5.6.3 Other Safety Issues

Significant insights into exposure response and PK/PD relating to safety were gleaned from several phase I trials. Originally the reviewer was told not to review these studies (i.e. early phase I studies, studies of development formulations, and the QT study) and the reviewer had to agree in writing, however the reviewer included the provision that if any information pointed to the need to examine these studies in more detail then this reviewer would do so.

Review of the PET studies indicated dose and time dependent hepatotoxicity had been seen with high oral doses. However review of the original data was not pursued by this reviewer, rather the medical officer was informed. Then on April 10, 2008 while checking the history of the formulation for the executive summary of the review (i.e. §2.2.3 Pertinent Clinical Pharmacology and Biopharmaceutic Questions) this reviewer sereptitiously came across descriptions of serious cardiotoxicity in the early phase I studies. Since a potential myocardial infarction was identified in the paroxetine drug-drug interaction study (25525) that was dismissed as musculoskeletal in origin, this reviewer examined these cases more closely prior to communication with the medical officer. It was then noted that some of these serious cardiac toxicities were noted in the QT study but that they hadn't been highlighted and had been explained largely as vasovagal in origin. While looking into the cardiotoxicity issue additional pertinent information on hepatotoxicity came to light.

Upon further examination of the various study designs it was noted that virtually all studies used low doses of short duration and tended to avoid subjects who might be at increased risk of hepatotoxicity. In addition in those studies where the risk might be apparent, i.e. the QT study and the adolescent study laboratory and other data were not reported so that a safety assessment could not be performed. In addition, the medical team leader requested a review of the adolescent study on Friday April 11, 2008 immediately prior to the DFS due date (April 14, 2008) when a quick review was likely to overlook this important safety information, (see §6.6 April 11, 2008 Consult Request from Medical Team Leader).

With regards to cardiotoxicity there appears to be a high incidence of AV block with junctional rhythms. Thus the vaso-vagal explanation for the large number of subjects fainting is suspect. Generally this is not a great concern clinically however, in the elderly and in the presence of certain other drugs this could be quite important. This asw well as the risk of agranulocytosis may explain why the sponsor did not include data in elderly subjects in this submission.

A synopsis of a PK study in the elderly was accidentally found in the 120 day safety report several levels down under a folder for an efficacy study. This study synopsis was only identifiable by a study report code without a title and was only looked at because the study code did not match the study code for higher level folder. As with the adolescent study only mean PK data was provided without any safety information or laboratory values.

Abbreviated information on these serious AEs follow:

5.6.3.1 Hepatotoxicity

5.6.3.1.1 Single Rising Dose Oral Study 85029

The clinical study report for study 85029 was dated November 1989. However based on the study title, (A Phase I, double-blind, placebo controlled, single rising oral dose study with Org 5222 in healthy male volunteers to assess tolerance and safety), it appears to be the first in human study. In the background information for this study, dose and time dependent hepatotoxicity in dogs were noted as shown in Figure 197.

Figure 197 Background Information on Preclinical Safety for First in Man Study - Study 85029

A 13 week oral toxicological study in dogs has been completed. Doses used were 1.25, 7.5 and 20 mg/kg/day. Interim analysis was performed after one month because in previous studies the lowest dose (20 mg/kg/day) still caused hepatotoxicity. The interim analysis did not show any abnormality of some biochemical (in particular plasma liver enzyme concentrations) and haematological parameters in the 1.25 and 7.5 mg/kg/day groups. In the 20 mg/kg/day group a slight increase in plasma liver enzyme concentrations was elicited, although the values observed were still within normal limits. The final analysis of this study indicated signs of hepatotoxicity in some (but not all) dogs treated with 7.5 and 20 mg/kg/day. No indications of hepatotoxicity were apparent in the 1.25 mg/kg/day dose group of dogs. Neither reproductive toxicological nor mutagenicity studies revealed any effects which preclude evaluation in man.

No significant adverse events were reported for this trial.

5.6.3.1.2 PO MRD PK S/T Study 85136

Although this clinical study report, (Feb 3, 1988), predates the previous study report. The title, (A Phase I, double-blind, placebo controlled, sub-chronic study with increasing doses of Org 5222 up to 30 mg daily in healthy male volunteers) and other indicators suggest that study 85136 was the second study in man.

