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 (Mira)
Establishment Licence number	X81BD37B1
Name of PPL holder	Rachel Watson
PPL number	PP6298217
Protocol no	11
Protocol title	Investigation of the effect of test agents delivered directly to the liver
Severity classification	Moderate
1. Date of incident	22/10/2024
2. Species	Mouse

3. Brief details of study and how the limits or constraints have been breached	The aim of this study is to determine the short- and long-term viability of human iPSC derived hepatocytes (developed by our client) directly injected into NSG mouse livers. It is hoped that these proprietary cells will engraft and support normal liver function, demonstrating their potential as a 'bridging' therapy (test agent) in chronic liver disease patients waiting for transplants. Having been injected into the hepatic portal vein, the viability/pharmacokinetics of the cells in-vivo and their effect on biomarkers will be assessed over at least 21 days by repeated measurement human albumin levels in the mouse serum. 22 female NSG mice have been recruited to this study. When starting the study the surgeries were observed by both the NVS and NACWO. Adverse effects due to too high a cell density were observed in the first two cohorts ('ASRU_University of Cambridge_PP6298217_Watson_070824_SC18' and ASRU_University of Cambridge_PP6298217_Watson_140824_SC18'); with continued reduction in cell density to 10^6 and other refinements this lead to a successful third cohort of 6 mice all showing a good recovery and completing the study. The only issue of note was a very transient reduction in respiration rate. On 22/10/24, we aimed to inject 6 more mice, 1x vehicle and 5x cell injections at 10^6 cells dose concentration. All the mice were given sub-cut Metacam (1.5 mg/ml at 5 mg/kg) and buprenorphine (0.015 mg/ml at 0.1 mg/kg) 30 minutes prior to being placed under isoflurane anaesthesia. As in previous cohorts a laparotomy was performed, and the intestines were gently manipulated out of the peritoneal cavity and onto a sterile wettened gauze pad, exposing the hepatic portal vein. 100 µl of pre-warmed vehicle, with or without cells, was injected into the hepatic portal vein. One of the mice ceased breathing ~1 min after being injected with cells. Stimulation of the thorax failed to recover her, and death was confirmed by a Sch1 method

	The following mouse had the same surgical procedure, except that no change in respiratory rate was observed during or immediately after the cell injection. The surgical site was closed with sutures, and she seemed be recovering well 1hr post-surgery, actively exploring her cage. At 1.5hrs post-surgery, she was found unresponsive and was culled immediately. A post-mortem was carried but no obvious cause of deterioration was determined. The liver, lungs and heart have been taken from both mice for histological analysis.
4. Have you taken advice from the Named Animal Care and Welfare Officer/Named Veterinary Surgeon/others?	I spoke with the NACWO following surgery and discussed the possible causes of death based on our findings from the post-mortems.
5. Cause of Problem, if known	The mice died deteriorated very suddenly, one during surgery and one 1.5hrs after recovery from anaethesia. Neither experienced significant internal bleeding or showed any abnormal physiology during post-mortem, leading the team and the NACWO to suspect the density of iPSC derived human hepatocytes in the injection to has caused adverse effects, despite the previous successful cohort.
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)*	We will have a meeting in the next few days to reduce the cell density further and implement any other possible refinements for future studies.
7. Reported by (name)	Sam Hilton (on behalf of Rachel Watson)
8. Date	24/10/24

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

Inspector's comments and recommendations:

Comments and recommendations	
Inspector name	
Date	