pain as presented by the sponsor are not robust/consistent as detailed below.
2. The physical functional domain and global QoL scale analysis suggest that the Tarceva treated group was worse than the placebo group (HR of 1.5 and 1.2 respectively). These are not consistent with the reported results for dyspnea and pain.
3. Although dyspnea as measured in QLQ-C30 single question was significant per sponsor analysis, the dyspnea domain (3 questions) as measured in QLQ-C13 was not significant (p-value = 0.3452).
4. Also, although pain as measured in QLQ-C30 single question was significant per sponsor analysis, chest pain as measured in QLQ-C13 was not significant (p-value = 0.06). It is also noted that Tarceva was worse for sore mouth and diarrhea.
5. The QoL analyses were based on the subgroup of patients who had baseline and at least one follow-up measurement (approximately 63% of the overall population for cough, 74% of the overall population for dyspnea and pain).

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/s/

Paul Zimmerman
10/15/04 09:55:25 AM
CSO

2 pages redacted from this section of
the approval package consisted of draft labeling

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/s/

Paul Zimmerman
10/15/04 10:00:33 AM
CSO
Text of the 10-15-04 QOL communication

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, October 12, 2004 1:37 PM
To: 'Boisclair, Christine'
Subject: NDA 21-743 for Tarceva

Regarding Phase 4 commitments we have the following concerns:

1. We recommend that a study be performed to determine the pharmacokinetics of erlotinib in hepatically-impaired cancer patients. The study will have two phases. For both phases the primary objective is pharmacokinetics. In the first phase, an assessment of whether pharmacokinetic changes occur due to hepatic impairment will be made. Assuming that significant pharmacokinetic changes occur, the results will be population modeled and simulations will be used to choose a dose adjustment strategy. FDA will review the chosen strategy prior to initiation of the second phase of the study. The second phase of the study will verify the dose adjustment strategy by using it in a cohort of hepatically-impaired patients and measuring their pharmacokinetics.
2. We recommend that a study be conducted to assess the ability of dose adjustment to compensate for the large decrease in erlotinib AUC seen when TARCEVA is co-administered with a strong enzyme inducer. The primary objective of the study is to determine a dose of TARCEVA that, when administered to subjects receiving rifampicin, will produce plasma concentrations approximating those seen in patients receiving 150 mg QD TARCEVA without rifampicin. Study design will be driven by population pharmacokinetic modeling and simulation using the current data on the interaction of rifampicin and erlotinib. FDA will review the chosen strategy prior to initiation of the study.
3. We recommend that the Applicant agree to complete the ongoing midazolam drug interaction study. The results of this study will determine the need to accomplish additional in vivo and in vitro drug interaction studies.
4. We recommend a dissolution specification of $Q = \square$ @ 45 minutes, \square Apparatus 2 (Paddle) @ \sim RPM, \square
5. We recommend that the Applicant explore the contribution of non-CYP routes to the metabolism of erlotinib.

Zimmerman, Paul F

From: Zimmerman, Paul F

Sent: Thursday, September 30, 2004 12:45 PM

To: 'Boisclair, Christine'

Subject: NDA 21-743 for Tarceva

Please submit any information OSI has on Tarceva ILD in patients without lung cancer.

APPEARS THIS WAY
ON ORIGINAL

Zimmerman, Paul F

From: Zimmerman, Paul F

Sent: Wednesday, September 29, 2004 7:52 AM

To: 'Boisclair, Christine'

Subject: NDA 21-743 for Tarceva-Phase 4 commitment

Please propose specific clinical trials where the relation of EGFR status to treatment effect on survival and tumor response rate will be assessed and make known EGFR status or at least availability of suitable material to test and patient consent for its use an eligibility requirement.

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/s/

Paul Zimmerman
9/29/04 07:57:25 AM
CSO

September 22, 2004 NDA 21-743 for Tarceva Team and PSC Meeting minutes

Attendees:

DODP:

Grant Williams, John Johnson, Martin Cohen, Paul Zimmerman, et al.

ODS: Robert Kang, Jennie Chang, Kate Phelan, Susan Lu

Discussion:

There was discussion regarding the following ODS concerns and there was agreement on the action items listed below.

1. Under the "Warnings" subsection of "Warning" section, include the percentage of fatal cases that occurred in the studies, comparable to the Iressa label. Only the incidence of interstitial lung disease is provided.
2. In the "Adverse Reactions" section of the label, Grade 3/4 rash was observed in the patients; however, a description as to the type of rash would be useful for oncologists in evaluating the rash. How rapidly did the rash progress? Did the rash resolve upon discontinuation of erlotinib? What treatment was required? Any rechallenge experiences?
3. Provide a quantitative characterization and the incidence of the elevations in liver transaminases, which were also discussed in the "Adverse Reactions" section. The product label states that the liver function abnormalities were "mild or moderate in severity", but it would be useful for oncologists to know how elevated they were above normal, i.e., 2-3 x ULN.
4. Should a section of hepatotoxicity be included in the "Precautions" section of the label, comparable to that of Iressa?
5. Under the "Precautions" section of the label, international normalized ratio (INR) elevations are discussed. The reports are stated as "infrequent", but providing the incidence of INR elevations would be more useful for the treating oncologist.
6. For adverse events pertaining to the eye, such as keratitis and corneal ulcerations, submission of these adverse events as unlabeled reports, i.e., 15-day reports, would be helpful to determine the extent of them.

Action Items:

Dr. Cohen will address the following. Provide a quantitative characterization and the incidence of the elevations in liver transaminases, which were also discussed in the "Adverse Reactions" section. The product label states that the liver function abnormalities were "mild or moderate in severity", but it would be useful for oncologists to know how elevated they were above normal, i.e., 2-3 x ULN.

Dr. Cohen will address the following. Provide a section of hepatotoxicity be included in the "Precautions" section of the label, comparable to that of Iressa.

Dr. Cohen will address the following. Under the "Precautions" section of the label, international normalized ratio (INR) elevations are discussed. The reports are stated as "infrequent", but providing the incidence of INR elevations would be more useful for the treating oncologist.

ODS requests that all eye-related adverse drug experiences be submitted as though they are unexpected. That is, any adverse events affecting the eye, including keratitis and corneal ulceration, that meet the regulatory definition of serious (21CFR 314.80) should be submitted as 15-day reports.

**APPEARS THIS WAY
ON ORIGINAL**

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, September 17, 2004 10:35 AM
To: Boisclair, Christine
Subject: NDA 21-743
(From our Statistcal folks)

Please submit the adjudicated PFS dataset (dataset that FDA and sponsor have agreed to).

APPEARS THIS WAY
ON ORIGINAL

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, September 07, 2004 3:11 PM
To: Boisclair, Christine; 'Wariabharaj, Darshan'
Subject: NDA 21-743 for tarceva

The Reviewer (Biopharm) is unable to locate the in-assay bioanalytical reports for studies BR21 and OSI2298g. Can you direct us to their location in the NDA? If they are not present in the NDA, please submit them as soon as possible.

APPEARS THIS WAY
ON ORIGINAL

There was no Advisory Committee meeting for NDA 21-743 for Tarceva

**APPEARS THIS WAY
ON ORIGINAL**

RECORD OF TELEPHONE CONVERSATION

DATE: August 31, 2004

NDA: 21-743

DRUG: Tarceva

BETWEEN: Grant Williams, John Johnson, Martin Cohen, and Paul Zimmerman, FDA

AND: OSI/Genentech: Christine Boisclair, Darshan Wariabharaj, Robert Simon, Gary Clark, Sandra Nino, Pam Kline, et al.

TELEPHONE NUMBER: 1-877-393-3856

The applicant requested this telecon to respond to our requests about obtaining additional EGFR data. The applicant noted that NDA provides EGFR data on 238 patients. The applicant noted that they expect to have EGFR data on approximately an additional 40 patients and estimates it will be available for submission to the FDA in 6 to 8 weeks.

**APPEARS THIS WAY
ON ORIGINAL**

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, August 30, 2004 1:59 PM
To: 'Wariabharaj, Darshan'; Zimmerman, Paul F
Cc: Boisclair, Christine
Subject: RE: NDA 21/743 for Tarceva: Question Regarding Patient 'BRRJ0229' in Data File QOL.XPT
(I noted earlier today that you should provide the 8-30-04 response below to the NDA.)

Our reviewer asks that you provide the re-analyses for time to deterioration on major symptoms by using the corrected data and submit that to the NDA. We understand the changes are minimal. In addition, please provide the programs for the pattern mixture model analyses for QOL data. Please submit this also to the NDA. (Please also send all of this by e-mail if possible to expedite the review.)

