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Sent: 18 August 2006 11:11
To: Elliott Barry GBAP
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Subject: Supporting data

Barry (and sub-team)

As discussed, I have managed to locate more historical data from the vaults.

The tack I have been following is... **What data do we have that would indicate that a 200g/L commercial Gramoxone product, containing 0.5g/L emetic and BIW (G) is likely to be toxic at a 16mg/kg PQ ion dose in our proposed acute study?**

The evidence...

1. 0.5g/L emetic is below the threshold for effective emesis (prior to peak) in this species (Pharms studies). Therefore emeticised and non-emeticised G could well be equivalent at 16mg/kg which only delivers a threshold emetic dose.
2. Extent of PQ systemic exposure at 8mg/kg in emeticised G (CTL studies) is not far below a toxic systemic exposure in non-emeticised G (IRI studies).
3. Lack of effective emesis in G containing the standard 0.5g/l emetic at 8mg/kg (several CTL studies). In many cases no emesis occurred at all at 8m/kg in emeticised G.
4. High levels of emetic, equivalent to 2.4g/L (5X emetic) in G were toxic at 48mg/kg and only offered limited safening (CTL studies). This option was not supported by the TRC in 1991 since Magnoxone gave a superior performance at just 3X emetic - non toxic at 200mg/kg.
5. In various attempts to safen G, containing standard emetic, a toxic response occurred at 16mg/kg. This included some of the Multiple Emulsions, Microcapsules, Dextrin sulphate binders, SDS granular formulations and G containing MgSO₄. These research studies are summarised in various Category C TRC reports at Jealotts Hill. The point here is we have high systemic exposure and intervention with significant toxic signs for a number of attempts at safening the G product. Often the "failures" went down at 32mg/kg but some of the above did not even pass 16mg/kg. [Only Magnoxone (triggered trisilicate gel, 3x emetic and MgSO₄ purgative) made it and went on into full development. It was non toxic at 200mg/kg].

It will be difficult to make a case using the previous formulation types. The variables are too complex and it may not be helpful to surface all our attempts, including Magnoxone. However, with the MgSO₄ part of the story we have an opportunity to position this as a component of INTEON. The challenge we had in 1991 was... why do we need MgSO₄ in Magnoxone? Does it really add benefit beyond the elevated emetic and gel etc. Does it really cause purgation? Although a cheap additive could we leave it out? You could argue the same question applies to INTEON in 2006.

To address this question we ran several studies circa 1991. We tested 100, 50 and 10g/L MgSO₄ in standard Gramoxone (NB we need to verify that it was emeticised, but I think the IRI non-E batch in 1987 was a one-off to address a separate tox question). The CTL studies showed that 16mg/kg of G containing 10 or 50g/L MgSO₄ was toxic (high AUCs of 30-40 ug/ml.h) and included a lethal event at the lowest Mg dose. Only the high MgSO₄ at 100g/L (the level in Magnoxone and INTEON) was successful at clearing the PQ from the blood (mean AUC = 16). However, at 24mg/kg, MgSO₄ at the highest loading did not safen and had high peak and AUC (mean 42 ug/ml.h). The view was the purgative alone only offered about 2X, but was nevertheless a useful additive to Magnoxone, where we had seen purgation as a clin obs at the high doses. Indeed, further titration of MgSO₄ in full Magnoxone showed a dose-related reduction in AUC/toxicity as the MgSO₄ was lowered. We ended up putting as much MgSO₄ in as we could dissolve without crystallisation on storage (100g/L in Magnoxone M19). The useful data in here is the fact that we have data with G containing MgSO₄ showing toxicity as low as 16mg/kg. - my original question above.

Any thoughts? I would welcome comments from our study review team, although I recognise you may not have time to read this before our telecon later?

Jon

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