Home Office

PPL Standard Condition 18 Notification Form

Please use this form to notify the Animals in Science Regulation Unit (ASRU) of procedural-related adverse effects that have exceeded or are likely to exceed the severity limitations or controls described in the project licence. ASRU will use this information to determine whether any further action is required.

Do not use to report:

- adverse effects that are due to non-procedural issues;
- potential non-compliance (report by other means);
- issues without adverse welfare consequences.

If you are in doubt whether or not you need to fill in this form, please contact your assigned Inspector.

Please clearly title your document: **'ASRU_establishment name_PPL number_PPLh surname_date_sc18'** and send to your Inspector (e.g. using cjsm) with the subject heading 'PPL SC 18 Notification PPL [Number] – **Check Home Office's Updated Bridging Ways of Working for updated advice on email addresses and subject headings. Cjsm no longer necessary.**

Establishment Licence name	University of Cambridge
Establishment Licence number	X81BD37B1
Name of PPL holder	Brian Huntly
PPL number	PP3042348
Protocol no	9
Protocol title	Study of the genetic and therapeutic vulnerabilities of pre-leukaemia and leukaemia (Mice)
Severity classification	Moderate
1. Date of incident	17/5/24

2. Species	Mouse
3. Brief details of study and how the limits or constraints have been breached	We have identified that the combination of inhibitors of CREBBP and Venetoclax synergise in the treatment of B cell acute lymphoblastic leukaemia (B-ALL). Our previous work has demonstrated the efficacy of daily oral combination treatment in NSG mice engrafted with B-ALL cell lines. This work has been reviewed at Nature Cancer, and all the reviewers have requested confirmation of these findings in primary human PDX models. We have therefore transplanted NSG mice with B-ALL PDXs and, having confirmed engraftment, have started to treat them on one of four arms (Vehicle/Inobrodib/Venetoclax/Combination) by daily oral gavage (daily dosing excluding Saturday and Sunday), expecting to see benefit in the Combination arm. These drugs are in use in clinical trials and have been combined in patients with minimal toxicity. On the fifth day of dosing (39 days post transplantation) one mouse on the Venetoclax only arm (HUAS73.1e) was found dead shortly after dosing.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	Yes – discussed with NVS
5. Cause of Problem, if known	The Research Assistant is extremely experienced in this procedure. Autopsy did not show any evidence of trauma to the oesophagus and the drug (which is yellow) was clearly visible in the stomach, indicating the procedure was not traumatic or delivered dose to the lung. We think that the animal may have reacted to the dosing abnormally by experiencing heightened levels of stress. Although unlikely, this might also have been caused by impurities in the drug/vehicle or this animal may have been harbouring a subclinical infection that weakened its constitution.

6. Action that has been or will be taken *(For example, formulation of drug changed, supportive treatment given, study design modified). If no action needed, indicate why (for example, none required as study has been terminated and will not be repeated)*	The incident happened on a Friday. We immediately contacted the named vet and kept the rest of the animals under surveillance during the weekend period, as no more dosing was planned on these two days. We re-made all the drugs and vehicles in case of contamination. By the 20th of May, 5 control animals have been culled showing signs of disease, and so, after discussions with the NVS we have continued dosing from 20th May, as we think the combination arm may well be gaining significant survival benefit. These procedures went without incident. **Please note:** Prior to this further dosing, the named Vet inspected the remaining animals and authorised us to continue dosing, with the provision that dosing should stop immediately if any other animals show any unexpected reactions to treatment. Following our discussion with the NVS, we have also: 1) Confirmed that the pH of all the drugs and vehicles is tolerable (pH 5-6). 2) Sent tissues from other animals for histology. We will continue to monitor all animals post treatment for any abnormal signs and communicate any concerns with the named Vet in the first instance.
7. Reported by (name)	Simon Richardson
8. Date	21/5/24

**********For official use**********

Inspector's comments and recommendations:

Comments and recommendations	
Inspector name	
Date	