

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.

Animal Studies

CV247 has been investigated in 2 studies undertaken in dogs. This paper concerns the second study.

1 A Clinical Study of CV247 for the Treatment of Cancer in Dogs

Introduction

The study was conducted following the granting of an Animal Test Certificate No. ATC18130/0001.

The study was undertaken in 3 veterinary practices:

Study Objectives

The study objectives were to assess disease response, quality of life, and tolerability to CV247 in dogs with diagnosed cancer. Owners gave written consent following perusal of the information sheet provided.

Overall Study Design

The study was designed as an open label evaluation of the effectiveness and tolerability of CV247 in 50 dogs with malignant disease over a 6 month period. Dogs were to have uncontrolled progressive disease at trial entry, ideally histologically proven. CV247 was administered orally, at a dose level range, which was weight dependant, and continued daily until the point where either the owner wished to withdraw, or the investigator recommended withdrawal due to disease progression, or death. Though the investigative period was for 6 months, dogs could remain on the medication indefinitely, if benefit continued. Owners were asked to attend the clinic at fortnightly intervals for assessment of tumour progression. A quality of life questionnaire, as detailed in the protocol was completed at intervals by the owners. A quality of life score was subsequently assigned by the investigator Scoring was as per the following:

- 1=poor (dull, listless, moribund)
- 2=poor (marginal improvement on 1)
- 3=below average (eating and drinking)
- 4=below average (marginal improvement on 3)
- 5=satisfactory (good appetite)
- 6=above average (good appetite & animal is alert)

- 7=above average (marginal improvement on 6)
- 8=good (6+animal active with good exercise tolerance)
- 9=very good (health restored to level prior to illness)
- 10=excellent (health exceeding that prior to illness)

Symptom response was independently assessed, and took into account, quality of life over the study duration for each animal, tumour regression and symptom relief, and the duration of treatment. Response was recorded as either:

- a) disease progression
- b) disease stabilisation
- c) disease regression

Selection of Study Population

Dogs were selected on the grounds of having uncontrolled progressive disease on trial entry. Alternative treatments or actions had been offered but declined by the owners.

Inclusion Criteria

- a) Histologically proven cancer with documented prognosis, except where such intervention would prove detrimental to the animals well-being.
- b) Agreement by the owners to present their animals for regular clinic visits
- c) Agreement by the owners to adhere to the dosage regimen for the duration of the treatment period
- d) Agreement by the owners to adhere to the recommended diet
- e) Agreement to allow a post mortem to be carried out in the event of death during the study, where practicable

Exclusion Criteria

- a) No quantitative means of identifying the presence of cancer
- b) Prognosis of less than 28 days
- c) Owners unwilling to attend regular clinics, adhere to the dosing regimen, and adhere to the diet recommendations
- d) Dogs responding to other cancer treatments
- e) Dogs that have undergone radiotherapy treatment

Removal of dogs from therapy or assessment

Owners who wished to withdraw their pets could do so at any time. Dogs would have been withdrawn from the study should any side effect, in the opinion of the investigator, and despite any reduction in dose administered, be of sufficient severity or cause

unacceptable levels of distress. Dogs would also have been withdrawn with significant abnormal laboratory values, an unsatisfactory therapeutic effect or protocol violation.

Treatments

Treatments Administered

All dogs were treated with CV247.

Identity of investigation product

The study was open label.

Selection of doses in the study

Dogs were dosed within a range according to weight. Each ml of CV247 contained:

40mg Ascorbic acid
35mg Sodium salicylate
2mg Manganese gluconate (equivalent to 0.25mg manganese)
2mg Copper gluconate (equivalent to 0.28mg copper)

The formulation was made up immediately prior to use as an aqueous solution

This dose selection was based upon doses which might be administered when the individual components were taken either as dietary supplements or, in the case of sodium salicylate, as recommended as a therapeutic medicament, all adjusted for weight. The dose range used was:

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

The required volume was administered daily into the back of the mouth using a syringe. Doses could be divided if preferred.

Prior and concomitant therapy

All additional medication was documented and was not permitted without prior consultation with the investigator.

Owners were required to ensure that their pets adhered to a diet which provided high quantities of nutrients, vitamins and minerals but which avoided so far as was possible, artificial colourants, flavourings and preservatives.

Treatment compliance

Treatment compliance was monitored throughout the study, so far as was possible by the investigators.

Efficacy and Safety Variables

Efficacy

The primary efficacy assessment was made by the investigator using the 10 point quality of life check list detailed above. This was based upon both the investigators observations and the owner's quality of life check-list. The latter included questions relating to general appearance and activity levels and required the owner to score accordingly, as detailed in the protocol.

Tumour regression or progression was either observed or measured. Visible tumours were measured using calipers. Internalised tumours were, where possible, assessed by palpitation. Occasionally, X-ray, scan or biomarker data was also available. When not measurable, tumour status was judged by changes in symptoms. Life expectancy was a subjective judgement made from the time of diagnosis, taking into account age and disease severity.

A global judgement of tumour status for each animal, was made by an independent veterinary expert on completion of the trial and recorded as either disease progression, stabilisation or regression.

Safety

Adverse events were recorded following both spontaneous declarations by owners at the clinic visits and by direct questioning by the investigators.

