

# ANIMAL CLINICAL TRIALS

***THE OPINIONS GENERATED FOR STUDIES ARE BASED UPON INDEPENDENT EXAMINATION AND EVALUATION OF ANIMALS. THESE DATA SHOULD NOT BE CONSTRUED AS DEMONSTRATING THE SAFETY OR EFFICACY OF CV 247 SINCE THE PRODUCT HAS NOT RECEIVED REGULATORY APPROVAL TO DATE.***

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## **Animal Studies**

CV247 has been investigated in 2 studies undertaken in dogs. This paper concerns the first study undertaken during the period from 1988 to 2000.

### **2 An open clinical assessment of CV247 for the treatment of cancer in dogs**

This open study was undertaken in a single veterinary practice to assess the effect of CV247 in treating neoplasms in dogs (and cats). All cases were independently monitored by the named Veterinary Surgeon of the Imperial Cancer Research Fund.

A total of 51 dogs were monitored in the study. All cases were firmly diagnosed by Veterinary Hospitals, independent veterinary surgeries or laboratories.

A number of different parameters were monitored during the course of the study and the effectiveness of treatment was analysed against:

1. Tumour regression
2. Extension of life beyond forecast.
3. Quality of remaining life.
4. An Overall success factor

### **Tumour Regression**

Tumour regression was either be observed or measured or both. In cases where the tumour was internal it was sometimes possible to determine regression by palpation or judged by the elimination of symptoms.

### **Extension of life beyond forecast**

Whilst life expectancy is a subjective, the actual life span experienced from the time of diagnosis is factual. The difference between these periods of time was used to express the success of the treatment. The forecast of life expectancy was listed on each record sheet, either as had been quoted by the local Veterinary Surgeon during original treatment or Pathology laboratory after analysis of the biopsy. A panel of Veterinary Surgeons also reviewed each case and it was their collective view of "reasonable expectation of life" after careful examination of all relevant facts.

## Quality of Life

The analysis used in this study was based upon a judgement of the animal's general condition compiled at the time of examination and subsequently assessed by the Veterinary Panel. A hierarchical scale was developed for this purpose:

1	Poor	Dull, listless, moribund.
2	Poor	Marginal improvement on 1
3/4	Below average	Eating & drinking
5	Satisfactory	Eating & drinking. Good appetite
6/7	Above average	As stated at 5. Animal is alert
8	Good	As stated at 6. Animal is active with good exercise tolerance.
9	Very Good	Behaviour as before. Health restored to previous level.
10	Excellent	Health exceeding that experienced before illness

## Overall success of the treatment

A subjective assessment of the overall effectiveness of the treatment was made by reference to all measures including tumour regression, life expectancy and quality of life.

The Veterinary Panel considered all cases in the study and gave their combined view of the overall effectiveness of the treatment. Three categories were used:

- i) Success
- ii) Qualified Success
- iii) Failure

The amount of drug received varied according to body weight.

<15lb	15-30lb	30-45lb	45-60lb	60-75lb	>75lb
1.5ml	3ml	4.5ml	6ml	7.5ml	9ml

## Results

### Duration of Treatment

Duration of treatment in months	total number of dogs
0.5-3	20
4-6	12
7-9	9

10-12	2
>12	7

The duration of treatment ranged between 0.5 and 25 months.

### **Safety**

No adverse effects were reported in the study. 3 dogs died of renal failure but the likelihood of this being linked to treatment by CV 247 was ruled out by the Veterinary Panel, because of the respective animal's history and age.

### **Efficacy**

#### **Tumour Regression**

The probability of tumour regression amongst all animals studied, irrespective of cancer type was:

A total of 17 tumours appeared following examination to have regressed as tabulated below:

Whether this is treatment related cannot be confirmed at this point in time.

Table 1 Tumour regression as assessed by independent review

<b>tumour type</b>	<b>total presenting</b>	<b>total regressed</b>
sarcoma	21	5 (24%)
carcinoma	24	9 (38%)
lymphoma	3	2 (66%)
melanoma	2	1(50%)

The probability of regression is shown in the following table:

Table 2 All cancers as assessed by independent review

	<b>Probability of Regression</b>	<b>Upper 95% confidence limit</b>	<b>Lower 95% confidence limit</b>
Dogs	0.37	0.58	0.23

An additional 6 tumours reduced in size but is not included in cancer regression analysis above.

There are also data to suggest that some tumours that did not regress nor reduce but were held in abeyance.

## Extended Life.

Of the 51 dogs that formed this study 38 (74.5%) were considered by the veterinary assessors as possibly exhibiting an increase in their life expectancy beyond that which would have been a “reasonable expectation” at the time the prognosis was made. However this is a qualitative determination based upon individual judgement. On this basis the mean total life beyond total expectancy was 44.2 weeks for all dogs for all cancer types. The average life extension for dogs with carcinomas was 27.2 weeks, and sarcomas 55.4 weeks. Analysis for each species and for each major cancer type is as follows:

Table 3 All Cancers as assessed by independent review

	No. with an increased life	Mean of the total recruited	Mean of the total with an increased life
Dogs	38/51 (74.5%)	44.2 weeks	59 (range 3-399) weeks

Though the majority of cases have been cancers invading soft tissue, the study did include cases of cancers infiltrating hard tissue. Osteosarcoma was diagnosed in 4 dogs (cases 003, 006, 012 and 026). Life expectancy varied considerably and the following table examines the difference between results in hard and soft tissue cancers.

