5. REASSURANCE WAS REQUIRED ON LONG-TERM SAFETY OF LEUSTAT

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

Response

Safety data are discussed in three sub-sections:

5.1. Long-term safety data from the follow-up of the [redacted] & [redacted] studies

5.2. Effects on CD4 and CD8 counts

5.3. Safety data arising from the [redacted] study

5.1. Long-term safety data from the follow-up of the [redacted] & [redacted] studies

One hundred and two of 124 (82%) patients enrolled and treated in the two clinical studies at [redacted] and [redacted] had follow-up information available to assess significant safety issues following cladribine therapy in the period 30th September 1991 to 30th June 1993 (Appendix 7). Fourteen of the 102 patients received a second course of cladribine therapy and one patient received a third course. Table 9 presents, by body system, significant adverse events reported by the 102 patients who were followed up in the period from 30th September 1991 to 30th June 1993.

A total of 19 patients (19% of the population) reported at least one adverse event in the follow-up period.

TABLE 9

Patient Incidence of Adverse Experiences Summarised by Body System
Efficacy and Safety update as of 30th June 1993
All ADVERSE Experiences from 30th September 1991 to 30th June 1993

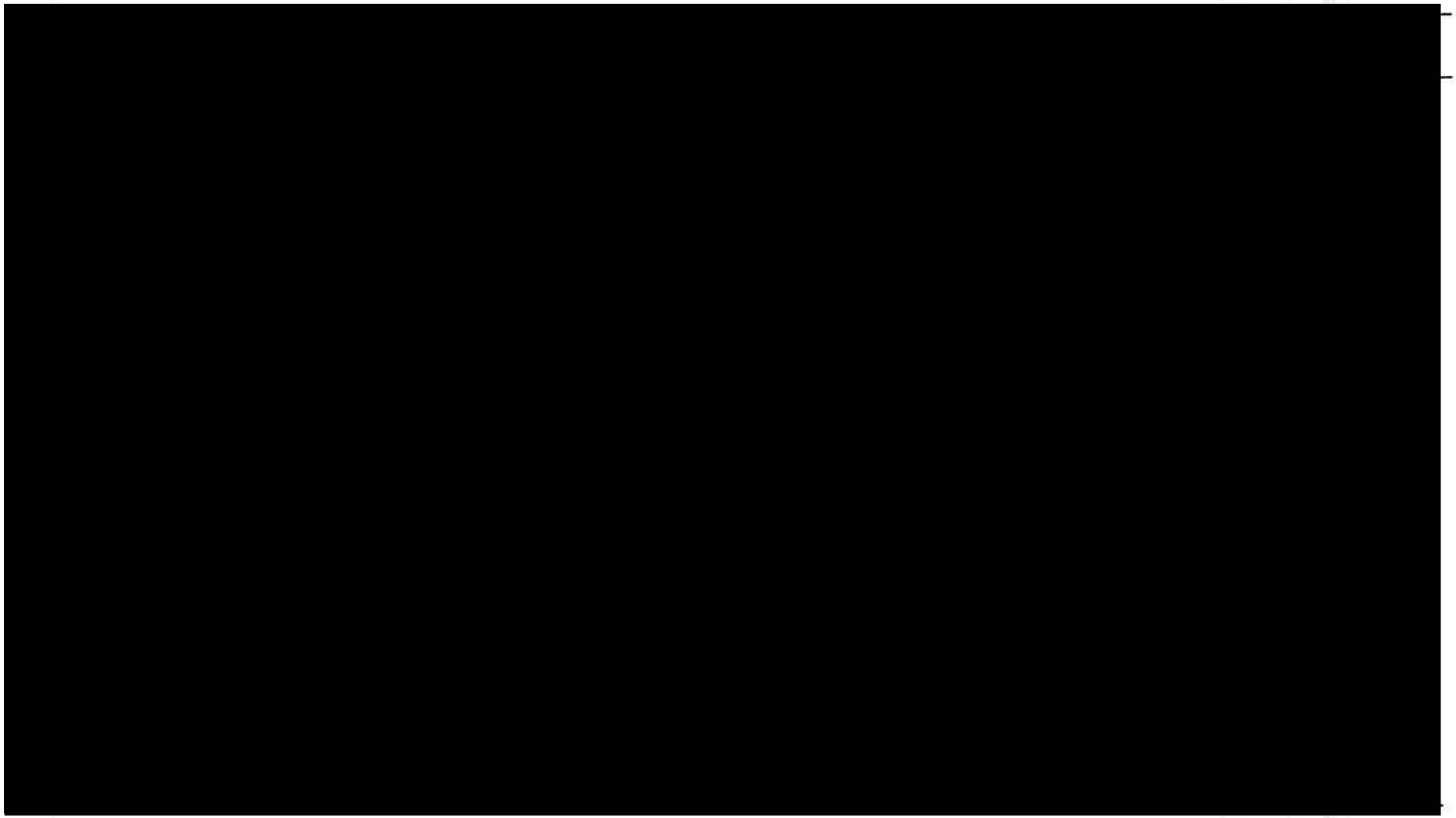
Adverse Experience by body system	Number
Body as a whole	3
Haemic and lymphatic system	1
Special senses	3
Cardiovascular system	1
Respiratory system	8
Gastrointestinal system	5
Genital/reproductive system	1
Urinary system	3
Skin and subcutaneous tissue	1
Musculoskeletal system	1

Table 10 presents a by-patient list of all recorded adverse experiences.