-----Original Message-----

From: Wariabharaj, Darshan [mailto:DWariabharaj@OSIP.com]
Sent: Monday, August 30, 2004 9:16 AM
To: 'ZIMMERMANNP@cder.fda.gov'
Cc: Boisclair, Christine
Subject: RE: NDA 21/743 for Tarceva: Question Regarding Patient 'BRRJ0229' in Data File QOL.XPT
Importance: High

Dear Paul:

The attached has been prepared by our statistics and data management group in response to your question regarding patient 'BRRJ0229' in data file 'QOL.XPT'. Let me know if this response will suffice to address this question.

Regards, Darshan

-----Original Message-----

From: Zimmerman, Paul F [mailto:ZIMMERMANNP@cder.fda.gov]
Sent: Thursday, August 26, 2004 1:06 PM
To: 'Boisclair, Christine'
Subject: NDA 21/743 for Tarceva

(This is from our Statistical reviewer)

In the data file 'QOL.XPT', why does patient 'BRRJ0229' have two data entries for the scheduled time period PR, i.e., prior to randomization. In those two entries the scores for all measures are the same except the variable 'QOLDT'. Please explain why this prior to randomization data was used to compute the time to deterioration of cough, dyspnea and pain.

8/25

Zimmerman, Paul F

To: Boisclair, Christine

Subject: NDA 21-743 for Tarceva

We received your August 18, 2004 response to our inquiry about EGFR data from the BR.21 study. We would like to receive all additional EGFR data from the BR.21 study as soon as possible. What is the earliest date that you can provide additional BR.21 study information on EGFR status even if incomplete?

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/s/

Paul Zimmerman
8/25/04 01:11:25 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, August 19, 2004 9:39 AM
To: Pazdur, Richard; Williams, Grant A; Johnson, John R; Cohen, Martin H; Sridhara, Rajeshwari; Hsieh, Li Shan; Benson, Kimberly; Leighton, John K; Booth, Brian P; Chidambaram, Nallaperum; Williams, Gene M; Grillo, Joseph; Lu, Susan; Kang, Robert; Chen, Yeh-Fong; Phelan, Kathleen (ODS); Chen, Xiao H
Subject: 8-18-04 NDA 21-743 for Tarceva Team Meeting outcome
8-18-04 NDA 21-743 for Tarceva Team Meeting

The team agreed that the NDA is filable (except that Biopharm noted that it may not be filable if the dissolution data that was requested is not provided. The firm indicated that this information will be provided by August 20, 2004. The NDA will then be filable.)

The team agreed that primary reviews are due September 15, 2004.

The targeted action date is 9/15/2004.

Dr. Gan should provide an update regarding the Clinical inspections.

The selected ODAC consultants are conflicted. 2 new consultants will be screened.

QOL consult will be sent to the appropriate FDA group.

The firm will be asked to estimate when additional EGFR data will be available.

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Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, August 16, 2004 8:16 AM
To: 'Boisclair, Christine'
Subject: NDA 21-743 for Tarceva

Does the progression free survival results included in module 2: Section 2.7.3 (July 29, 2004) Summary of Clinical Efficacy include the revised progression and censor dates that were agreed to by OSI and by FDA (The exceptions noted in your communication of 7/29/04 are accepted)?

If not, please provide a PFS and response duration update.

APPEARED
ON ORIGINAL

8/12/04

Zimmerman, Paul F

To: Boisclair, Christine

Subject: NDA 21-743 for Tarceva

(Please estimate when we may expect your response to following request from our Biopharm reviewer.)

On page 79 of RESEARCH REPORT No. 1010649 (Clinical Study Report – Protocol NP16793) the following (as well as other items) are listed:

- Subject Listing of ECG Interval Data
- Subject Listing of ECG non-Interval Data
- vs05_b Listing of QTcF Data with Change from Baseline and Risk Assessment by Trial Treatment and CRTN/Subject Number
- vs05_a Listing of QTcB Data with Change from Baseline and Risk Assessment by Trial Treatment and CRTN/Subject Number
- vs04_a Listing of Vital Signs by Trial Treatment and CRTN/Subject Number with Change from Baseline

PHARMACOKINETIC DATA

Bioanalytical Report

Please submit the above 5 bulleted items in SAS Transport format. Please submit the bioanalytical report in pdf format.

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/s/

Paul Zimmerman
8/12/04 11:08:40 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, August 09, 2004 2:25 PM
To: 'Boisclair, Christine'
Subject: NDA 21-743 EGFR status

Regarding NDA 21-743 for Tarceva, as discussed in our telephone conversation today (with Dr. Richard Pazdur, Dr. John Johnson, Dr. Rajeshwari Sridhara and Paul Zimmerman), Dr. Pazdur noted that EGFR status has been provided for approximately 33% of patients on trial BR21. Dr. Pazdur requested that you provide to the NDA as soon as possible the EGFR status of all patients on trial BR21. If the EGFR status is not available for some patients, a list of those patients and the reason why the EGFR status is not available for each patient should be provided.

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/s/

Paul Zimmerman
8/9/04 02:49:40 PM
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FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Christine Boisclair

Fax: 631 962-2076

FROM: Dotti Pease, Project Manager

Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 8-4-04

COMMENTS: Re: your pending NDA 21-743 for Tarceva, we have the following questions regarding bioequivalence issues. (The reviewer will probably want an estimate of your response time also)

Page 14 of Module 2.6 (Nonclinical Written and Tabulated Summaries) references (references 2. and 3 on page 23 of Module 2.6) the following documents:

2. EGFR Inhibitor Project: Compound Pipeline (Pfizer Project Team Handout). Pfizer. 16-Jun-1995. (Available upon request.)
3. EGFR Analog Research Database Spreadsheet. OSI Pharmaceuticals. 12-May-1995.

(Available upon request.)

Please submit these data, as well as any additional information not currently in the NDA, regarding the activity (both pharmacologic and toxicologic) of the erlotinib metabolites that were identified in the human mass balance study (Study #248-006, Table 8, p. 149).

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§ 552(b)(5)

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, July 01, 2004 10:22 AM
To: 'Boisclair, Christine'
Subject: NDA 21-743 for Tarceva

The NDA 21-743 protocol states that patients with deteriorating health status requiring discontinuation of treatment without objective progression be reported as having "symptomatic deterioration" and that every effort should be made to document objective progression.

This being the case, it seems appropriate to censor patients with "symptomatic deterioration" at the time that they were removed from study. Did you do this in your analysis of TTP? If not, please provide such an analysis .

**APPEARS THIS WAY
ON ORIGINAL**

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, July 01, 2004 9:52 AM
To: Gan, David; Ball, Leslie
Cc: Johnson, John R; Cohen, Martin H
Subject: DSI Inspections for NDA 21-743 for Tarceva (OSI Pharmaceuticals)
 DSI Inspections for NDA 21-743 for Tarceva (OSI Pharmaceuticals)

Tarceva is a NME which has been shown to prolong life in patients with advanced lung cancer in whom other chemotherapy has failed. Tarceva is a priority review and a rolling NDA under the FDA Pilot 1 Program. The NDA is supported by one large RCT (BR-21). We have just received the data for the RCT. All of the other review disciplines are well along with their reviews and we expect to take an action on this NDA by September 1, 2004.

We are requesting an audit of the only RCT (BR-21). Please audit DSI's choice of any two of the four sites in the Table below. We suggest the two Canadian sites. The four sites in the Table are the largest accruers to the RCT. There are no U.S. sites.

Site code Site # Investigator Address

BRPL	495	Jose Rodrigues Pereira, MD 92 pts	Instituto do Cancer Arnaldo Vieira de Carvalho R. Dr. Cesario Motta Jr., 112 Sa 01221-020 Brazil 55 11 222 7877
CAMG	240	Frances Shepherd, MD 22 pts	Princess Margaret Hospital 610 Univeristy Avenue Suite 5-104 Toronto ON M5G 2M9 Canada 416 946 4522
CAHC	190	Vera Hirsh, MD 26 pts	McGill University Clinical Trials Operations 546 Pine Avenue West Montreal Q Canada 514 842 1231
RORC	280	Tudor Ciuleanu, MD 65 pts	Oncology Institute Ion Chiricuta 34-36 Gh. Bilascu Street Cluj-Napoca 3400 Romania 40 2 64 198361 ext 229

Dr. Martin Cohen is the Medical Officer. Telephone # 301-594-5740.

