Royal Veterinary College
University of London

Summary Minutes: AWERB: PPL review meeting

Status: FINAL

Meeting held: Tuesday 6 August 2024 at 10am

Present: 16 plus 1 in attendance, 4 by invitation, 12 apologies

1 DOG UNIT: UPDATE ON A PILOT STUDY

AWERB were reminded that at a recent meeting queries had been raised about a study which involved the DMD dogs receiving subcutaneous injections of a new therapeutic drug. The dogs were vocalising during and immediately after the dosing though no other aversive behaviour was being seen and they were otherwise interactive. The project licence holder (PPLH) had been invited to this meeting to further discuss the study.

A background to the study was provided, including why it was being undertaken, the aims, the timepoints and why they were crucial. The original plan was for this to be an oral study. This had led to several problems though and it had been necessary to change the manner of the daily dosing to subcutaneous injections. The PPLH was very aware of the concerns about the dogs' response to the injections. This study though was needed in order to determine whether human clinical trials could be undertaken. If they were able to prove that this treatment was effective, not only would it have a major influence on patients with Duchenne Muscular Dystrophy but also potentially those with other degenerative diseases that involve inflammation and mitophagy defects in humans, dogs and other animals.

Postmortems had been carried out which showed no evidence of inflammation or degeneration at the sites of the subcutaneous injections. It therefore seemed to be a brief, transitory, painful response that the dogs were experiencing.

The following queries/comments were raised by AWERB:

- **One of AWERB's roles was to carry out a harm/benefit analysis of work that was undertaken within the units. The information provided highlighted the benefit analysis of this work but was there a timeline for when it was anticipated enough meaningful data will have been obtained?**
  Data from the study was already being collected and analysed from the first group of dogs who have received two months' worth of treatment. Once a sufficient number of dogs have completed the first two months of treatment, then an initial evaluation of the efficacy of the drug would be undertaken.

- **How many dogs were currently on the trial and how many were required?**
  A new group of dogs had recently been recruited and were due to start the trial shortly. Their 40 weeks would finish in 2025. In addition, from the pilot data collected it should be able to gauge whether there was early evidence of this treatment having an effect.

- **Could the formulation that was being injected be modified to make it less painful?**

The collaborating company had investigated whether modifying the temperature of the drug would have any major effect on the pharmacokinetics of the drug once it got into the body and determined that it wouldn't. Trials would therefore be undertaken with the next cohort of dogs to see if changing the temperature (either through cooling or warming) made the injections less painful. Ice packs/spray would also be applied at the time of injection as again it had been determined that de-sensitizing the skin would not affect the trial.

- **Could the side effects that the dogs were experiencing from the injections also occur in humans?**
  For the human clinical trials, patients would receive the drug in tablet form rather than through injections. The original plan had been to provide the drugs to the dogs in tablet form but that had not been successful, so an alternative method had to be identified.

- **As the dogs were having to be staggered through the trial did that give opportunity to consider how to lessen the harms to the dogs as the trial continues?**
  As this was a clinical trial, the goal posts should not be moved part way through. Only items that would not affect the trial and compromise the dogs that have been studied so far could be considered. If major changes were made then the trial would need to be restarted.

- **Could a port be used for the injections, so avoiding the requirement of using a needle stick?**
  As it seemed that what was causing the pain was the drug hitting the subcutaneous tissues, rather than the insertion of the needle, using a port would not make any difference.

- **Could the vehicle be altered?**
  A standard vehicle for dissolving and administering the drug was being used. If the vehicle was altered it would mean having to restart the trial as it would have a major effect on both the pharmacokinetics and also the rate of absorption.

- **Would it be an issue to restart the trial if it meant the new dogs did not react to the injection?**
  Realistically it would take a year or so before an alternative subcutaneous vehicle could be trialled, as a lot of work was needed to validate PK data, and would also require additional animals.

- **Would the side effects of the injections be mentioned in any future publications and advice given that ideally this vehicle should not be used in future studies?**
  Yes this would be included.

- **Would it be possible to add "stop/go" elements, in relation to temporarily stopping recruiting dogs, whilst available data was evaluated whether the study was progressing in a negative or positive fashion.**
  This would be acceptable. Once the initial dogs have had two months' worth of treatment then biomarker data would be available to be evaluated, so should provide information to determine whether it was worth continuing with the study.

There was a discussion about cumulative harms arising from the phenotype. AWERB were informed that the researchers were already identifying what practical steps could be undertaken to reduce the cumulative harm, for example through bringing forward humane endpoints.

AWERB concluded that:

- The project was still scientifically valid
- The trial was at a pivotal point and needed to continue
- Valuable data was already being obtained from the dogs
- If any major changes were made at this stage, then the trial would need to start again

AWERB however did need to re-evaluate the harm benefit analysis in light of the data that was being obtained to determine whether further information needed to be added to the project licence in relation to adverse events.