In summary, analysis of safety data available after a doubling of the median follow-up period for the 124 patients originally presented in report MR92049 reveals that the safety profile is acceptable and continued follow-up reveals no new trends in adverse events reported.

TABLE 10

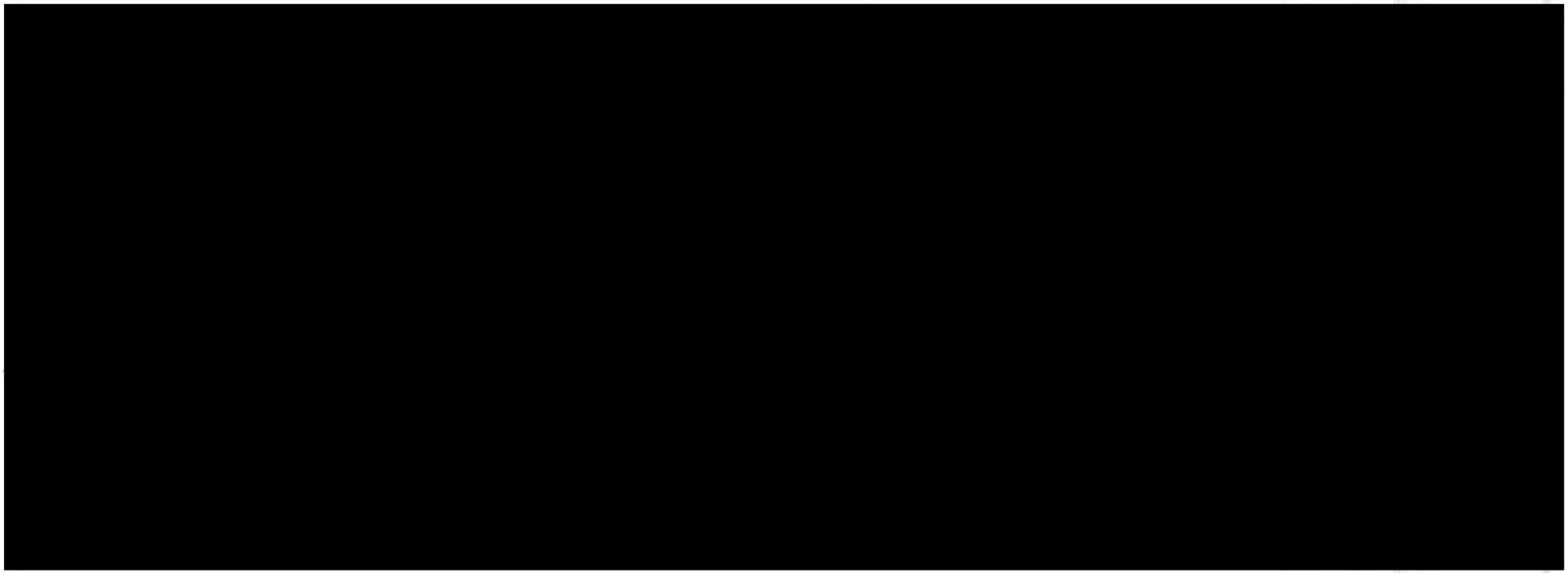
Adverse Experiences from 30th September 1991 to 30th June 1993



(Continued)

TABLE 10 cont...

Adverse Experiences from 30th September 1991 to 30th June 1993



5.2. Effects on CD4 and CD8 counts

Like 2'deoxycoformycin (Nipent), cladribine is immunosuppressive and causes decreases in B and T lymphocyte counts (both CD4 and CD8). Recovery tends to occur between 6-12 months after treatment[1].

In May 1994 [redacted] published data which updates the severity and duration of drug-induced lymphocytopenia in patients with hairy cell leukaemia who had responded to cladribine therapy. A copy of this paper is included as reference (22). [redacted] initial report of this cohort of patients was reported in [redacted]. The findings from the 1994 paper are summarized below.

Forty-six patients received a single course of cladribine therapy at 4mg/m^2 daily by continuous infusion for 7 days. Forty patients who responded were followed for a median of 100 weeks. Four patients had evidence of relapse, although none sooner than 38 weeks following response. No patients died. The actuarial relapse-free survival rates were 97% and 90% at one and two years, respectively.