Dr. John Johnson is the Medical Team Leader. Telephone # 301-827-1524.

Paul Zimmerman is the Project Manager. Telephone # 301-594-5775.

MEMO

To: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products, HFD-150

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Carol A. Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

CC: Paul Zimmerman
Project Manager, Division of Oncology Drug Products
HFD-150

Date: May 27, 2004

Re: ODS Consult 01-0132-2, Tarceva™ (Erlotinib Hydrochloride) Tablets, 25 mg (base),
100 mg (base), and 150 mg (base)
NDA 21-743

This memorandum is in response to a March 19, 2004, request from your Division for a final review of the proprietary name Tarceva. Container labels and carton labeling from the sponsor's May 12, 2004, submission were printed from the electronic document room and reviewed by DMETS for safety related issues relating to possible medication errors.

1. PROPRIETARY NAME REVIEW

The proposed proprietary name was found acceptable by DMETS on May 22, 2002 (See ODS Consult 01-0132). Since this initial review, DMETS has identified one additional proprietary name, Kariva, as having the potential to sound similar to Tarceva. Kariva is ethinyl estradiol and desogestrel tablets, indicated for the prevention of pregnancy in women. It is packaged in blister cards for 21 day and 28 day use. Sound-alike properties between Kariva and Tarceva may be attributed to the hard consonants "K" vs. "T" and same "ar" sounds in the first syllable, shared "ee" sound in the second syllable, and identical last syllable "va". Kariva and Tarceva share similar product characteristics, such as: dosage form (tablet), route of administration (oral), and dosing regimen (once daily). Although tablet strengths of Kariva and Tarceva share similar numerals (150 mcg desogestrel vs. 150 mg, respectively), Kariva will generally be prescribed as Kariva (without a strength) or Kariva 21 or Kariva 28 to indicate the days supply. Additionally, if the strength of Kariva is written, it will most likely include strengths for both active drug components, ethinyl estradiol and desogestrel. In contrast prescriptions for Tarceva will likely have a strength since more than one strength is available. Other product differences between Kariva and Tarceva include, indications (contraception vs. 2nd/3rd line treatment of non small-cell lung cancer) and packaging and patient information (21 or 28 tablet dispenser pack accompanied by mandatory patient information vs. prescription bottle), respectively. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on these product differences for Kariva and Tarceva.

2. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Tarceva, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. Revise the established name to include the dosage form (tablets) where it appears on labels and labeling.
2. Relocate the expression of strength to appear beneath the proprietary and established names on labels and labeling.
3. Using an asterisk or by some other means, clarify that the strength is in terms of erlotinib rather than erlotinib hydrochloride wherever the expression of strength occurs on labels and labeling.
4. The red color bars for the 25 mg and 150 mg strengths are not sufficiently different to provide adequate differentiation. Please choose a different color to differentiate one of the strengths from the other.
5. The logo appearing on labels and labeling is distracting. Please delete or decrease its prominence.
6. USP nomenclature conventions dictate that the established name of this product is "Erlotinib Tablets" since strength is based on the active moiety. DMETS recommends that the sponsor adopt this naming convention and that labels and labeling be revised accordingly.

B. CONTAINER LABELS (25 mg, 100 mg, and 150 mg, 30's)

1. See GENERAL COMMENTS above.
2. The 30 tablet container size appears to be a unit of use container. Please assure that the closure for your package sizes comply with the "Poison Prevention Packaging" standard. We refer you to the CFR 1700.14 and 1700.15 for guidance.

C. CARTON LABELING (25 mg, 100 mg, and 150 mg, 30's)

See GENERAL COMMENTS and comments for CONTAINER LABELS above.

In summary, DMETS has no objection to the use of the proprietary name, Tarceva. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document. DDMAC finds the proprietary name acceptable from a promotional perspective.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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this page is the manifestation of the electronic signature.**

/s/

Charles Hoppes
6/8/04 08:18:29 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/8/04 03:30:35 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/9/04 07:38:40 AM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

6/24/04

IND 53,728
NDA 21-743

OSI Pharmaceuticals Inc.
Attention: Christine Boisclair
Senior Director, Global Regulatory Affairs
58 South Service Road, Suite 110
Melville, NY 11747

Dear Ms. Boisclair:

We refer to your submission of October 17, 2003, requesting participation in the Continuous Marketing Application (CMA) Pilot 1 program for your new drug application, NDA 21-743. We have accepted the NDA into CMA Pilot 1. The following submissions have been received under this NDA and will be converted by us to reviewable units (RUs), effective the date of this letter, as follows:

Name of Drug Product: Tarceva (erlotinib hydrochloride) tablets, 25 mg, 100 mg and 150 mg

Date of Submission: January 20, 2004

Date of Receipt: January 21, 2004

Our Reference Number: NDA 21-743

Reviewable Unit: RUC 001

Date of Submission: January 20, 2004

Date of Receipt: January 21, 2004

Our Reference Number: NDA 21-743

Reviewable Unit: RUP 002

Unless we notify you otherwise within 60 days of the date of this letter, we will accept these submissions as RUs. The user fee goal date for us to complete our review of these RUs will be 6 months from the date of this letter.

Please cite the NDA number listed above and the specific RU on the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research

IND 53,728
NDA 21-743
Page 2

Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 594-5775.

Sincerely,

*{See **/S/** appended electronic signature page}*

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Dotti Pease

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MEETING MINUTES

After the December 8, 2003 FDA pre-meeting, the FDA responses to the sponsor's questions were sent by fax to the sponsor. On December 9, 2003, the sponsor noted that after reviewing the FDA responses, the meeting scheduled for December 10, 2003 is no longer needed and requested that a telecon replace the meeting for the purpose of discussing question 1. The FDA responses to the sponsor's questions which were sent by fax to the sponsor are included below. The telecon minutes are included after the FDA responses to the sponsor's questions below.

MEETING DATE: December 10, 2003 **TIME:** 12pm **LOCATION:** room 6002 (G)

Drug Name: Tarceva **IND:** 53,728 **Type of meeting:** preNDA follow-up

Sponsor: OSI

Meeting Request Submission Date: October 20, 2003

FDA Response Date: October 28, 2003

Briefing Document Submission Date: October 27, 2003

Additional Submission Dates: November 26, 2003

FDA Invitees, titles and offices:

Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
John Johnson, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Officer
Ning Li, Ph.D., Statistical Team Leader
Yong-Cheng Wang, Ph.D., Statistical Reviewer
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Kimberly Benson, Ph.D., Pharmacology Reviewer
John Leighton, Ph.D., Pharmacology Team Leader
Richard Lostritto, Ph.D., Chemistry Team Leader
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Brian Booth, Ph.D., Biopharmaceutics Reviewer
Gary Gensinger, Computer Specialist
Kathleen Phelan, R.Ph., Office of Drug Safety
Jonca Bull, M.D., Division Director, ODE V
Susan Johnson, Ph.D., OND
Armando Oliva, M.D., OND
Paul Zimmerman, R.Ph., Project Manager
(telecon attendees are bolded)

Sponsor, titles and offices:

OSI Pharmaceuticals Inc:

Robert Simon, Vice President Global Regulatory Affairs & CMC
Christine Boisclair, Senior Director Global Regulatory Affairs
Jessica LeFur, Director Document Management & Planning
Pedro Santabarbara, M.D., Vice President Clinical Oncology,
Janna Christy-Bittel, Director Clinical Research
Karsten Witt, M.D., Senior Medical Director, Drug Safety and Clinical Development
Gary Clark, Ph.D., Vice President Data Management and Biostatistics
George Hage, Senior Manager Statistical Programming

Genentech Inc:

Pamela Klein, M.D., Director Medical Affairs
Sandra Nino, Pharm D., Manager Regulatory Affairs
Kenneth Oh, Associate Director Regulatory Affairs

F. Hoffman La Roche:

Hans Niefenthaler, Ph.D, Global Regulatory Leader, Regulatory Affairs

Meeting Objectives:

To request consideration in the FDA Pilot 1 Program on CMAs, to update NDA filing plans, and to reach agreement on the technical filing proposal.

Background:

The sponsor plans to submit an NDA for Tarceva as a single agent in 2nd/3rd line NSCLC. Phase 2 and 3 studies are to be submitted, the latter conducted by NCIC.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Tarceva™ has been granted Fast-Track designation in 2nd/3rd line NSCLC and could be the first orally administered EGFR inhibitor to demonstrate a clinical benefit (survival advantage) in this indication, we believe that it qualifies as a therapeutic advance for inclusion in the Pilot 1 Program. Does the Agency agree?

