**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| 6000 Metro Drive, Suite 101<br>Baltimore, MD 21215<br>(410)779-5455 Fax:(410)779-5707 | 9/12/2016-10/3/2016*<br>FEI NUMBER<br>3012718293 |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kieron M. Dunleavy , MD

| FIRM NAME | STREET ADDRESS |
|---|---|
| Kieron Dunleavy | National Institutes of Health, Building 10, Room 4n115 |
| CITY, STATE, ZIP CODE, COUNTRY<br>Bethesda, MD 20892-0001 | TYPE ESTABLISHMENT INSPECTED<br>Clinical Investigator |

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

**DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:**

## OBSERVATION 1

An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

A. Protocol 14-C-0157-9577 (TEDDI-R) requires any Grade 3 to Grade 5 serious adverse events (SAE) be reported to the sponsor, whether or not they are considered related to the investigational drugs/intervention via CTEP-AERS within 24 hours of learning of the AE, following by a complete expedited report within 5 calendar days of the initial 24-hour report. In addition, Grade 1 or Grade 2 SAEs, resulting in hospitalization for 24 hours or greater must be reported to the sponsor within 10 calendar days. The following SAEs were not reported to the sponsor within the timeframe required by the protocol:

| SAE | Date of Event | Date CI Became Aware | Date Reported to Sponsor | Days Elapsed |
|---|---|---|---|---|
| Subject 1010003 [redacted] | | | | |
| Grade 3 Lung Infection – Pneumonia | December 8, 2014 | December 8, 2014 | February 25, 2015 | 79 days |

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|---|---|---|---|---|
| Pantocytopenia:<br><br>Grade 3 Anemia, Grade 4 Decreased Platelet Count<br><br>Grade 4 Decreased Neutrophil Count | December 8, 2014 | December 8, 2014 | February 25, 2015 | 79 days |
| Grade 3 Diarrhea | December 30, 2014 | January 20, 2015 | March 4, 2015 | 43 days |
| Grade 2 flu-like symptoms, resulted in hospitalization from December 30, 2014 to January 11, 2015 | December 30, 2014 | January 20, 2015 | March 4, 2015 | 43 days |
| Grade 4 Lung Infection – pneumonia | March 9, 2015 | March 23, 2015 | April 1, 2015 | 9 days |
| Grade 3 Diarrhea | March 5, 2015 | March 23, 2015 | April 1, 2015 | 9 days |
| Grade 4 sepsis | March 8, 2015 | March 23, 2015 | April 1, 2015 | 9 days |
| Death | March 21, 2015 | March 23, 2015 | April 1, 2015 | 9 days |
| Subject 1010009 ([redacted] | | | | |
| Grade 4 Lung | May 3, 2015 | May 4, 2015 | May 13, 2015 | 9 days |

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|---|---|---|---|---|
| Infections - pneumocystis and aspergillus infections | | | | |
| Grade 4 Sepsis | May 4, 2015 | May 4, 2015 | May 13, 2015 | 9 days |
| Death | May 16, 2015 | May 16, 2015 | August 5, 2015 | 81 days |
| Subject 1010011 ([redacted]) | | | | |
| Grade 3 Lung Infection-suspected aspergillosis | November 4, 2015 | December 7, 2015 | May 25, 2016 | 170 days |
| Grade 4 mucositis | September 3, 2015 | September 14, 2015 | Not reported | |
| Grade 3 Hand Foot Syndrome | August 21, 2015 | September 14, 2015 | Not reported | |
| Grade 3 mucositis | July 25, 2015 | August 3, 2015 | Not reported | |
| Subject 1010015 ([redacted]) | | | | |
| Grade 3 Aspergillus Lung Infection | March 2, 2016 | March 2, 2016 | May 25, 2016 | 84 days |
| Grade 4 Decreased Platelet Count | March 28, 2016 | April 7, 2016 | Not reported | |

