Redacted under Section 40, Section 41 and Section 43 of the FOI Act.

THERE WAS CONCERN ABOUT POSSIBLE RENAL AND HEPATIC IMPAIRMENT. MONITORING OF HEPATIC AND RENAL FUNCTION WAS INADEQUATE DURING CLINICAL TRIALS

Response

2.1. **Pivotal studies: summary data**

The clinical protocols followed at [redacted] and [redacted] provided for monitoring of clinical chemistry values at Baseline, Days 4 and 7 [redacted] or at the start of each treatment cycle [redacted]. [redacted] have now carried out the retrospective data collection (refer to Questions 4 & 5) in which all available data were recovered; these are provided as raw data listings (Appendix 3). The grouped listings showed calculated mean values for each of the first 14 days, then weekly until Week 12, then monthly.

It was previously pointed out, in April 1993, in correspondence between [redacted] (Cilag Ltd) and [redacted] (MCA) (copies of correspondence in Appendix 4 for reference) that most of the rise in mean Bilirubin was due to abnormal values from two outlying patients, [redacted]. The clinical history for each of these patients was significant for serious systemic infection corresponding to the time of the rising Bilirubin. The summary of mean Bilirubin was re-run, omitting these two patients, and showed that the values for the rest of the study population remained within the normal limits for this parameter (refer to Appendix 4).

Additional analysis has been performed on the available chemistry laboratory data from the [redacted] and [redacted] studies, using a "Windowing" process (shown below), to more closely approximate the data collection points as specified in the protocol during the infusion and to capture data from patients who were tested, but not on the exact day specified in the protocol.

"Windowed" Day on Study	Definition
Baseline	Day 0 or closet day prior to infusion
Mid Infusion	Day 4 or 5 or 3
End Infusion	Day 7 or 8 or 6

The recalculated mean values for BUN, Creatinine, SGOT, SGPT, Bilirubin and Alkaline Phosphatase are presented in Appendix 5. With the exception of SGOT, baseline values for these parameters of renal and hepatic function were available for 84 to 88 of the 89 [redacted] patients and 34 of the 35 [redacted] patients. SGOT was infrequently performed at [redacted], and very few values are available for this parameter at Baseline, Mid or End Infusion. For other tests, Mid Infusion values were available for 52 to 55 [redacted] patients and 19 to 21 [redacted] patients. End Infusion values were available for 75 to 82 [redacted] patients and 23 [redacted] patients. The total number of patients from both centres with laboratory values, together with the mean values for the analyses, are shown overleaf in Table 4.

TABLE 4

Mean Laboratory Results

All Patients (N = 124)

PARAMETER	BASELINE		MID INFUSION		END INFUSION	
	N	Mean Value	N	Mean Value	N	Mean Value
BUN (mg/dL)	118	17.09	76	16.53	105	16.40
CREAT (mg/dL)	119	1.06	75	1.09	104	1.11
SGOT (U/L)	92	31.03	52	33.13	77	36.17
SGPT (U/L)	122	28.89	71	37.24	98	36.57
ALK PHOS (U/L)	121	89.55	71	85.27	100	98.31
BILIRUBIN (mg/dL)	118	0.70	71	0.76	100	0.99

With the exception of SGOT, at least 95% of the overall population had baseline values, 57% had Mid Infusion values, and 79% had End Infusion values, verifying that there was adequate monitoring of renal and hepatic function during the trials.

Based on these new summaries of renal and hepatic laboratory values as summarised in Table 4 and presented in full in Appendix 5, it can be seen that the mean values for parameters of renal and hepatic function remained within the normal ranges during the course of the infusion.

2.2. Pivotal studies: individual patient abnormalities

Data listings for individual patients in the [redacted] and [redacted] studies were reviewed to identify patients with serious laboratory abnormalities. There were no patients with WHO Grade 4 laboratory abnormalities (greater than ten times normal range). Patients with WHO Grade 2 (2.6-5 times normal range) and Grade 3 (5.1-10 times normal range) laboratory abnormalities are shown in Table 5 overleaf.

TABLE 5

[redacted]

Based on this review of individual patient data listings, it can be concluded that the clinically significant perturbations in Total Bilirubin and Alkaline Phosphatase appeared to be disease related. Other transient rises were also observed, but did not appear to be of clinical significance.

2.3. **European prospective trials: individual and summary data**

In addition, two ongoing prospective studies in patients with hairy cell leukaemia are being conducted by Cilag in the UK and in France, [redacted]. The planned enrolment for these studies is 30 patients each. Clinical chemistry data from these studies have been compiled for 38 patients (19 in P-101 and 19 in P-102) and are provided in Appendix 6 as listing by patient, with mean values calculated for the whole group. Mean values from Day 1 to 6 months for the various parameters are presented overleaf.

