

CLINICAL:

20. Subject VM-00995 is a 14 year old female with T-cell acute lymphoblastic anemia in consolidation who received 625 IU Varizig on June 11, 2011, and on June 16, 2011, experienced extreme fatigue with a hematocrit of 20% accompanied by pain and swelling in her left wrist, right elbow, and both hip joints. The following day she was hospitalized. She became febrile, and a chest x-ray showed “showed new medial retrocardiac opacity/infiltrate, not well-seen on lateral view, possibly representing atelectasis, infection or Mycoplasma pneumonia.” An infectious disease work-up was negative. After receiving one packed red blood cell transfusion, she was discharged on June 18, 2011. The investigator recorded 13 non-serious adverse events for this subject, and one serious adverse event, “serum sickness”, judged to be severe and related to the Varizig administration. “Arthritis” on day 12 after Varizig administration was judged to be “possibly” related, and the remaining adverse events were all judged to be “unlikely” to be related. The following table shows these 14 adverse events by day after Varizig administration:

MED_TERM	Day after last administration
Leukopenia	2
Neuropathy Peripheral	2
Neutropenia	2
Anaemia	5
Activated Partial Thromboplastin Time Prolonged	6
Serum Sickness	6
Weight Increased	9
Anaemia	10
Neutropenia	11
Arthritis	12
Hypomagnesaemia	16
Alanine Aminotransferase Increased	24
Hyperphosphataemia	24
Thrombocytopenia	27

The adverse event “serum sickness” is not a common adverse event after administration of a human immune globulin product, such as Varizig.

Please submit additional information on subject VM-00995 that explains why you conclude that each of the reported “unlikely related” adverse events are not related to the administration of Varizig. In particular, what information supports

the conclusion that the prolonged activated partial thromboplastin time on day 6 is unrelated to Varizig administration?

21. Subject VM-00301 is a 37 year old immunocompromised female with a history of lupus erythematosus, with a biliary stent for an unknown reason and chronic abdominal pain. Eight (8) days after receiving 625 IU Varizig she became febrile with acute abdominal pain, arthralgia, weakness and loss of appetite. She did not develop varicella, and a lupus flare was ruled out. The investigator considered these events to be significantly disabling, but not related to Varizig.

Please submit additional information on subject VM-301 that explains why you conclude that the serious adverse events “abdominal pain,” “arthralgia,” “asthenia,” “decreased appetite,” “fatigue,” and “pyrexia,” – all recorded as occurring on day 8 after administration of Varizig – were unrelated to Varizig administration.

22. The INDICATIONS AND USAGE section of the proposed package insert includes the following statement:

Administer Varizig as soon as possible following varicella zoster virus (VZV) exposure, ideally within 96 hours for greatest effectiveness, but not later than 10 days after VZV exposure.

Please submit the clinical data, and the considerations, that support the advice to give Varizig beyond the 96 hour time point.