It was noted that the reactions of the dogs were not getting worse over time, which indicated the dogs were not experiencing cumulative suffering.

AWERB agreed that it would be helpful for the technicians involved with the study to have a discussion with the research team about their work and why it was being done, and why the injections were needed, so they could see that their role was important. The ultimate aim was to improve the quality of life of boys with DMD and their survival. If the treatment works then it might also work in other degenerative diseases.

The project licence holder was thanked for attending the meeting.

2 CRERB APPLICATION

An application had been submitted to CRERB to carry out a preclinical assessment of a novel drug for osteoarthritis. This work was being carried out overseas. AWERB had been asked to review the study though, for if the work was being done in the UK, it would have needed a Home Office project licence.

The background to the study was provided and the following queries were raised:

- **Why had the work been outsourced. Was it not possible to do the work at the RVC?**
  The RVC did not have the expertise to conduct the required surgical techniques or the intraarticular injections. The overseas contract research organisation (CRO) that would be used were experts in intra-articular dosing in rodent models of osteoarthritis and had carried out similar long term dosing studies with this model for major pharmaceutical companies. As this study was part of a commercialisation project, it was important to use a reputable CRO, to provide confidence to potential investors that a true efficacy was being provided.

- **The study mentioned that weekly dosing would be carried out. Was that clinically relevant though? Also what about the cumulative effect on the animal?**
  Weekly dosing was common place in the field and there was no known negative effects on weight bearing or joint pathology. There was no known literature that suggests that weekly dosing could cause a welfare concern or joint problems.

- **How would the scoring system be utilised on the ground? The scoring system indicated that the humane endpoint was a score of six. However had consideration been given to those animals that scored between two and four but were suffering over a long period of time**.
  The scoring sheet was to be used directly after surgery if there were any welfare concerns about the animals. If there was no adverse or outward signs of pain then this would not be entered onto the scoring sheet. The animals would also be continually monitored during the study.

- **What monitoring would be done post 7 day following surgery? And what actions would be taken if changes were seen?**
  This information would be requested.

- **Why wasn't a sham control being used?**
  As studies have already been conducted about 20 times, the CRO already have data to show that the sham controls do not have disease. The aim now was not to use sham controls without due cause.

- **The application mentioned that the CRO had two very highly trained people who were very experienced in using the technique but no information had been provided on when they had last performed it or how regularly they have used it.**
  The CRO have subsequently advised that these two personnel have carried out approximately 20 successful studies in the last year between them and were deemed as experts in this technique. The CEO was also a lead author on papers that were deemed as gold standard in the field.

- **Could example calculations be provided on how the sample size had been obtained (using published data to provide effect size, variation etc).**
  These would be added.

- **Was there a reason that inhaled isoflurane followed by pneumothorax for euthanasia was being used as this was not a routine method in the UK?**
  This would be queried with the company and if it proved to be an issue they would be asked to use an alternative method.

- **What methods would be used for the blood sampling and from which veins? Were the intra-articular injections done under anaesthesia?**
  This would be clarified with the company.

- **How was the dose of the drug to be selected? This would affect efficacy (and toxicity) outcomes.**
  The CRO was experienced in dosing of drugs in this model and would help select the dose with reference to the current studies. This would be added to the application.

- **The rats would be housed in the US. Information needed to be obtained from the company on cage sizes that they used, husbandry that they would be providing and whether the rats would be housed socially. Would the cages be large enough to enable the rats stand up, which was critical for this project to enable them to use their joints? Also what environmental enrichment would be provided? Had the company been evaluated in terms of general animal health and welfare? Were they also following best practice in terms of injections? A copy of the CRO's accreditation was also needed.**
  A list of questions would be compiled for the CRO including how the procedures would be carried out; what pain relief would be provided and more information on the housing and husbandry. This information was needed to enable AWERB to carry out a thorough review from an ethical and welfare standpoint of what an animal would be going through.

The applicant raised a concern about the process to review the application. He had originally been advised to submit a CRERB application, however this form was not designed to enable the project to be assessed against the standards that a Home Office project licence would be assessed against. He suggested that the process for these types of applications therefore needed to be revised.

This was discussed further by AWERB. They recognised that there was no standard set process in place to deal with these types of studies, but that it was also difficult to have a set template that would provide the information needed. They generally needed to be dealt with on a case by case basis as different factors needed to be taken into account depending on the country and the animals being used. A guide however could be put together of what needed to be considered.

3 **MINUTES**

The minutes of the meeting held on 9 July were confirmed as an accurate record.

4 ANY OTHER BUSINESS

4.1 Thank you

A huge thank you was given to two PhD students, who were stepping down, for the services and support that they have provided. It had been a real pleasure working with them.

5 DATE OF NEXT MEETING:

28 August at 10am: PPL Review meeting.

Secretary
14 November 2024