U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Nasr, Samya, M.D. 1/28/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Springs, MD 20993

WARNING LETTER

CERTIFIED MAIL
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Ref: 10-HFD-45-01-03

Samya Nasr, M.D.
1500 East Medical Center Drive
L2221 Women's Hospital, SPC 5212
Ann Arbor, MI 48109-5212

Dear Dr. Nasr:

Between July 20 and August 25, 2009, Ms. Barbara Rusin and Ms. L'Oreal Fowlkes, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

Protocol CP-AI-005, entitled "A Phase 3, Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial with Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* Requiring Frequent Antibiotics (AIR-CF2)." of the investigational drug Aztreonam Lysinate, performed for Corus Pharma.

Protocol CP-AI-007, entitled "A Phase 3, Double-Blind, Multicenter, Multinational, Randomized, Placebo-Controlled Trial Evaluating Aztreonam Lysinate for Inhalation in Cystic Fibrosis Patients with Pulmonary *P. aeruginosa* (AIR-CF1)," of the investigational drug Aztreonam Lysinate, performed for Corus Pharma.

Protocol 08-108, entitled "A Multi-Center, Double-Blind, Placebo-Controlled Randomized, Efficacy and Safety Study of Denufosol Tetrasodium (INS37217) Inhalation Solution in Patients With Mild Cystic Fibrosis Lung Disease," of the investigational drug Denufosol Tetrasodium, performed for Inspire Pharmaceuticals.

Protocol 08-110, entitled "A Phase 3, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of Denufosol Tetrasodium Inhalation Solution in Patients With Cystic Fibrosis Lung Disease and FEV1 ≥ 75% but ≤ 110% Predicted," of the investigational drug Denufosol Tetrasodium, performed for Inspire Pharmaceuticals.

Protocol 0000726, entitled "A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Efficacy and Safety of ALTU-135 Treatment in Patients with Cystic Fibrosis-Related Exocrine

Pancreatic Insufficiency," of the investigational drug ALTU-135, performed for Altus Pharmaceuticals.

Protocol 0000767, entitled "An Open-Label Clinical Study Evaluating the Long-Term Safety of ALTU-135 for the Treatment of Patients with Cystic Fibrosis-Related Exocrine Pancreatic Insufficiency (ALTUS-767)," of the investigational drug ALTU-135, performed for Alnara Pharmaceuticals.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected. From our review of the establishment inspection report, the documents submitted with that report, and your written responses dated September 16, 2009, and November 24, 2009, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, FDA investigators presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You failed to obtain the informed consent of each human subject, in accordance with 21 CFR part 50 [21 CFR 312.60].

FDA's regulations at 21 CFR 50.20 state that except as provided in 21 CFR 50.23 and 21 CFR 50.24, no investigator may involve a human being as a subject in research covered by the regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. The regulation specifies that an investigator shall seek such informed consent only under circumstances that provide the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

Section 50.27 of FDA's regulations further states that except as provided in 21 CFR 56.109(c), informed consent shall be documented by the use of a written consent document, which is to be signed by the subject or the subject's representative at the time of consent.

a. The objective of Protocol CP-AI-005 was to assess the safety and efficacy of a 28-day treatment with Aztreonam Lysinate for Inhalation (Cayston™) and the ability of this treatment to maintain or improve clinical status following a 28-day course of Tobramycin Solution for Inhalation therapy in cystic fibrosis (CF) patients with pulmonary *Pseudomonas aeruginosa*. The original informed consent form approved by the IRB on April 7, 2005, however, incorrectly stated that the purpose of the study was to see if an investigational inhaled antibiotic, Aztreonam Lysinate for Inhalation, "can stop Pa *[Pseudomonas aeruginosa]* from coming back into your lungs."

