From:	Hanna Ng
To:	Innis, Robert (NIH/NIMH) [E]
Cc:	Lohith, Talakad (NIH/NIMH) [E]; Minh Bui; Howard Stock; Driscoll, Jamie (NIH/NIMH) [E]; Hanna Ng
Subject:	RE: M038-13
Date:	Monday, March 03, 2014 6:17:24 PM

Hi Bob,

The 3 Add on groups, 25, 50 and 100x HED (22.0, 44.1, or 88.1 µg/kg). While no ataxia was noted in the repeat 100x HED group, ataxia (slight) was observed immediately post-dose in one of 10 male rat (#065) in the 50x HED (44.1 µg/kg) dose group. This animal returned to normal by the second time point clinical observation at 15 min post dose.

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-----Original Message-----
From: Innis, Robert (NIH/NIMH) [E] [mailto:innisr@mail.nih.gov]
Sent: Monday, March 03, 2014 2:36 PM
To: Hanna Ng
Cc: Lohith, Talakad (NIH/NIMH) [E]; Minh Bui; Howard Stock
Subject: RE: M038-13

Dear Hanna,

Thanks for this follow-up information. To be sure I understand, in the add-on groups, was ataxia noted at all five time points: 15, 30, 60, 90, and 120 minutes post dose? We could not find these individual observations in the final report, but may have overlooked them.

Many thanks,

Bob Innis

-----Original Message-----
From: Hanna Ng [mailto:hanna.ng@sri.com]
Sent: Monday, March 03, 2014 5:22 PM
To: Innis, Robert (NIH/NIMH) [E]
Cc: Lohith, Talakad (NIH/NIMH) [E]; Minh Bui; Howard Stock; Hanna Ng
Subject: RE: M038-13

Hi Dr. Innis,

We retrieved the data binder from the archives. The in -life data capture system doesn't give time stamps less than 1 minute, so all of the time stamps for the iv injections is 1 minute although the iv slow bolus injection was less than 1 min. Dose volume is 5 ml/kg, animals received 0.85-1.5 ml solution with body weight 168-290 gram; males got more dose volume. Since we saw slight ataxia immediately post dose in 10 of 10 males and 6 of 10 females, I agree it can be caused by transiently high plasma concentration of drug. We did clinical observation immediately post dose and saw the effect. By the next clinical observation, 2-4 hrs later, the animals returned to normal, although this may have happened much sooner. Although the technical staff remember that the duration may be short (10-15 minutes), the formal clinical observation recording was only done 2-4 hr later by the protocol.

Therefore, in the add -on groups, clinical observation was done immediately post dose and approximately 15, 30, 60, 90, and 120 minutes post dose. I would say that the transient clinical observation in the first treated group was minimal, and was not dose limiting effect. The clinical observation for the second add-on groups had more time points, and should be weighed in more. However, we had to report what we observed, and mostly aiming on the safe side for the toxicity study. Hope this is helpful.
Hanna

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-----Original Message-----
From: Innis, Robert (NIH/NIMH) [E] [mailto:innisr@mail.nih.gov]
Sent: Monday, February 24, 2014 3:45 AM
To: Hanna Ng; Minh Bui
Cc: Lohith, Talakad (NIH/NIMH) [E]
Subject: M038-13

Dear Hanna and Minh,

I am trying to find two pieces of information in the report.

1) Over what period of time was the drug injected? If the period is not specified in this report or some other Standard Operating Procedure, do you have an approximate range (e.g., ~0.5 to 1.0 min) for this volume of fluid? The toxicity (ataxia) was likely caused by transiently high plasma concentration of drug. We plan to decrease the potential incidence of this side effect in humans by extending the period of injection. Thus, we want to know how long was the injection in rats.

2) How long did the ataxia last? I know that the first study made only one observation shortly after injection. You but planned to observe at a few time points for the second study with lowered doses. Within the study itself, I cannot locate the time points and the observations.

Thanks for your help.

Bob Innis