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|---|---|---|---|---|
| Grade 4 Anemia | March 28, 2016 | April 7, 2016 | Not reported | |
| Grade 3 Pneumocystis jiroveci (PCP) pneumonia | February 24, 2016 | February 24, 2016 | May 25, 2016 | 91 days |
| Subject 1010001 ([redacted]) | | | | |
| Grade 3 Syncope | January 16, 2015 | January 27, 2015 | February 27, 2015 | 32 days |
| Subject 1010004 ([redacted]) | | | | |
| Death | March 10, 2015 | March 10, 2015 | March 17, 2015 | 7 days |
| Subject 1010005 ([redacted]) | | | | |
| Grade 3 Lung infection | April 2, 2015 | April 22, 2015 | June 30, 2016 | 456 days |
| Subject 1010006 ([redacted]) | | | | |
| Grade 4 Febrile Neutropenia | May 5, 2015 | May 14, 2015 | Not reported | |
| Grade 4 Febrile Neutropenia | May 27, 2015 | June 9, 2015 | Not reported | |
| Subject 1010012 ([redacted]) | | | | |

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|---|---|---|---|---|
| Grade 3 Febrile Neutropenia with important medical events resulting in hospitalization December 12, 2015 to December 16, 2015 | December 12, 2015 | January 4, 2016 | Not reported | |
| Subject 1010013 ([redacted]) | | | | |
| Grade 3 encephalitis infection | November 22, 2015 | November 23, 2015 | November 27, 2015 | 4 days |
| Subject 1010014 ([redacted]) | | | | |
| Grade 3 Lung Infection | January 19, 2016 | May 9, 2016 | May 31, 2016 | 23 days |
| Grade 4 Febrile Neutropenia | February 23, 2016 | March 1, 2016 | Not reported | |

B. Protocol 14-C-0157-9577 (TEDDI-R) requires all Events of Special Interest be reported to the sponsor via CTEP-AERS within 24 hours of awareness even if they do not meet serious criteria. The protocol lists major hemorrhage as an Event of Special Interest and notes GI bleed as an example of major hemorrhage. On May 18, 2016, Subject 1010015 ([redacted]) experienced Grade 3 GI Bleed and received blood and platelet transfusions; however, this Event of Special Interest was not reported to the sponsor as required by the protocol.

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C. Protocol 14-C-0157-9577 (TEDDI-R) requires NCI-IRB expedited reporting of unanticipated problems, and death. The protocol Principal Investigator will report to NCI-IRB: all deaths except death due to progressive disease; all protocol violations or deviations; all unanticipated problems; and all serious non-compliance. Reports must be received by the NCI-IRB within 7 working days of Principal Investigator awareness via iRIS. The following unanticipated problems and deaths were not reported to the NCI-IRB within the timeframe required by the protocol:

| **Unanticipated Problem/Death** | **Date of Event** | **Date CI Became Aware** | **Date Reported to NCI-IRB** | **Working Days Elapsed** |
|---|---|---|---|---|
| Subject 1010003([redacted]) | | | | |
| Death | March 21, 2015 | March 23, 2015 | April 2, 2015 | 8 days |
| Subject 1010004 ([redacted]) | | | | |
| Death | March 10, 2015 | March 10, 2015 | Not reported | |
| Subject 1010006 ([redacted]) | | | | |
| Serious protocol deviation- patient took 11 extra drug doses | March 17, 2015 | March 17, 2015 | April 6, 2015 | 14 days |
| Subject 1010007 ([redacted]) | | | | |
| Death | May 12, 2015 | May 12, 2015 | June 8, 2015 | 18 days |
| Subject 1010009 ([redacted]) | | | | |

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| | | | | |
|---|---|---|---|---|
| Death | May 16, 2015 | May 16, 2015 | August 6, 2015 | 56 days |
| Subject 1010016 ([redacted]) | | | | |
| Death | April 15, 2016 | April 22, 2016 | May 26, 2016 | 24 days |

D. Protocol 14-C-0157-9577 (TEDDI-R) dosing schedule for cycle one (1) and cycle two (2) is one (1) pill for ten (10) consecutive days.

1. Patient 1010005 ([redacted]) on cycle two (2) day 20 took one (1) extra dose of ibrutinib.
2. Patient 1010006 ([redacted]) completed cycle one (1) and continued to take an additional 11 pills for 11 consecutive days.

E. Protocol 14-C-0157-9577 (TEDDI-R) requires screening evaluation to include ophthalmologic evaluation. Patient 1010001 ([redacted]) was enrolled in this protocol August 14, 2014 without any ophthalmologic evaluation.

***DATES OF INSPECTION**
9/12/2016(Mon),9/13/2016(Tue),9/14/2016(Wed),9/19/2016(Mon),9/20/2016(Tue),9/21/2016(Wed),9/22/2016(Thu),9/23/2016(Fri),9/26/2016(Mon),9/28/2016(Wed),10/03/2016(Mon)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."