FDA response: The decision on Pilot 1 status will be deferred at this time; however, you may proceed with a rolling NDA.

2. Is the proposed approach of initiation of the rolling NDA in advance of knowing the outcome of Study BR.21 acceptable to the Agency?

FDA response: Yes.

3. Is the proposed breakdown of 4 Reviewable Units (RUs) and the anticipated filing schedule acceptable to the Agency?

FDA response: Yes.

4. Does the Agency agree with the new approach of filing a single study report for BR.21 as opposed to the previous proposal of providing the data in two components?

FDA response: Yes.

5. Does the Agency agree with the more detailed proposal for the technical aspects of the filing and specifically, are the following acceptable?

a. Overall organization/structure:

- i. Structure & filing as per eNDA guidelines
- ii. The proposed 75MB file size
- iii. The overall approach to tables of content (TOCs) and linking, where possible, between sections, in light of the rolling nature of the filing

FDA response: In this case, the 75MB file size is acceptable.

b. CMC:

- i. The proposed c

ii. The folder structure and linking between documents

c. Nonclinical:

- i. Submission of PDF files for scanned reports
- ii. The folder structure and linking between documents

d. Clinical:

- i. Submission of PDF files of the clinical study reports

FDA response:

The following apply to question 5. a.b.c.and d. Please refer to all relevant guidance for industry documents regarding electronic submissions. The guidance document entitled "Providing Regulatory Submissions in Electronic Format - General Considerations, dated January 1999" would be especially helpful and can be found at <http://www.fda.gov/cder/guidance/index.htm>. The EDR staff informs us that you are encouraged to bring your questions regarding electronic submission format directly to Randy Levin or Ken Edmonds at 301-594-5411 or to e-mail them directly at esub@CDER.FDA.gov.

6. In the minutes of the pre-NDA clinical meeting on July 22nd, 2003, the Agency requested submission of [] in the NDA. In the absence of any official guidance on the submission of such [] could the Agency please confirm the areas needing to be addressed [] ?

FDA response:

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- **If there is any information on product medication errors from the clinical IND, ODS requests that this information be submitted with the NDA application.**
 - **The Sponsor needs to submit the proprietary name and all associated labels and labeling for review as soon as possible.**
7. As a follow-up to one of the questions raised for the July 2003 meeting (for which a response was not received); for those studies being filed as study report synopses only, can the Agency please clarify their expectation for any safety tables or listings required to support each synopsis?

FDA response: Since all except one of the synopsis studies were combination chemotherapy trials or non-therapeutic trials nothing more than the synopsis is required.

8. Will the Agency please clarify the request in the Agency minutes of the July 2003 meeting to "provide all dates in date/time format e.g. 1/1/03" (i.e. should this be month/date/year or day/month/year)?

FDA response: mm/dd/yyyy

- **There was discussion regarding the Pilot 1 guidance criterion “demonstrated in clinical trials significant promise as a therapeutic advance”. The applicant may submit evidence/justification that the criterion is met.**
- **It was agreed that the NDA may be submitted for rolling review. It was also noted that the NDA may be converted to Pilot 1 status as the rolling review continues if it is found to qualify.**
- **Dr. Pazdur noted that if the applicant is aware of any problems/issues regarding the application, they should bring them to the attention of the agency (regardless whether a rolling review or CMA is in effect) so they may be addressed as soon as possible.**
- **Dr. Pazdur requested that the sponsor present the NDA Clinical and other pertinent findings to the Division soon after the submission of the final Clinical section.**
- **Regarding the submission of the electronic NDA, it was agreed that paper copies for the reviewers are not needed.**

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/s/

Grant Williams
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MEETING MINUTES

MEETING DATE: July 11, 2003 **TIME:** 11am **LOCATION:** room 6041 (I)
DRUG NAME: Tarceva (OSI-774) **IND:** 53,728 **MEETING TYPE:** CMC preNDA

SPONSOR: OSI **Meeting Request Submission Date:** May 13, 2003
FDA Response Date: May 19, 2003
Briefing Document Submission Date: June 9, 2003

FDA Invitees, titles and offices:

Richard Lostritto, Ph.D., Chemistry Team Leader
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Brian Booth, Ph.D., Biopharmaceutics Reviewer
Murad Melhem, Ph.D., OCPB Fellow
Sean Bradley for Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:

OSI Pharmaceuticals Inc.
Christine Boisclair, Director, Regulatory Affairs
Charmaine Quarterman, PhD, Director, Manufacturing & Clinical Supplies
Robert Simon, Vice-President, Global Regulatory Affairs & CMC
Darshan Wariabharaj, Regulatory Affairs Manager
Roche
Patricia Norman, International DRA Manager
Genentech
Kenneth Oh, Senior Manager, Regulatory Affairs

Meeting Objective(s):

To discuss filing, format and content issues pertaining to the CMC component of the upcoming NDA for Tarceva

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Drug substance (erlotinib HCl):

Question 1:

Does the agency agree that the proposed approach for the particle size distribution acceptance criteria is appropriate?

FDA response:

No. Your approach may be acceptable. Based on material presented today, your approach appears reasonable. However, in the absence of appropriate data and proposed specifications the adequacy of your approach cannot be evaluated. Full evaluation is a review issue. We also note that the particle size distribution may impact the quality of the drug substance as well as drug product content uniformity, friability, and dissolution behavior of the final drug product.

OSI presented information on an overheads concerning particle size, Schwarz ζ η tablet trials at Schwarz, tablet stability.

Question 2:

Does the FDA agree that the proposed ζ η method is an appropriate method for adequately controlling ζ η of erlotinib HCl?

FDA response:

Yes, the proposed method for controlling [redacted] appears to be appropriate. However, full evaluation is a review issue when all of the data are provided in the NDA submission.

Question 3:

Does the Agency agree with OSI's proposal to replace the current quantitative test [redacted] in erlotinib HCl with a qualitative identification test? If not, what additional information is needed in the NDA?

FDA response:

Your approach appears to be acceptable. However, full evaluation of this test will be an NDA review issue.

Question 4:

Does the Agency agree with OSI's approach to establishing the erlotinib HCl specification for specified impurities for the NDA? If the Agency does not agree with the approach then would the Agency provide their position on this matter?

FDA response:

Yes, we agree, it is reasonable to eliminate those impurities which have not been detected in the past batches. However, if any impurity exceeds 0.1%, it needs to be reported, identified, quantified, and/or qualified as per ICH guidelines.

Drug Product (TarcevaTM tablets): dissolution and impurities.

Question 5:

Dissolution:

Does the Agency agree that, based on the data provided for the recommended methodologies, the preferred dissolution method [redacted] using USP Apparatus 2 ([redacted] Paddle at [redacted] rpm) is acceptable as the commercial QC method?

FDA response:

No.

- The acceptability of the dissolution methodology and acceptance criteria are NDA review issues
- We reiterate that a speed at [redacted] rpm for USP Apparatus 2 ([redacted] Paddle) is not acceptable. We recommend that you consider [redacted] using USP Apparatus 2 at [redacted] rpm as the commercial QC method.
- Hard core tablets: These studies are inconclusive. No f2 comparison is provided to make an objective comparison. At [redacted] rpm, there appeared to be no differences among the different tablets tested. At [redacted] rpm, the [redacted] batch, which had the hardest core ([redacted] dissolved similarly to the soft tablets, whereas the [redacted] batch (hardness of [redacted] dissolved more slowly.

- Formulations: Both the ≤ 100 rpm methods discriminated between the reference and test batches. This supports the use of ≤ 100 rpm method.
- Stressed batch testing: Most of the studies are performed with the ≤ 100 rpm method, with a single exception. Again, no f2 testing is provided to make an objective evaluation, and these results are inconclusive.
- Schwartz Pharma Lots: No differences between the ≤ 100 rpm methods were demonstrated. This supports the use of ≤ 100 rpm method.

CMC - We recommend that the ≤ 100 rpm paddle speed be used. We acknowledge the physicochemical limitations of this drug regarding dissolution testing. Specifically, solubility, tablet hardness, drug substance particle size, disintegration time, etc., have only partially understood effects on dissolution performance in this case. We also recognize that the proposed method and media contain elements ≤ 100 rpm, which introduce compensations ≤ 100 rpm.

To accommodate these limitations but which may tend to minimize otherwise relevant dissolution variability. Given these physicochemical and methodological limitations, we feel that ≤ 100 rpm provides a clearer distinction of the true dissolution behavior that may better correlate with drug product quality and performance. The cited occurrence of ≤ 100 rpm testing at ≤ 100 rpm better reflects the physicochemical limitations and their impact on performance.

