From:	Heylings Jon GBAP
Sent:	12 November 2007 14:34
To:	Elliott Barry B GBAP; Botham Phil GBJH; Allen Sandra GBAP; Akins Jonathan USGR; Lewis Dick GBJH
Cc:	Sheldon Ros GBJH; Brammer Alison GBAP; Bembridge John GBJH; Brown Doug GBJH
Subject:	RE: URGENT consideration please: INTEON vs Gramoxone toxicity - next steps at MPI 5

Barry

Your inbox must be bulging but here are my own views on the MPI data and what we could do next.

Point 1

We have got to assume that everything has been conducted correctly at MPI. This includes the actual dose article used, its composition and the dispensing and volume given.There is no evidence to say this is not the case. Indeed, some of the positives in this project are the consistency of clinical observations and 24h AUC values between CTL and MPI, right down to individual animals. In addition there is reproducibility of plasma exposure and obs for the Inteon US K variant between CTL and MPI.

Point 2

I also support a null effect of capsule dosing compared with gavage due to the crossover evidence of bioequivalence at CTL and MPI and the consistency of the Tmax and Cmax between the two methods of dosing. The studies show that PQ is being released at equivalent rates. Any capsule delayed breakdown, capsule binding or direct delivery through the pylorus would affect Tmax and would surely change the plasma profile. We have no evidence to support that capsule dosing is responsible for the unexpected results.

Point 3

If we had only tested the Gramoxone ROW 200g/L formulation with and without the Inteon technology we would have been happy with the outcome. To my knowledge, Gramoxone Max nor any other high strength surfactant-free PQ formulation has been tested in the dog before. We are therefore interpreting a study that has not been done before, as opposed to data that are inconsistent with other previous studies at IRI or CTL.

Point 4

The 2 dose response curves that don't fit our expectations are the 2 surfactant-free formulations without Inteon technology and with standard emetic levels of 0.5g/L. These animals are receiving very high oral PQ loadings yet the 2 dose reponses are essentially flat at the mid to upper end to date. How do we interpret this? The IRI data in 1987 clearly demonstrates that much lower doses of unemeticised PQ are toxic to dogs. This was not a one off observation at IRI. This occurred with 4 different formulations. There is other published data from Widdop et al showing that Gramoxone is lethal to dogs below 50mg/kg. Furthermore, our own CTL data with Gramoxone formulations fortified with extra emetic are all toxic at doses well below these 64/128mg/kg recent MPI doses.

Point 5

The common thread with the unexpected observations is the lack of surfactants. My hypothesis is we have under-estimated the potential of the emetic agent alone to safen these non-wetted formulations. However, I would like to qualify this by the fact that this has been seen at moderate to high doses of PQ in the 2 non Inteon formulations where the dogs are receiving emetic doses above ED50. I would still be very concerned at the lower end where the emetic dose may be sub-threshold. Indeed, we have seen both 8 and 16mg being toxic in some dogs. The lack of reproducibility at 8mg/kg PQ with Max may be a function of the emetic dose being around threshold and therefore subject to variability.

Point 6

I would like to suggest that the saw tooth nature of the 2 non-surfactant formulations is the net result of the PQ and emetic dose response curves. We have evidence in pig, monkey and dog that the 2 dose response curves are both steep. The ED50 for prompt emesis within 30min is about 0.15mg/kg in all species. We are operating in this territory with these MPI studies so any factor that may influence GI tract function, including surfactant could shift the relationship between tox (PQ) and safening (Emetic). If only we had one dog that did not vomit in the recent round. If this assumption is correct and a non vomiting dog gave a very high PQ exposure and mortality this would support this working hypothesis. However, what we have with Max and the new 240 non Inteon is rapid and repeated productive emesis before the PQ has been absorbed. Are these dogs simply receiving an effective dose of emetic before the PQ reaches the blood? Indeed, we have evidence that surfactants promote passive PQ uptake through the intestines and surfactants delipidise membranes making them more permeable.

Point 7

What could we do? Scientifically, my first choice would be to take the emetic completely out of the non-surfactant formulations. We may be best doing this with the 240 variant. I would generate the full dose response from low (8mg/kg) to limit dose. Assuming the animals can no longer remove the PQ by vomiting then a steep dose/toxicity curve would be constructed. This should be in line with the IRI data and would show reproducibility of old and new data for unemeticised products. The important feature of this experiment is there should be no saw tooth just a straight dose/exposure/tox effect.

I favour this over adding surfactant back to the 240 non Inteon since we would still have the blind emetic dose response curve complicating the interpretation.

This non-emeticised 240 would at least re-set the benchmarking for PQ tox in the dog in the new lab and there would then be a number of options to pursue. For example, we complete the low end of Study 008 to see if there was toxicity at the low end. Alternatively, we could examine the full Inteon technology with high emetic in the 240 or the Inteon technology with standard emetic in the 240.

However, we cannot predict 2 experiments ahead at the moment but I just want to see a steep dose response to start with.

Regards

Jon

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From: Elliott Barry B GBAP
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Cc: Sheldon Ros GBJH; Brammer Alison GBAP; Bembridge John GBJH; Brown Doug GBJH
Subject: URGENT consideration please: INTEON vs Gramoxone toxicity - next steps at MPI

All,

In response to the latest data on A7813R (Gramoxone formulation with 240g/l PQ, 1x emetic, low adjuvants), which show no sigificant toxicity at 64 or 128mg/kg PQ, we have a need for a project review insofar as these data were not expected, and indicate that we cannot make simple comparisons of INTEON to such data and conclude a signficant reduction in toxicity of INTEON as we have previously, where we have assumed standard dose response curves (as seen with the IRI studies), and toxicity (with start of terminations) likely to be seen at around the 12-24 mg/kg PQ area, for 1x emeticised Gramoxone formulations.