The sponsor's conclusions that are shown in the following figures clearly indicate a dose and time dependent direct hepatocellular hepatotoxicity (see Figure 198 to Figure **200**), and that occurs sooner with higher doses and later with lower doses, (i.e. as soon as Day 2 with 20 mg PO BID and no sooner than day 10 with 10 mg PO BID and below), (see Figure 201). Although transaminases declined with drug discontinuation in two of the nine subjects LFT increases were greater than 3 fold, (see Figure 202 and Figure 203).

Figure 198 Sponsor's Safety Conclusions Regarding Hepatotoxicity – Study 85136

V. Conclusion

1. ORG 5222 caused mild to moderate liver enzyme increases probably due to direct hepatocellular toxicity.

Figure 199 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued A) – Study 85136

In summary, 9 out of 20 subjects given active medication developed changes in plasma liver enzymes during the study. Three of six subjects who received the highest dosage of ORG 5222 experienced elevation of AST and/or ALT to greater than twice the upper limit of normal. One of 8 placebo subjects had an elevated alkaline phosphatase throughout the study and had a single mildly elevated ALT level recorded.

Figure 200 Sponsor's Safety Conclusions Regarding Hepatotoxicity (Continued B) – Study 85136

The pattern of enzyme changes - elevation of transaminases with normal alkaline phosphatase and no accompanying rise in total bilirubin - suggests direct hepatocellular toxicity rather than cholestasis as the underlying mechanism. Enzyme induction alone is unlikely to have caused such changes in the plasma liver enzymes.

Figure 201 Sponsor's Table of Subject Characteristics for Cases of Hepatotoxicity – Study 85136

Group No.	Subject No & Initials	Dose	Abnormal Tests	Day of Onset of rise	Time of Peak of rise	Day of 1st subsequent normal value	Severity
II	14.	3 mg bd	ALT	10	10	14	++
III	18.	10 mg bd	ALT	10	11	21	++
			AST	10	11	13	+
IIIA	101	20 mg bd	T.bili	2 & 10	2 & 10	5 & 14	+ & +
	102	Placebo	Alk Phos	Raised at screening and throughout			+
			ALT	14	14	21	+
	104	20 mg bd	ALT	10	15	-	++
			AST	0	2 & 14	5 & 21	+
IV	28.	30 mg bd	ALT	9	9	-	+++
			AST	9	9	-	+++
	29.	30 mg bd	ALT	0	12	15	+++
			AST	10	12	14	+
			GGT	0	6	15	+
	30.	30 mg bd	ALT	6	11	-	+++
			AST	6	9	37	+++

b(6)