OSI response:
OSI agrees.

Question 6:
Impurities:

Does the Agency agree with OSI's approach to setting the specification for impurities in TarcevaTM tablets? If the Agency disagrees with the approach taken by OSI then would the Agency provide their position on this matter?

FDA response:

No, we do not agree the NDA setting for the impurity specifications. Without appropriate batch data, it is difficult to justify the proposed limits for total impurities, unspecified impurities, and degradants. Please explain why do you propose to remove the visual inspection of Tablets. With regard to the dissolution, please refer to the response to question 5, above.

OSI presented information on an overhead.

FDA response:

Your approach appears reasonable at this time. Full evaluation is a NDA review issue. We understand OSI's plan to incorporate a visual inspection of tablets criteria into the appearance testing.

Changes in analytical methods for erlotinib HCl and TarcevaTM tablets.

Question 7:

Does the Agency agree that OSI's approach for the analytical bridging studies will support the adoption of these improved analytical methods for the future release & stability testing of erlotinib HCl and TarcevaTM tablets? If not, would the Agency provide an indication of what additional studies should be undertaken in order that OSI can conclude this activity?

FDA response:

Your approach appears reasonable. To bridge the old to the new analytical method, appropriate validation and comparative data (e.g., specificity, sensitivity, variability LOD, LOQ, etc.) are required. In addition, the particle size distribution of drug substance may also affect the quality and stability of the finished tablets (e. g. friability, dissolution, stability, etc.). The drug product batches compared may not share the same physical characterization. Appropriate comparative data need to be provided.

Erlotinib HCl stability data package anticipated at NDA filing.

Question 8:

Does the Agency agree that, subject to continued demonstration of erlotinib hydrochloride stability in all of our stability studies, the revised primary stability data package will be sufficient to support the assignment of an appropriate re-test period of _____ for erlotinib HCl? If no, can the Agency provide their position on this matter.

FDA response:

In order to assign _____ re-test period for the drug substance, acceptable real-time long-term data out to _____ years should be provided with _____ acceptable accelerated data at the time of submission. The determination of the adequacy of any proposed drug substance re-test period is a review issue. We remind you that the value of supporting stability data in establishing a re-test period is an NDA review issue.

OSI presented information on an overhead.

FDA response:

Your approach appears reasonable to establish a _____ retest period pending thorough review of the NDA.

TarcevaTM tablets stability data package anticipated at NDA filing.

Question 9:

Does the Agency agree that, subject to continued demonstration of stability in all of our studies, the proposed primary stability data package will be sufficient to support the assignment of an appropriate expiration period of 2 years for TarcevaTM tablets? If no, can the Agency provide their position on this matter.

FDA response:

No. In order to assign a 2-year drug product shelf-life, acceptable real-time long-term data out to _____ years should be provided with _____ acceptable accelerated data at the time of submission. The

determination of the adequacy of any proposed expiry period is a review issue. We remind you that the value of supporting stability data in establishing a shelf-life is an NDA review issue.

OSI presented information on an overhead.

FDA response:

Your approach appears reasonable to establish a 2-year shelf-life pending a thorough review of the NDA.

**Scope of information pertaining to the starting materials ()
that we propose to include in our NDA.**

Question 10:

Does the Agency agree that the information pertaining to the erlotinib HCl starting materials proposed for inclusion within the NDA is adequate? If no, can the Agency elaborate on what would constitute adequate information?

FDA response:

Yes, we agree.

Filing, format & content of the CMC sections of our upcoming NDA.

Question 11:

Does the Agency agree with OSI's approach to the compilation of the CMC component of the application including the provision of the "regional information"?

FDA response:

From the technical CMC perspective, your approach appears reasonable. However, CTD format may not be deviated from. Please seek appropriate Agency concurrence at CTD@CDER.FDA.GOV that your proposal fits in with the broader scope of the CTD format.

Scheduling of pre-approval inspection for our contracted quality control, manufacturing and packaging facilities.

Question 12:

In light of the high probability of a "rolling" NDA submission and that the CMC section may be submitted several months prior to the final NDA components, when will the FDA request site inspections and will the Agency notify OSI when the inspection requests have been submitted?

FDA response:

As is our usual practice, we will request all inspections for all listed sites shortly after we receive the appropriate CMC modules of your submission. We do not have to wait for the entire NDA package to be submitted to submit inspection requests. However, it is not within our purview, practice, or policy to discuss inspection scheduling with the applicant. Furthermore, we remind you that at the time the appropriate CMC modules are submitted all sites should be ready for pre-approval inspection.

IND 53,728
Meeting Minutes
Page 6

The FDA requested the sponsor to submit the information they presented at the meeting (overheads) to the IND.

Overheads presented by OSI at the meeting are attached

The meeting was concluded at 12:30pm.

**APPEARS THIS WAY
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Topics for Discussion
FDA Pre-NDA (CMC) Meeting: 11-Jul-03

- Question 5: Dissolution Methodology**
- Question 8: Drug substance stability - clarification of the Agency position**
- Question 9: Tarceva™ tablet stability - clarification of the Agency position**
- Question 6: Tarceva™ tablet specifications**
- clarification of approach to setting impurity specifications
 - explanation for removal of tablet visual inspection
- Question 7: Analytical methods**
- clarification of approach to “bridging” between “old” & “new” methods
 - approach to “bridging” dissolution methodology
- Question 1: Drug substance particle size - specification criteria**
- Question 3: [] to be filed to the NDA**
- Question 10: CTD submission**
- Clarification “However, CTD format may not be deviated from”
 - Alternative forum for discussion
 - Continuous Marketing Application Pilot 1 – Reviewable Units For Fast Track Products

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and/or confidential

commercial information

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/s/

Paul Zimmerman
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Richard Lostritto
7/24/03 05:09:54 PM

MEETING MINUTES

MEETING DATE: April 11, 2003 **TIME:** 1:30pm **LOCATION:** room B

Drug Name: OSI-774 **IND:** 53,728 sn300 **Type of meeting:** Biopharm/CMC

Sponsor: OSI Pharmaceuticals **Preparation package:** dated March 21, 2003
(meeting request fax received February 27, 2003)

FDA Invitees, titles and offices:

Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
Martin Cohen, M.D., Medical Officer
Richard Lostritto, Ph.D., Chemistry Team Leader
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Michael Staschen, Ph.D., Biopharmaceutics Reviewer
Brain Booth, Ph.D., Biopharmaceutics Reviewer
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:

OSI Pharmaceuticals Inc.
Christine Boisclair, Director, Regulatory Affairs
Charmaine Quarterman, PhD, Director, Manufacturing & Clinical Supplies
Robert Simon, Vice-President, Global Regulatory Affairs & CMC
Darshan Wariabharaj, Regulatory Affairs Manager
Roche
Kenneth Oh, Senior Manager, Regulatory Affairs

Meeting Objective(s):

To seek agency agreement on an acceptable dissolution method for Tarceva tablets.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1:

Does the Agency agree that the in vitro dissolution data previously submitted and complemented by additional information provided herein supports a waiver for the need to determine bioequivalence of the 100mg tablet given the intention to demonstrate bioequivalence of 6 x 25mg & 150mg tablets and the pharmaceutical equivalence of the 100mg & 150mg tablets?

FDA response:

FDA's response: Yes.

A waiver to determine the bioequivalence of the 100 mg to the 150 mg tablet is granted based on the analysis of the submitted dissolution profiles.

However, we remind you to generate comparative dissolution profiles of all tablet strengths (25, 100, and 150 mg) manufactured at  and Schwarz Pharma using a reliable dissolution method. Twelve tablets should be used and the paddle speed should be set  rpm. This data will allow the Agency to evaluate the pharmaceutical equivalence between the tablets manufactured at  and Schwarz Pharma. If the dissolution comparison between the different sites fails to show equivalence, an in vivo bioequivalence study may be required.

See also our SUPAC-IR Guidance for Industry: "Immediate release solid oral dosage forms. Scale-up and postapproval changes: chemistry, manufacturing, and controls, in-vitro dissolution testing, and in vivo bioequivalence documentation" posted on FDA website.

If PK data in the package insert is generated using [redacted] manufactures tablets, a link between [redacted] and Schwarz Pharma tablets using dissolution profile comparison is needed.