You were notified by **(b)(4)** in an e-mail dated June 28, 2005, that the sponsor required a number of revisions to be made to the approved informed consent form, including these: "(Purpose): 2nd to last sentence, please change 'new drug' to 'investigational or experimental drug'. Please change the last sentence in this section to correctly reflect the purpose of this study - to see if Al [Aztreonam Lysinate] is safe and effective in CF patients with lung infections, not to see how well Al [Aztreonam Lysinate] can stop PA *[Pseudomonas aeruginosa]*from coming back into patients *[sic]* lungs." Your site resubmitted a revised informed consent form (version 2) to the IRB; that form was approved on August 25, 2005.

In an e-mail dated September 12, 2005, however, the sponsor informed you that there were still problems with the revised informed consent form. The sponsor noted that the statement in section 2.1 of the informed consent form stating that Aztreonam Lysinate can stop *Pseudomonas aeruginosa* from coming back to your lungs could be considered coercive because Aztreonam Lysinate was still an investigational drug. According to the e-mail, you had requested that the sponsor approve shipment of the study drug and allow patients to be enrolled with the current IRB-approved version of the informed consent form. The sponsor approved the shipment of study drug to your site with the conditions that you submitt a revised informed consent form addressing all outstanding issues to the IRB and that you reconsent all patients enrolled in the study. The sponsor further approved your use of the current IRB-approved version of the informed consent form, provided that on the informed consent form you document that (1) female patients of childbearing potential were notified of the serum pregnancy test at Visit 1; (2) all patients consented with the current version were notified that they would be required at a later date to reconsent, using a revised consent form; and (3) all patients consented with the current IRB-approved version of the informed consent form were notified that Aztreonam Lysinate has not been proven to stop *Pseudomonas aeruginosa* from coming back into the lungs, as is implied in section 2.1, and

that the purpose of the study was actually to see if Aztreonam Lysinate is successful in treating *Pseudomonas aeruginosa* lung infections in CF patients. In an e-mail dated September 14, 2005, you were again reminded to send the updated, corrected informed consent form to the IRB. The IRB approved version 3.1 of the informed consent form on March 9, 2006.

FDA's investigation found that for all six subjects enrolled into the study, there was no documentation on either the informed consent form or the assent forms that you told the subjects about the true purpose of the study, as required by the sponsor. In addition, handwritten notes documenting the sponsor's requirements regarding the serum pregnancy test and the reconsenting of subjects were either (1) not documented on the informed consent form and/or the assent form, and/or (2) not consistently documented on all copies of the informed consent form and/or the assent form. Furthermore, Subjects 004, 005 and 006 were not reconsented with revised informed consent form version 3.1 until July 2006, approximately three months after the IRB had approved version 3.1.

In your written responses, you acknowledged that you failed to recognize any substantive difference between articulations of the study purpose as stated in informed consent form version 2 versus that in the protocol. You also acknowledged that you failed to correct this oversight in a timely manner when the sponsor first brought it to your attention in July 2005. You further stated that while handwritten statements were added to the consent forms prior to the subject's/parent's consent, you now recognized and understand that these statements should not have been added to the consents at any time. Your corrective actions to this finding included the development of new standard operating procedures (SOPs) including: "Completing the eResearch Application" to ensure that a member of the study team reviewed the consistency of the information in the protocol, investigator's brochure, consent document and the eResearch submission; "Responding to Monitoring Reports" which required prompt response to any observations and a formal report to the IRB for further consideration; and "Obtaining Informed Consent" which will prohibit handwritten statements on the informed consent form.

Your response is inadequate. In review of the SOP entitled "Standard Operating Procedure for eResearch Submissions", there were no procedures detailing the methods used by your site to verify consistency of all elements between the informed consent form, protocol, investigator's brochure and eResearch submission as noted in your promised corrective action. Your assertion that handwritten statements were added prior to consents being given to the subjects could also not be verified. In many cases the copy of the informed consent form in your research record was different from the copy found in the medical record.

b. No informed consent form and/or assent form could be found for Subjects 385-003 and 385-007, who were screened for Protocol 08-108. However, study-related screening procedures were performed on these subjects (on February 22, 2007, and September 5, 2007, respectively).