Registration are keen to move forward as swiftly as possible and asked for a conclusion on the next study by next Wednesday (14 Nov). Any next study will require SAERC approval, and should be done when there is a clear way forward. The situation is complicated. I have tried to distill some of the main points below and given some proposals. Many of the team are unavailable for meetings in the next few days, and I am not keen to rush the PS part of this.

Please let me have your views on the items below, including the specific options, and priorities you see, and also a comment on the timing aspect (conclusions by Wed 14th). I will be with Roland (all being well) on Monday afternoon.

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Previous PS team conclusions have been abstracted from the minutes of the TMT meeting of 5 Oct are below:

In response to the specific questions posed:
(1) Are the MPI data robust?
There is no evidence of technical deficiencies in any of the studies conducted at MPI in this programme of work. After evaluation we have no evidence that the data are not robust. We are confident in placing further studies and in accepting the data.

(2) What is the toxicity of a USA formulation relative to INTEON A7813K (USA)?
Can we draw a conclusion?
Do we understand the shape of the dose response curve?
Although the USA formulation tested (Max) gives rise to higher paraquat blood levels and a higher incidence of mortality than Inteon A7813K at comparable dose levels , it is difficult to make an accurate quantitative assessment of the degree of safening provided by the Inteon formulation. This is due to variability and the shape of the dose response curve for the USA formulation. We cannot draw conclusions relating to the toxicity of other formulations on sale in the USA.
The reasons for both the variability and the dose response are not currently understood.

(3)What is the toxicity of a ROW formulation relative to INTEON A3879EN (ROW)?
Can we draw a conclusion?
..with the current dataset it is not possible to make a quantitative assessment of the reduced toxicity provided by the INTEON (ROW) formulation. We also cannot draw conclusions relating to the toxicity dose response of other non-INTEON formulations with the present dataset.

(4) What is the toxicity dose response for Gramoxone ROW formulation (A3879R)
Is the saw-tooth dose response restricted to Max?
Do we need to test A3879R higher (to 4/4)

As indicated above, there are concerns that A3879R could display the same saw-tooth dose response described for Max if tested at higher dose levels. In order to study this possibility and to provide comparative data to answer question (3), from a technical perspective, the TMT would recommend that A3879R is tested at at least one higher dose level (initially 64mg/kg).

- However, the TMT recognises that, following discussions with regulatory colleagues, the preferred way forward is to use a surrogate formulation to A3879R – the 'USA variant 3' of slide 10 - to provide a full dose response. This surrogate formulation contains a similar PQ concentration, but has a different alerting agent and has a different spectrum and concentration of adjuvants. The TMT urges caution in bridging the data from this formulation to A3879R as attempting to predict the extension of the dose response of one formulation by using a similar but non identical formulation makes the assumption that the different components do not exert an influence on the outcome. We do not know this. The TMT did recognise that if the surrogate formulation were tested at the same dose levels used with A3879R and gave comparable outcomes (for both blood paraquat levels and toxicity) then this may suggest a possible similarity in response of the two formulations, however a confident statement on A3879R could only be made by extending the dose range higher with A3879R itself.

These conclusions have not been challenged by the data from the A7813R formulation tested since, and should therefore still be considered valid.

I would therefore propose, that we can therefore now conclude:

1. USA, where existing G formulations do not have significant adjuvants:

We have two formulations tested in the dog, that do not show the expected dose response, and are not inducing the expected toxicity at around the 64-128mg/kg PQ level.
There is some evidence for toxicity at lower PQ doses, but this does not increase with increasing PQ dose.

The simple parallel dose response curve evaluations that we have made in the past to assess the reduction in toxicity, and the corresponding levels of reduced toxicity are therefore not supported by the latest data. We would need to examine A7813R at lower dose levels (as with G Max) before we could comment on the full shape of the dose response curve and conclude on toxicity at lower levels. Any evaluation of G Max or of A7813R will provide data relevant to those formulations and may indicate trends for non-adjuvant formulations, but given the potential differences in formulations, and comparison of INTEON with any other formulation (eg any other on sale) would need data on that formulation composition itself to make a confident statement. It is likely that formulations with 5x emetic will have a different profile of toxicity, and we do not understand what that is at this time.

2. ROW, where existing G formulations do have significant adjuvants:
We have no current data to allow a conclusion on what happens at around the 64-128mg/kg PQ level for a current wetted formulation.

We therefore do not know whether the simple parallel dose response curve evaluations that we have made in the past to assess the reduction in toxicity, and the corresponding levels of reduced toxicity are correct.

Options for discussion:

A. Find out whether the current ROW formulations with significant adjuvants produce a dose response that supports the claims we have made, ie produces the expected profile.
A1 This can be done with confidence using A3879R
A single dose of 64 should give a good indication since there are already data on lower levels

B. Investigate what formulation components may have resulted in the unexpected dose response and reduced toxicity of the G formulations tested cf the IRI formulations.
B1 Take A7813R and prepare a formulation with adjuvants similar to A3879R
B2 Take A7813R and prepare a formulation with no emetic.
A single dose of 64 should give a good indication of outcome, however lower levels would be required to confirm the dose response across the required range.

C. Determine what the toxicity of on-sale composition Gramoxone formulation in the USA is.
C1 This requires a new formulation to be selected and tested across a wide dose range.

D. Determine the toxicity profile of INTEON formulations at the dose levels where inconsistent toxicity was seen with G Max, to be confident in toxicity comparisons at like for like dose levels
D1 Test INTEON A7813K (and A3879EN) at 8mg/kg PQ

Barry