Question 2:

Does the Agency agree that, based on the data provided for the recommended methodologies, the preferred dissolution method ([redacted] using USP Apparatus 2 ([redacted] Paddle) at [redacted] rpm) is acceptable as the commercial QC method?

FDA response:

FDA's response: No.

The acceptability of the dissolution methodology and acceptance criteria are NDA review issues.

We re-iterate that a speed at [redacted] rpm for USP Apparatus 2 ([redacted] Paddle) is not acceptable. We recommend that you consider [redacted] using USP Apparatus 2 at [redacted] rpm as the commercial QC method.

Action items:

The sponsor will submit the information/overheads/etc. presented at the meeting to the IND.

The sponsor plans to discuss the [redacted] RPM issue at a pre-NDA CMC meeting possibly in June 2003.

The meeting was concluded at 2:50pm.

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/s/

Atiqur Rahman
4/15/03 09:33:04 AM

MEETING MINUTES

After the January 28, 2003 FDA pre-meeting, the FDA responses to the sponsor's questions were sent by fax to the sponsor. On February 10, 2003, the sponsor noted (serial number 287) that after reviewing the FDA responses, the meeting scheduled for February 13, 2003 is no longer needed. The FDA responses to the sponsor's questions which were sent by fax to the sponsor are included below.

MEETING DATE: February 13, 2003 **TIME:** 1:30pm **LOCATION:** room 2064 (B)

Drug Name: OSI-774 **IND:** 53,728 **Type of meeting:** EOP2 follow-up

Sponsor: OSI **Preparation package:** dated December 18, 2002
(meeting request dated December 20, 2002)

FDA Invitees, titles and offices:

Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
Martin Cohen, M.D., Medical Team Leader
Gang Chen, Ph.D., Statistical Team Leader
Ning Li, Ph.D., Statistical Reviewer
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Richard Lostritto, Ph.D., Chemistry Team Leader
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Carl-Michael Staschen, Ph.D., Biopharmaceutics
Reviewer
Paul Zimmerman, R.Ph., Project Manager

Sponsor, titles and offices:

OSI Pharmaceuticals Inc:
Christine Boisclair, Director Regulatory Affairs
Robert Simon, Vice President Global Regulatory Affairs
and CMC
Nicole Onetto M.D., Executive Vice President Oncology
Pedro Santabdrbara M.D., Vice President Clinical
Research Oncology
Gary Clark Ph.D, Senior Director Biostatistics and Data
Management

Genentech Inc:
Robert Mass M.D., Associate Director, Oncology
Medical Affairs
Lisa Bell Ph.D, Manager, Regulatory Affairs F.

Hoffman-La Roche Ltd.:
Hans Niefenthaler, Ph.D, Global Regulatory Leader,
Regulatory Affairs

Meeting Objective(s):

To seek agreement on the proposed approach of filing for accelerated approval, the definition of failure regarding eligible patients, and the core efficacy and safety data for such a filing.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

FDA overall comments:

In view of the relatively small number of patients included in your planned submission, it is preferable that results of the ongoing NCIC CTG phase III trial be included in the NDA submission. Accrual to that trial is nearly complete (Feb 2003).

Even including the "intolerant" patients (which we question) you have only a database of approximately 77 patients with a response rate of about 10%. This is an inadequate database to support filing of an NDA for the treatment of lung cancer, the most common fatal malignancy in the United States.

Question 1:

Does the agency agree with our proposal of filing for accelerated approval of Tarceva in refractory NSCLC based on positive data from our completed open-label Phase II trial (A248-1007) complemented with blinded response data from the on-going randomized, placebo controlled Phase III trial (NCIC-CTG BR.21)?

FDA response:

See question 3.

Question 2:

In light of the recent approval of docetaxel in first-line NSCLC in combination with cisplatin, would the agency consider a new proposed definition of "failure" as it relates to the intended patient population in such a filing being "Patients who have failed a platinum and a taxane, either concurrently or in sequence, unless patients are intolerant"?

FDA response:

Patients who are refractory to a platinum and a taxane should constitute the eligible population. Intolerance is a subjective interpretation and should not be in the eligibility definition.

Question 3:

Is the proposed size of the core efficacy database (41 of 57 patients meeting the above definition for study A248-1007 and approximately 56 of 150 patients meeting the above definition for study BR.21) acceptable for the assessment of efficacy?

FDA response:

This is a marginal database to support an approval. We strongly encourage you to await the completion of your Canadian Phase 3 trial to provide a better evaluation of your drug.

Question 4:

Is the proposed size of the core safety database (approximately 440 patients) acceptable for the assessment of safety?

FDA response:

Please include the safety data from the Phase 3 trial in Canada and all other available safety data on the use of this agent.

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/s/

Paul Zimmerman
2/11/03 08:29:25 AM

MEETING MINUTES

MEETING DATE: November 13, 2002 **TIME:** 11am **LOCATION:** room 6002 (G)

Drug Name: OSI-774 **IND:** 53,728 **Type of meeting:** EOP2 follow-up

Sponsor: OSI **Preparation package:** dated October 15, 2002
(meeting request received September 19, 2002)

FDA Invitees, titles and offices:

Robert Temple, M.D., Director, ODE1
Rachel Behrman, M.D., M.P.H., Deputy Office Director
Richard Pazdur, M.D., Division Director
Grant Williams, M.D., Deputy Division Director
Donna Griebel, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Team Leader
Gang Chen, Ph.D., Statistical Team Leader
Ning Li, Ph.D., Statistical Reviewer
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:

OSI Pharmaceuticals Inc.

Christine Boisclair, Director, Regulatory Affairs
Robert Simon, Vice President Global Regulatory Affairs and CMC
Nicole Onetto M.D., Executive Vice President Oncology
Pedro Santabarbara M.D., Vice President Clinical Oncology
Gary Clark, Senior Director Data Management and Biostatistics
Frances Shepherd, M.D., NCIC-CTG
Lesley Seymour, M.D., NCIC-CTG

Roche

Hans Niefenthaler, DRA

Genentech

Cheryl Madsen, Regulatory Affairs
Robert Mass, Genentech

Meeting Objective(s):

To discuss the clinical development program for OSI-774 in relapsed NSCLC including the significance of symptom improvement if survival does not reach the specified target, and the SAP with regard to symptom improvement.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1:

Does the Agency agree with our proposal of filing for accelerated approval of Tarceva™ in third-line NSCLC with our completed open-label Phase II trial (A248-1007) complemented with blinded response data from the ongoing randomized, placebo-controlled Phase III trial (BR.21) (as presented in Section 2.1)?

FDA response:

Before we can answer this question we need to know how many of the 57 patients enrolled in A248-1007 had "failed" more than one chemotherapy regimen and what the response rate was in that patient population. A similar problem exists for study BR.21.

Please provide the definition of "failed". We have defined failed as refractory/intolerant to platinum and a taxane regimen.

After this meeting, the sponsor will provide copies of the slides/information presented at this meeting to the FDA and submit them to the IND.

The sponsor intends to request a follow-up meeting/telecon following the December ODAC.

Question 2:

Does the agency agree that the full analysis of study BR.21 will provide the validation for the conversion of the accelerated approval to full approval and would it allow for the expansion of the indication in line with the protocol design/entry criteria for this study?

FDA response:

This is a review issue. See answer to 1. Be aware that for a single randomized trial to support an NDA, the trial must be well designed, flawlessly executed, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.

No alpha adjustment will be necessary for an interim analysis of blinded response.

Question 3:

If the Agency would not accept blinded data from our pivotal Phase III study, does the Agency have other suggestions for assessing the response rate without jeopardizing the scientific integrity of the study?

FDA response:

We will accept blinded response rate data from the randomized trial.

If the FDA requires the codes, NCI Canada will prove them. These codes will not be provided to the sponsor.

Question 4:

Does the Agency agree that the final analysis of BR.21 will qualify for full approval, provided that at least one of the definitive endpoints, ie, survival (33% improvement) and/or symptom benefit/quality of life demonstrates patient benefit as defined in our analysis plan?

FDA response:

The primary study objective is to compare overall survival. If you do not win on survival then symptoms and Q of L may not be analyzed. It also seems unlikely that a single study claiming a Q of L benefit would suffice to support a marketing application.

Question 5:

Does the Agency agree with the selection of dyspnea, cough and pain as the main disease related symptoms in the clinical benefit assessment?

FDA response:

Yes.

Question 6:

Does the Agency agree that symptoms collected both on the CRF and on the self-assessment questionnaires should be considered independently in the assessment of clinical benefit?