In your written responses, you acknowledged this finding. You noted that your corrective action to prevent the recurrence of this finding included the development of new SOPs including "Obtaining Informed Consent", "Document Management and Storage", and "Patient Completion/Early Termination/Screen Failure" and the education of your study team on these SOPs. These corrective actions appear adequate.

c. The following was noted for Protocol 08-110:

i. The informed consent documents for Subjects 385-101 and 385-102 did not have check marked responses to show whether consent was given either to participate in or to abstain from having saliva collected for P2Y2 genotyping. However, you collected these subjects' saliva samples and sent them to the central laboratory for testing.

ii. The original informed consent document signed by Subject 385-104 and dated January 9, 2009, did not have a checkmark in the box noting whether the subject elected to participate in or to abstain from having saliva collected for P2Y2 genotyping. However, you collected a saliva sample from this subject and sent it to the central laboratory for testing. A checkmark showing that the subject elected to participate in the collection of saliva for genotyping was subsequently made on February 13, 2009, which was after the time of saliva sample collection.

In your written responses, you acknowledged this finding and stated that your site detected the error in failing to get appropriate consent "before any genetic analysis" was performed on the samples from these subjects. Your corrective action included a policy for changing the check box for the optional tests to the last

page of the informed consent document. You stated that if the IRB endorsed this new approach, it would be included in the newly created SOP on "Obtaining Informed Consent".

Your response is inadequate. We found no evidence that your site detected this error before genetic analysis was performed on these samples. Rather, it appears that the lack of consent of subjects to having samples taken for testing was identified during the FDA inspection. Furthermore, documents provided by you during the inspection showed that when the sponsor was informed of the lack of consent of Subjects 385-101 and 385-102 to the testing in an email dated July 23, 2009, the sponsor stated that the samples were to be destroyed. The sponsor's email made no mention that the samples had not undergone any genetic testing. In addition you provided no evidence to show that the error was detected before testing occurred. We also note that even if genetic analysis was not performed, this does not negate the fact that samples should not have been drawn from subjects without their consent.

d. The informed consent documents signed by Subjects 009-001 and 009-002 for Protocol 0000726 did not include a reference to testing of blood samples for Vitamin K levels. However, you tested these subjects' blood samples for Vitamin K.

In your written responses, you acknowledged this finding and stated that you had developed an SOP for "Managing Investigational Materials and Supplies" which would serve as corrective actions to prevent the recurrence of this finding.

Your response is inadequate. You provided no corrective action plan to ensure that only those tests included in the informed consent document would be performed on study subjects. In addition, in review of the SOP for "Managing Investigational Materials and Supplies", your procedure stated that your staff would examine the "contents of study kits to validate that only collection tubes for IRB-approved tests are included in the kit before it is delivered to the research phlebotomy team." There were no clear procedures for how your site would verify that the test or tests in the kit are in line with the currently approved protocol or protocol amendment that is in effect at the time of arrival of the kit.

2. You failed to ensure that the investigations were conducted according to the investigational plans [21 CFR 312.60].

a. Protocol 08-110 stated that either a chest X-ray must be performed at Visit 1, or there must be a chest X-ray, high resolution computed tomography (HRCT), chest CT scan, or MRI of the lung performed 12 months before Visit 1. Subject 385-101 was enrolled into the study on September 10, 2008, and received study drug on September 17, 2008 at Visit 2. However, no chest X-ray was performed for this subject at Visit 1, and there is no documentation indicating that either a chest X-ray, high resolution computed tomography (HRCT), chest CT scan, or MRI of the lung had been performed 12 months before Visit 1. Source documents confirm that the chest X-ray for this subject was taken on September 17, 2008, approximately an hour after the subject had received the first dose of investigational drug.

In your written responses, you acknowledged this finding and stated that you had developed SOPs for "Protocol Deviations and Study Amendments" and "Document Management and Storage" which would serve as corrective actions to prevent the recurrence of this finding.