TABLE 6

UK and French Trials

Mean Chemistry Values for 38 Patients

Parameter	Day 1		Day 4		Day 7		Day 14		Day 28		3 mths		6 mths	
	N	mean value	N	mean value	N	mean value	N	mean value	N	mean value	N	mean value	N	mean value
Urea (IU/L)	38	6.3	38	6.4	38	5.6	30	6.2	34	5.8	27	5.7	30	6.0
Creat (µmol/L)	38	98	38	96	38	94	31	94	34	93	27	96	30	97
SGOT (U/L)	38	21	34	19	38	17	26	19	26	18	24	17	25	20
SGPT (U/L)	38	19	36	17	38	17	26	22	33	19	27	17	30	18
Alk Phos (U/L)	38	125	36	126	37	125	27	163	34	132	27	120	30	135
Bilirubin (µmol/L)	38	15	36	14	38	17	27	14	34	15	27	12	30	14

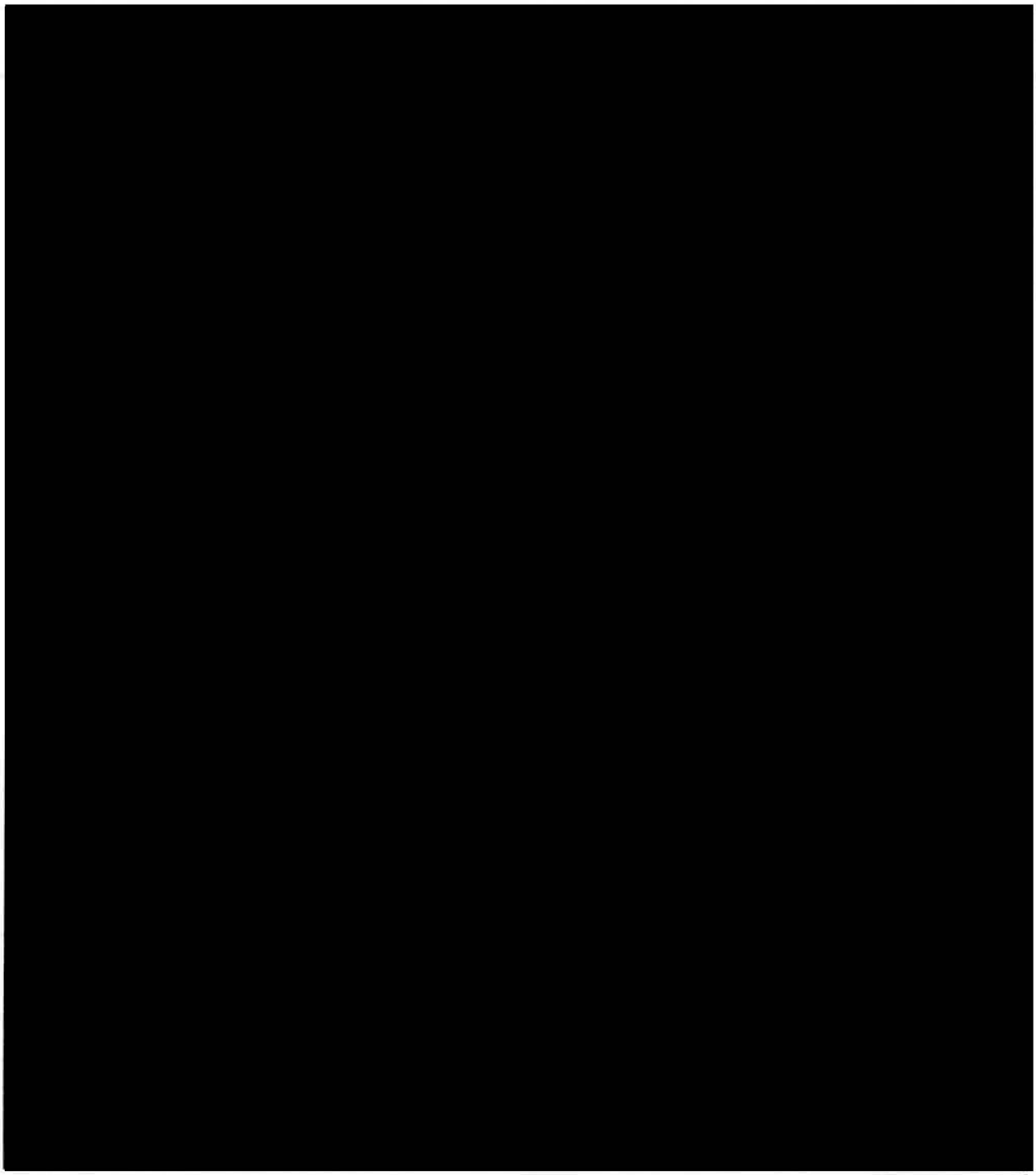
From a review of the summary in the table above, as well as the listings in Appendix 6, it can be seen that the mean values for each parameter during the period of the infusion and during the follow-up period remain within normal limits.

In addition, the patient listings were reviewed to identify individual patients with laboratory abnormalities as defined by the WHO grading system. There were no Grade 4 laboratory abnormalities. The Grade 2 and 3 abnormalities are listed in Table 7. Only two Grade 3 abnormalities were noted. Patient [redacted] had a single elevated urea on Day 4, with subsequent values all in the normal range. Patient [redacted] had an elevated SGPT at Month 2; no subsequent values are available yet. No Grade 2 or Grade 3 abnormalities of Creatinine were noted. Mild Grade 2 abnormalities of liver function were noted in several patients, and are described overleaf. In general, the abnormalities appeared to be transient and were not felt to be of clinical significance.

TABLE 7

UK and French Trials

Laboratory Abnormalities for Individual Patients



The data presented confirm that the mean laboratory values were within normal limits. Those individual results outside the normal limits were either transient or related to the underlying disease condition or did not appear to be related to direct drug toxicity.