\+ = 0-49%
++ = 50-99%
+++ = 100%+

Figure 202 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 1 – Study 85136

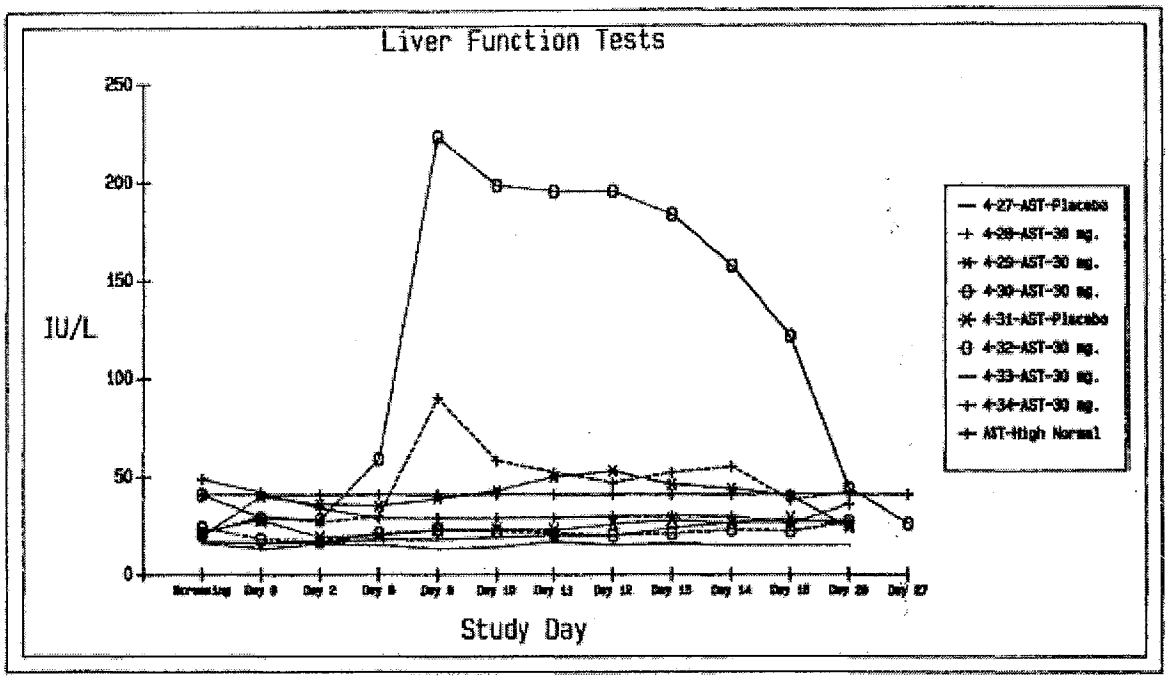
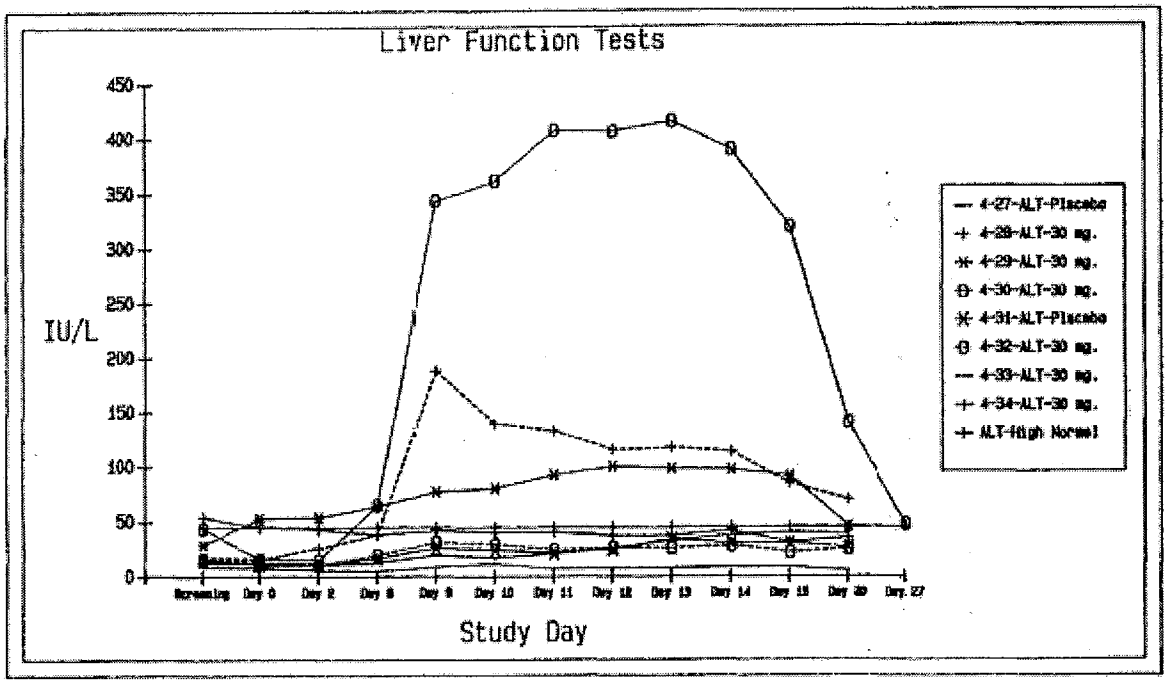


Figure 203 Plot of Significantly Elevated Liver Function Tests (> 3X ULN) vs. Time - Case 2 – Study 85136



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