We acknowledge that in your letters, you describe the corrective actions you have taken to prevent the recurrence of this finding. While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here, raising concerns regarding the adequacy of human subject protections at your site.

b. Protocol 0000726 defined an Adverse Event (AE) as any untoward medical occurrence in a patient or clinical investigation patient, regardless of its causal relationship to study drug. According to the protocol, all AEs were to be collected beginning on Study Day B1, and would continue inclusive of the 2-week follow-up visit. In addition, the protocol stated that all study staff were responsible for ensuring that complete safety information was recorded on the case report form (CRF). FDA's investigation found that several AEs noted in the progress reports were not recorded onto the CRF. Examples include the following:

Subject	AE	Date(s) AE noted in the source records
009-001	Flatulence	10/22/07 10/29/07 11/05/07
009-001	Crackles and Diminished Breath in Right Lung	10/24/07 10/29/07
009-002	Bilateral Crackles in Bases of Lungs	12/03/07
009-002	Darkened Sputum	12/03/07
009-002	Bilateral rhonchi noted in the upper and lower lobes of the lungs	12/06/07
009-005	Mild Rhonchi	03/03/08
009-005	Boggy, swollen turbinates with cloudy discharge	03/05/08 - 3/07/08

In your written responses, you stated that with some exceptions, including the items noted with an asterisk (*) above, you acknowledged this finding. You stated that you would provide documentation that those exceptions were reported. You further stated that as you were conducting the protocol, you interpreted "untoward medical occurrence" to mean something new or different in a patient, and your corrective action to prevent this finding is to more carefully analyze the protocol for unclear language. In addition, you developed an SOP for "Adverse
Events" to ensure that similar deviations and misunderstandings were avoided in future studies.

For the items noted with an asterisk (*) above, there was no supporting documentation found in the information you provided in your written responses to verify that these AEs were reported in the CRF. However, we acknowledge that in your response letters you describe the corrective actions you have taken to prevent this from happening in the future. While these corrective actions appear appropriate, it was the absence of such measures during the conduct of these trials that led to the violations listed here.

c. Protocol 08-108 specified that all medications that the patient has taken from 28 days prior to Visit 1 (screening visit) through the follow-up visit were to be recorded in the CRF. The generic name of the drug, dose, route of administration, duration of treatment (including start and stop dates), frequency, and indication were also to be recorded for each medication.

i. For Subject 385-002, Lacinex chewable tablets, taken by the subject and identified in the progress note dated November 1, 2007, were not listed on the prior and concurrent medication and therapies log.

ii. For Subject 385-004, Benadryl, taken by the subject and identified in the progress note dated May 23, 2007, was not listed on the prior and concurrent medication and therapies log.

In you written responses you acknowledged this finding. You, however, provided no corrective action to prevent the recurrence of this finding.

3. You failed to promptly report to the IRB all changes in research activities and made changes in the research without IRB approval [21 CFR 312.66].

FDA's regulations at 21 CFR 312.66 state that an investigator shall not make any changes to the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects. Protocol CP-AI-005 was approved by the IRB on April 7, 2005. In monitoring letters dated February 26, May 9, July 18, and September 1, 2006, you were asked whether you had requested approval from the IRB for tote bags, diary cards, and subject calendars that were given to subjects participating in the study. You failed to inform the IRB of the changes you had implemented to the research by distributing these items. The IRB was not made aware of these changes until March 22, 2007, which was one month before the study was terminated with the IRB (on April 12, 2007).

In your written response, you acknowledged these findings and stated that while the IRB eventually approved

the use of the subject diary cards, by that time, enrollment had ended. Your corrective action was the development of a new SOP for “Protocol Deviations and Study Amendments” to assure appropriate procedures are followed to avoid unauthorized deviations, and in the event they occur, proper procedures were followed for promptly reporting and correcting them. You also state that study team members will be re-educated about "the IRB application and amendment processes" and to the fact that all items and services given to study subjects must be approved by the IRB in advance. These corrective actions appear appropriate.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at 301-796-3397; FAX 301-847-8748. Your written response and any pertinent documentation should be addressed to:

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Sincerely yours,
{See appended electronic signature page}
Leslie K. Ball, M.D.
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/s/

LESLIE K BALL
01/28/2010

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