FDA response:

Symptom improvement data based on CRFs and on self assessment questionnaires can be submitted. You should prespecify your symptom benefit analysis plan. If you choose one of the two sources for symptom benefit claims you should evaluate the other source for agreement/correlation.

We encourage the sponsor to submit the final analysis plan prior to unblinding the study.

Question 7:

Does the Agency have other specific comments/recommendations on the current draft statistical analysis plan for BR.21 study, especially regarding symptom benefit/quality of life?

FDA response:

It probably will be most useful to focus on amelioration of specific symptoms rather than on global QOL. In order for us to make that determination you will need to submit your final analysis plan along with CRFs and questionnaires.

The meeting was concluded at 12:30pm.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Paul Zimmerman
11/19/02 11:12:06 AM

Martin Cohen
11/19/02 01:03:55 PM

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301) 594-5775 **FAX:** (301) 827-4590

TO: Christine Boisclair/ OSI
631-962-2023

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 5

Date: November 19, 2002

COMMENTS: Attached please find the November 13, 2002 meeting minutes concerning IND 53,728 .

15 Pages Redacted of
Deliberative Process
§ 552(b)(5)

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



DIVISION OF ONCOLOGY DRUG PRODUCTS

**HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857**

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PHONE: (301) 594-5775 FAX: (301) 827-4590

**TO: Christine Boisclair/OSI
5631-752-3880**

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: October 10, 2002

COMMENTS: The following concern IND 53,728 for OSI-774, serial number 228 dated October 7, 2002.

Your letter, dated October 7, 2002 concerns the possible impact of ODAC recommendations for Iressa on your registration plan for OSI-774 in NSCLC.

We do not believe that there is any impact. Your phase 2 trial appears to be a second-line trial. As docetaxel is approved for that indication there is not an unmet medical need.

Your phase 3 NSCLC trials, first-and second-line, might support accelerated approval based on a surrogate endpoint such as response rate or time to progression if dramatic efficacy results are achieved. This possibility can be more fully discussed during the November 13, 2002 meeting.

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/s/

Paul Zimmerman
10/10/02 10:02:50 AM
CSO

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



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**HFD-150, 5600 Fishers Lane
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PHONE: (301) 594-5775 FAX: (301) 827-4590

**TO: Christine Boisclair/OSI
631-962-2023**

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: September 11, 2002

COMMENTS: The following concern IND 53,728, serial number 208 and is a clarification of the statement "The sample size may be increased as requested" which was sent earlier today.

The proposed change to increase the sample size is acceptable provided that no interim analysis had been done and the decision was made based upon the information not related to the undergoing trial. Please submit the DSMB meeting minute or interim analysis results if any.

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/s/

Paul Zimmerman
9/11/02 11:15:40 AM
CSO

**FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I**



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PHONE: (301) 594-5775 FAX: (301) 827-4590

**TO: Christine Boisclair/OSI
631-962-2023**

FROM: Paul Zimmerman, Project Manager

Total number of pages, including cover sheet 1

Date: September 11, 2002

COMMENTS: The following concern IND 53,728, serial number 208.

The sample size may be increased as requested.

As discussed, please request a meeting/telecon to address the survival and the symptom benefit issues, including justification/rationale regarding the acceptability of the proposed 33% increase in survival rather than a 50% increase, as well as, complete justification/rationale regarding your proposal for approval based on symptom benefit alone.

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/s/

Paul Zimmerman
9/11/02 09:40:25 AM
CSO

MEETING MINUTES

MEETING DATE: July 9, 2002 **TIME:** 10:30am **LOCATION:** room 6002 (G)

Drug Name: OSI-774 **IND:** 53,728 **Type of meeting:** CMC

Sponsor: OSI **Preparation package:** meeting request dated May 15, 2002

FDA Invitees, titles and offices:

Richard Pazdur, M.D., Division Director
Richard Lostritto, Ph.D., Chemistry Team Leader
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Kimberly Benson, Ph.D., Pharmacology Reviewer
John Leighton, Ph.D., Pharmacology Team Leader
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Gene Williams, Ph.D., Biopharmaceutics Reviewer
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices

Christine Boisclair, Director, Regulatory Affairs
Charmaine Quarterman, PhD, Director, Manufacturing & Clinical Supplies
Robert Simon, Vice-President, Global Regulatory Affairs & CMC
Darshan Wariabharaj, Regulatory Affairs Manager
Roche
Hans-Peter Nowotny, PhD, Global Technical Leader
Pharmaceutical Development
Genentech
Kenneth Oh, Senior Manager, Regulatory Affairs

Meeting Objective(s):

To discuss the proposed CMC program for OSI-774 Oral

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

The Sponsors provided an additional meeting information package (presentation) at the meeting commencement.

Question 1:

Does the agency support OSI's designation of starting materials for the synthesis of OSI-774-01?

FDA response:

No. Adequate information to support your claim is not provided. For the [] material listed on page 33, [] Further documentation beyond patent references is necessary to support any claim that the same route of synthesis is used by your multiple suppliers. Since this drug substance involves [] the impurities present in the [] may significantly affect the impurity profile in the final API. Therefore appropriate analytical data from different suppliers [] needs to be provided. The acceptance criteria for the proposed starting materials need to be established.

Meeting Addendum:

The Sponsors commit to provide further data to support the additional claims.

Question 2:

Does the agency accept the ~ test approach for the purpose of adequately demonstrating the [] OSI-774-01?

FDA response:

No, although the — method (replacement pages 37-41) appears promising, more data needs to be provided. We recommend that you either provide adequate comparative data in the NDA to support your proposal, or continue with the — method until such time that adequate comparative data — which is more conclusive can be provided post approval.

Meeting Addendum:

The Sponsors commit to provide more comparative data to support their — method as the regulatory method for —

Question 3:

Does the agency accept that OSI's proposed primary stability data package will be sufficient to support the proposed retest period for API?

FDA response:

Yes, based on the Sponsors presentation and their commitment to provide written follow-up to the IND (including their July 9, 2002 presentation).

Question 4:

Does the FDA agree that OSI adequately demonstrated equivalence of tablets manufactured by — and Schwarz to an extent that complies with the SUPAC guidance relating to Level 3 site changes and that in so doing obviate the need for in vivo bioequivalence testing?

FDA response:

CMC:

No. The Sponsors agree to provide comparative release data and characterization data (dissolution profiles) to support their claim of equivalence.

OCPB:

The SUPAC IR guidance bases the need for *in vivo* bioequivalence testing on 4 factors: components and composition, site, batch size, and manufacturing process. If the composition, batch size, and manufacturing process are not at all altered, and dissolution profiles are sufficiently similar between sites, an *in vivo* bioequivalence study is not needed for a site change. In order to determine if this is the case for your product, we ask that you submit a table of the following format:

		batch 1	batch #
components & composition	ingredient 1	mass	
	ingredient #	mass	
site		site	
batch size		# tablets	
manufacturing process		description or footnote #	
dissolution profile		location of table (page and table #)	

In order to maintain a reasonable size to the table, the dissolution profiles need not be included in the table, but a reference to where the profiles can be found (page and table # in the submission) should be included. The dissolution profiles should be for each unit, not just means across units.

In addition to a table, specify each batch-batch comparison you would like us to assess for similarity and the decision that will arise from a conclusion of similarity.

Note that, from a clinical pharmacology and biopharmaceutics perspective (not a chemistry perspective), if a sufficient amount of Phase 3 data is obtained using the to-be-marketed formulation/site/size/process it may not be necessary to conclude similarity between the Phase 3 drug product and earlier drug products. In this case, similarity need be concluded only if the results from the non-Phase 3 products are judged critical for product labeling and potentially different from what would have been obtained had the to-be-marketed product been studied.

We recommend that you schedule a meeting to discuss the clinical pharmacology and biopharmaceutics data acquired to date and the data planned to be acquired prior to NDA filing. Our general thoughts on what clinical pharmacology and biopharmaceutics data is important for NDA filing can be found in the following guidance documents:

Biopharmaceutics

- Bioanalytical Method Validation
- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations
- Dissolution Testing of Immediate Release Solid Oral Dosage Forms
- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.

Biopharmaceutics (Draft)

- Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis, and Labeling

Chemistry

- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation
- SUPAC-IR Questions and Answers about SUPAC-IR Guidance

- SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum

Clinical Pharmacology

- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro
- Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application
- In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling
- Pharmacokinetics in Patients with Impaired Renal Function
- Population Pharmacokinetics

Clinical Pharmacology (Draft)

- Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications
- General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products
- Pharmacokinetics in Patients With Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

Electronic Submissions

- Regulatory Submissions in Electronic Format; General Considerations
- Regulatory Submissions in Electronic Format; New Drug Applications

Question 5:

Does the agency accept that OSI's proposed primary and supportive stability data package will be sufficient to support the proposed expiration period for drug product?