Table 4 Effect of CV247 on hard and soft tissue sarcoma cases in dogs as assessed by independent review

	Independent estimation of total life beyond expectation for whole treatment group	Average	Sample size
All dogs with sarcoma	887 weeks	55.4 weeks	16
Soft Tissue cases	844 weeks	70.3 weeks	10
Hard Tissue cases	43 weeks	10.7 weeks	4

## Quality of Life

Case notes for individual animals could suggest that some improvement in the well being of the majority of animals following treatment with CV 247 occurred. Of the 51 dogs treated, 2 had inadequate records and only 4 dogs showed no improvement in quality of life scores.

Table 5 Change in Quality of Life score as assessed by independent review

<b>Change in Q of L score from point of entry until study termination</b>	<b>Total number of dogs</b>
9	3
8	11
7	3
6	4
5	5
4	4
3	6
2	6
1	3
0	4

The range of quality of life scores for each dog from the point of entry into the study until the end of the treatment or observation period is presented in the following table

Table 6 Quality of Life scores as assessed by independent review

<b>Dog number</b>	<b>score on entry</b>	<b>score on termination</b>	<b>treatment period</b>
01	1	9	6.5 months
02	4	7	4 months
03	4	9	3 months
04	1	9	1.5 months
05	4	10	4 months
06	1	9	3 months
07	2	9	5 months
08	1	9	3 months
09	1	9	1 month
10	6	8	5 months
11	3	7	1 month
12	3	7	2 months
13	8	9	6 months
14	1	9	0.5 months
15	6	9	11 months
16	1	9	2 months
17	1	9	7 months
18	2	8	2 months
19	1	10	8 months
20	1	9	5 months
21	1	10	8 months
22	1	10	8 months
23	3	10	25 months
24	2	9	7 months
25	2	10	4 months
26	2	8	6 months
27	4	9	24 months
28	3	6	4 months

29	4	4	2 months
30	4	9	25 months
31	3	9	7 months
32	4	9	22 months
33	5	8 (3)	4 months
34	4	6	2 months
35	5	5	3 months
36	5	5	1 month
37	3	7	1 month
38	4	5	2 months
39	3	6 (3)	8 months
40	4	9	7 months
41	6	8	4 months
42	3	5	1 month
43	1	9	n/r
44	n/r	9	13 months
45	6	8	15 months
46	5	9	18 months
47	6	7	5 months
48	2	5 (4)	11 months
49	1	3	1 month
50	n/r	n/r	1 month
51	3	3	1 month

Number in brackets refers to final quality of life score where this is worse than the highest scored during the treatment or observation period

A rating of 8 and above (good or better) was considered to be in keeping with the normal life style for the majority of animals whilst a rating of 10 is considered excellent and provides a life style not previously seen in the animal.

The table below shows the number of cases that have scored 8 or above during treatment with CV 247.

Table 7 Quality of Life rated good or better as assessed by independent review

	<b>Quality of life good or better (8,9 &amp;10)</b>	<b>Quality of life Excellent (10)</b>	<b>Sample size</b>
Dogs	34 (66.6%)	6 (11.8%)	51

### **Overall success of the treatment**

The Veterinary panel considered each case in the study to assess the overall effectiveness of treatment. Their findings are shown in the following tables.

Statistics have been compiled showing the probability of an outright success but often those marked “qualified success” were qualified because there was insufficient treatment

time that had elapsed to confirm the findings. However there was evidence to suggest that there could have been a successful outcome.

Table 8 Overall success of treatment as assessed by independent review

	Success	Qualified Success	Failure (inconclusive)
Dogs	19 (37.3%)	18 (35.3%)	13 (1) (27.5%)

The probability of animals responding to treatment and the 95% confidence limit is expressed in the following tables:

Table 9 Probability of successful treatment as assessed by independent review

	Success	Success plus Qualified Success	Sample Size
Dogs	0.41	0.79	51

Table 10 95% Confidence limits for a successful treatment as assessed by independent review

	Success.Upper 95% limit	Success. Lower 95% limit	Success plus qualified success.Upper 95% limit	Success plus qualified success. Lower 95% limit
Dogs	0.56	0.24	0.89	0.65

## Global Analysis

A total of 104 dogs have been treated with CV247 for between 0.5 and 30 months (mean 6.9) in the 2 clinical studies. There were no reports of any adverse events.

The dogs were presented with a wide variety of tumour types, often in a poor state of health with a reduced quality of life. Most were given a guarded or poor prognosis.

Change in quality of life scores	Total number of dogs (Study 1)	Total number of dogs (Study 2)	TOTAL
9	0	3	3
8	2	11	13
7	11	3	14
6	6	4	10
5	5	5	10
4	6	4	10
3	6	6	12

2	3	6	9
1	1	3	4
0	8	4	12
not recorded	5	2	7
TOTAL	53	51	104