The percentage of CD4+ and CD8+ lymphocytes were determined using standard flow cytometric techniques. The normal ranges for absolute CD4+ and CD8+ lymphocytes were 365-2400/µL and 270-1600/µL, respectively. Seventeen patients had pre-therapy CD4+ and CD8+ count measurements. The median baseline CD4+ count was 743/µL (range: 58-2210/µL). The median baseline CD8+ count was 288/µL (range: 75-2342/µL).

All 18 of the patients with baseline evaluations had at least one post-therapy determination at a median of 23 months after therapy. CD4+ counts remained significantly lower than baseline at follow-up; all 18 patients had CD4+ counts in the normal range post-therapy. CD8+ counts in the 18 patients at 23 months were not significantly different from baseline.

The reversibility of CD4+ lymphocytopenia was evaluated in the 31 patients who had more than one lymphocyte subset determination following treatment. Evaluation of these sequential determinations of CD4+ and CD8+ counts showed a significant increase in both CD4+ and CD8+ counts was noted at the median interval of 22 months. The median incremental change in absolute CD4+ lymphocyte counts was 136/µL.

Among the 40 patients evaluated, and despite the documented myelosuppression, no opportunistic infections or secondary malignancies were recorded. Based on the findings in this report, CD4+ counts increase somewhat after cladribine therapy but do not return to baseline levels even one year following a single course of cladribine. As CD8+ counts were indistinguishable from baseline levels at a median of 23 months after treatment, it appears that cladribine is selectively cytotoxic for CD4+ lymphocytes.

Other investigators have reported on the reduction of CD4+ and CD8+ cells following treatment with cladribine: [redacted] and [redacted].

In the study by [redacted] the median post-treatment CD4 lymphocyte count was 540/mm^3 after 12 months.

In the paper by [redacted], a rapid recovery of subgroups of activated lymphocytes was demonstrated following administration of cladribine to patients with hairy cell leukaemia. Phenotypic studies of leukaemic cells from peripheral blood and the bone marrow of 75 symptomatic patients with hairy cell leukaemia were characterized by flow cytometry for a variety of surface markers. The hairy cells always expressed CD19, CD20, HLA-DR, CD45RA; the majority also expressed B-Ly-7. Other markers, such as CD38, CD5, CD15, CD4, CD10 and CD45RO were occasionally expressed.

Lymphocyte subsets have also been assessed in a small cohort of five patients with complete remissions following treatment with cladribine who were resistant to previous treatment with deoxycoformycin treatment or did not tolerate the drug [redacted].

The results are presented in tabular form below:

TABLE 11

Changes in Lymphocyte Subsets Following Cladribine Therapy

[redacted]

The immunophenotypic profile of Patient [redacted] was not determined. This patient achieved only a partial response after cladribine therapy and died 6 months after treatment. The course of [redacted] disease was complicated by bacteraemia and cutaneous Herpes zoster.

In the case of 2'-deoxycoformycin, CD4 and CD8 lymphocyte counts fall below 200 per cubic millimetre in all patients[1]. These changes persisted throughout the 14 month therapy and for up to several years after discontinuation. The shorter duration of immunosuppression that follows the administration of cladribine compared to 2'-deoxycoformycin may be due to the shorter duration of treatment.

It is concluded that cladribine does cause a decrease in CD4 and CD8 counts. The CD4 counts can remain below baseline levels for at least one year after a single course of cladribine therapy, although the CD8 counts recover more rapidly. The follow-up of patients in the clinical studies has not suggested any pre-disposition to opportunistic infections or other consequences of prolonged immunosuppression.

5.3. Safety data arising from the [redacted] study

The [redacted] Group C protocol was set up as a treatment IND to enable physicians to use cladribine while the New Drug Application was undergoing assessment at the FDA.

The annual reports of this study dated August 1992 and August 1993 have been submitted to the FDA and are presented in Appendix 8, together with the [redacted] Abstract as presented at ASCO in May 1993 (Appendix 9).

981 patients were registered on the study by 657 physicians in 12 months (March 1992-March 1993), including 343 from outside the USA. Median follow-up at the time the ASCO presentation was compiled was four months. 944 patients received at least one course of cladribine given as a 7-day infusion of 0.1mg/kg/day. To date, 27 patients have received a second course. The Group C protocol closed to accrual on 26th March 1993 when cladribine became commercially available in the USA. Data collection continues as patients are being followed for survival.

Serious adverse reaction data current as of August 1993 are tabulated in Table 12. This table itemises 7 deaths and includes the four early deaths considered by [redacted] The remaining three deaths occurred more than one week after the end of the 7-day infusion period.

This short-term safety data on a large number of hairy cell leukaemic patients has been included as an extension to the data already provided. It is compatible with the experiences in the [redacted] and [redacted] study and does not have any impact on the labelling of the product.