FDA response:

No. Although your approach is reasonable, the establishment of an expiry period is a review issue. Your NDA primary drug product stability batches (three batches or more per strength) should utilize all of the qualified to-be-marketed drug substance suppliers (at least one batch per supplier). These data should be used to support your proposed expiration period as well. Likewise, your post-approval stability commitment should include annual batches utilizing drug substance batches from each of your qualified suppliers.

Meeting Addendum:

The Sponsors commit to provide further clarification and data to support their claims as discussed at the meeting.

The meeting was concluded at 12pm.

/s/

Paul Zimmerman, Project Manager/date

/s/

Concurrence: _____
Richard Lostritto, Ph.D., Chemistry Team Leader/date

/s/

Concurrence: _____
Gene Williams, Ph.D., Biopharmaceutics Reviewer/date

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/s/

Richard Lostritto
8/9/02 02:33:56 PM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

<p>1. APPLICANT'S NAME AND ADDRESS OSI Pharmaceuticals, Inc. 58 South Service Road, Suite 110 Melville New York USA 11747</p>	<p>4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 021-743</p>
<p>2. TELEPHONE NUMBER (Include Area Code) (631) 962-2156</p>	<p>5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>3. PRODUCT NAME Tarceva™ (erlotinib hydrochloride)</p>	<p>6. USER FEE I.D. NUMBER 4697</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
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<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE </p>	<p>TITLE Senior Director, Global Regulatory Affairs</p>	<p>DATE January 20, 2004</p>
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MEETING MINUTES

MEETING DATE: December 20, 2000 **TIME:** 9am **LOCATION:** room 6002 (G)

Drug Name: OSI-774 **IND:** 53,728 **Type of meeting:** EOP2

Sponsor: OSI Pharmaceuticals. **Preparation package:** dated November 21, 2000
(meeting request received October 12, 2000)

FDA Invitees, titles and offices:

Robert Temple, M.D., Director, ODE1
Rachel Behrman, M.D., M.P.H., Deputy Office Director
Richard Pazdur, M.D., Division Director
John Johnson, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Officer
James Krook, M.D., ODAC representative
Gang Chen, Ph.D., Statistical Team Leader
Ning Li, Ph.D., Statistical Reviewer
Atiqur Rahman, Ph.D., Biopharmaceutics Team Leader
Lydia Kieffer, Pharm.D., Biopharmaceutics Reviewer
Kimberly Benson, Ph.D., Pharmacology Reviewer
John Leighton, Ph.D., Pharmacology Team Leader
Li-Shan Hsieh, Ph.D., Chemistry Reviewer
Rebecca Wood, Ph.D., Chemistry Team Leader
Paul Zimmerman, R.Ph., Project Manager
(attendees are bolded)

Sponsor, titles and offices:

Dr. Paul Nadler, Vice President Medical Affairs, OSIP
Dr. Nicholas Bacopoulos, Head of R&D, OSIP
Dr. John Slack, VP, Preclinical Development, OSIP
Dr. Arthur Bruskin, Executive VP Operations, OSIP
Ms. Christine Boisclair, Director, Regulatory Affairs
Dr. Charmaine Quarterman, Director, Preclinical Development, OSIP
Dr. Eric Rowinsky, Director, Clinical trials, CTTC
San Antonio, (Clinical Investigator)
Dr. Philip Bonomi, Director, Medical Oncology, Rush Presbyterian/St. Lukes, Chicago, (Clinical Investigator)
Dr. Jay Greenblatt, NCI, DCTD

Meeting Objective(s):

To discuss the on-going clinical development program for OSI-774.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Question 1

In a population of approximately 100 patients with metastatic NSCLC and disease progression after a first line regimen and docetaxel, would an objective response rate of approximately 15% with a duration of response of 3-4 months currently be sufficient for accelerated approval?

FDA response:

The FDA discourages a development program focused on gaining accelerated approval based on phase 2 studies in extensively pretreated patient populations refractory to multiple standard therapies. Accelerated approval is based on a surrogate endpoint (usually response rate) that is reasonably likely to predict clinical benefit. The FDA does not believe that response rates in the range of 10% to 15% and lasting 3-4 months are "reasonably likely" to predict clinical benefit. What would constitute an acceptable response rate and response duration for consideration of accelerated approval is a review issue. The FDA will not commit to specific numbers in advance.

If you wish to pursue development in heavily pretreated patients the FDA strongly suggests that randomized studies be performed. One possible design is randomization of the investigational treatment versus therapy based on physician's choice. That choice might include other chemotherapy regimens or best supportive care.

By the time that NSCLC patients reach third-line therapy and breast cancer patients reach third and fourth-line therapies most have poor PS and are not suitable for clinical trials. Assuming that one of the eligibility criteria for the proposed study would be a ECOG PS 0-2 you will be dealing with a highly selected patient population who presumably have less aggressive disease. Treatment conclusions, based on these patients, may not be generalizable.

The FDA also strongly recommends that the sponsor perform two trials for . indication since results of a single trial might not be overwhelmingly positive. It should further be mentioned that pursuing an accelerated approval strategy is risky since another drug might be approved for the proposed indication while the sponsor's studies are ongoing.

Question 2

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FDA response:

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Question 3

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FDA response:

Question 4

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FDA response:

Question 5

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FDA response:

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FDA Clinical Pharmacology and Biopharmaceutics Comments

Phase I studies in healthy volunteers

1. Please submit results from clinical trials in which PK studies were performed (248-001, -002, -004, -005, -006,) in order for the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) to provide suggestions into the development of OSI-774.
2. Based on the briefing packet, the dose of 150 mg/day for all subsequent clinical trials was partially based on the observed PK data obtained from the clinical trials above. Please submit this information to the Agency for our review.

Phase II studies in Advanced Cancer Patients

1. Please submit the PK data as soon as it becomes available for study A2481007 in NSCLC patients and any other studies not included in the packet in which the PK characterization of OSI-774 was performed.

Future Clinical Plan & Purpose of Proposed Meeting

1. We encourage the sponsor to submit any protocol proposals for review on the design of clinical trials with drug interaction analysis as an objective.
2. We remind the sponsor that a PK study in the targeted population upon NDA submission should be submitted.
3. The sponsor should attempt to make PK/PD correlations whenever possible throughout the development of OSI-774.
4. All assay validation data should be submitted from all clinical trials in which PK analysis was conducted.
5. Complete dissolution and bioavailability studies should be submitted.
6. If the clinical trial formulation is different from the to be marketed formulation, results of a bioequivalence study will be required upon NDA submission.

Additional Regulatory concerns

Financial Disclosure Final Rule:

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective, or that makes a significant contribution to demonstration of safety.

Please refer to "Financial Disclosure by Clinical Investigators Final Rule Summary".

Pediatric Exclusivity:

Under the Food and Drug Administration Modernization Act, you have the opportunity for an exclusivity extension if this drug is appropriate for an indication in pediatrics. If you choose to pursue pediatric exclusivity, your plans for a pediatric drug development, in the form of a Proposed Pediatric Study Requirement (PPSR), should be submitted so that we can consider issuing a Written Request.

Please refer to the "Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505 A of the Federal Food, Drug and Cosmetic Act" at Drug Information Branch (301) 827-4573 or <http://www.fda.gov/cder/guidance/index.htm>. You should also refer to our division's specific guidance on pediatric oncology Written Requests which is at <http://www.fda.gov/cder/guidance/3756dft.htm>.

Pediatric Final Rule:

Please note that you will need to address the December 2, 1998 Pediatric Rule (63 FR 66632) when you submit your NDA unless your product/indication has been designated an Orphan Drug. You may be eligible for a waiver under 21 CFR 314.55(c). Please refer to <http://www.fda.gov/ohrms/dockets/98fr/120298c.txt>.

Final Protocols

Please refer to the December 1999 DRAFT "*Guidance for Industry - Special Protocol Assessment*" (posted on the Internet 2/8/2000) and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A desk copy of this cover letter should be submitted to the project manager.

The meeting was concluded at 10:30am.

/s/

/s/

Paul Zimmerman, Project Manager/date
Minutes preparer

Concurrence: _____
Martin Cohen, M.D., Medical Officer/date

/s/

Martin Cohen
1/3/01 08:34:23 AM