Flow Chart

Procedure	entry	visit 1	visit 2	visit 3	visit 4	Contd
Consent	X					
Med Hist	X					
Phys exam	X	X	X	X	X	X
Q of L	X	X	X	X	X	X
ConMed	X	X	X	X	X	X
AEs		X	X	X	X	X

Med Disp	X	X	X	X	X	X
compliance		X	X	X	X	X
Diet check	X	X	X	X	X	X

Data was summarised with respect to demographic and baseline characteristics.. With regard to clinical response and quality of life these were examined at each clinic visit, and upon study termination for categorisation into, either progressive disease, stable disease, or disease regression.

For the purpose of analysis, the degree of change observed in quality of life was separated into 3 categories, no change, significant change and highly significant change. A significant change equated to a difference of 2 from the start of the study to termination/withdrawal, whilst a difference of 4 constituted a highly significant change.

Disposition of dogs

A total of 53 dogs with a wide variety of cancers were recruited, as detailed in table 1.

Protocol Deviations

Protocol deviations were mainly limited to the recording of extension of life expectancy. However it was not always possible for owners to visit the clinic at 2 weekly intervals, and thus data was not available for some dogs with that level of frequency. The study included dogs with all types of cancer and not just carcinomas. Proof of disease by histological examination was sometimes waived when a veterinary surgeon deemed it unnecessary on presentation of the animal. It was sometimes not possible to conduct a postmortem where dog owners chose to dispose of the dog themselves.

Data Sets Analysed

Any adverse events, and changes in vital signs were evaluated. All patient efficacy data was tabulated under intention to treat.

Demographic and Other Baseline Characteristics

A total of 53 dogs were recruited (25 female and 26 male, 2 were not recorded) with a mean age of 9.8 years (range 3-17), though details on dog 53 were not available for the independent assessment in table 3. Details are included in table 1 below.

Measurements of Treatment Compliance

Compliance was checked, so far as was possible, by the investigator No record was kept of drug returns.

Analysis of Efficacy

Table 1. Tabulated Summary of the Effects of CV247 in treating dogs with cancer as assessed by independent review

No	Breed	Age on entry yr	cancer type	prognosis on entry	Pd on CV 247	QofL Start	QofL end	disease respse P,S,R
1	Wirehair terrier	12	breast/lung	poor	1m	1	1	P dec
2	cross terrier	10	melanoma, squamous cell. R leg	guarded	22m	7	9	S
3	KingCharl spaniel	9	breast	poor	20m	3	6	P dec
4	pointer	6	adenocarc	poor	12m	1	6	S dec nr
5	bearded collie	6	nasal	guarded	6m	6	9	P dec
6	labrador	10	melanoma	poor	12m	9	9	S dec
7	bearded collie	13	rectal	guarded	8m	3	9	R dec
8	rottweiler	10	heart	poor	4m	1	8	S dec
9	collie cross	12	osteosarc	n/r	4m	2	9	R
10	labrador	9	melanoma	n/r	7m	n/r	8	R
11	whippet	6	lung	guarded	7m	4	10	S
12	collie cross	13	round cell	poor	2m	1	5	P dec
13	GS Dalmation	12	spleen	guarded	3m	1	8	P dec
14	Golden retriever	6	mast cell	n/r	17m	3	9	S
15	Wirehair terrier	13	adenoma	guarded	7m	7	7	S dec
16	Golden retriever	5	sarcoma	guarded	6m	2	7	R
17	terrier cross	8	brain	guarded	<1m	2	2	P dec
18	pointer	14	spleen	grave	7m	7	8	S dec
19	bearded collie	8	ovarian	v poor	8m	1	9	S dec
20	labrador	12	spleen	guarded	3m	1	5	P
21	labrador	7	pancreas	poor	2m	3	7	S
22	Cocker spaniel	12	bladder	v poor	16m	2	9	R
23	bearded collie	11	sarcoma	v poor	<1m	2	5	P dec
24	rough collie	8	squamous cell, r lip	v poor	13m	3	9	R
25	Cocker spaniel	10	anal adeno	v poor	9m	2	9	R dec nr

26	boxer	3	skin lymphosarc	n/r	9m	6	9	P dec
27	labrador	10	spleen	poor	7m	6	8	S dec
28	collie cross	12	haemangio pericytoma	good	8m	8	8	S
29	pomerania	11	brain?	open	30m	8	8	S
30	Golden retriever	17	peri anal adenoma	n/r	7m	2	6	S dec
31	cross breed	11	mast cell	n/r	10m	3	9	R
32	Patterdale terrier	15	spindle cell f leg	n/r	2m	n/r	n/r	P dec
33	boxer	11	prostate	n/r	1m	n/r	n/r	P dec
34	labrador	7	nasal	n/r	3m	2	9	S
35	airedale	10	melanoma	n/r	7m	4	10	R
36	lurcher	12	liver?	n/r	1m	n/r	n/r	P dec
37	labrador	9	lung	poor	12m	2	9	R
38	collie cross	13	breast	v poor	8m	2	9	S
39	Springer spaniel	11	osteo + lung mets	v poor	2m	3	8	S
40	B mountain dog	8	eye lymphoma	n/r	5m	8	8	S
41	Yorkshire terrier	9	lung	n/r	7m	5	5	S
42	Golden retriever	10	spleen + lung mets	v poor	2m	n/r	8	P dec
43	wirehair terrier	10	hepatoid gland	poor	13m	2	9	R
44	Yorkshire terrier	12	pancreas	v poor	9m	1	9	R
45	lurcher	9	lipoma	guarded	10m	2	9	S
46	boxer	7	round cell	n/r	4m	4	8	S
47	alsation	10	lung/spleen	poor	1m	4	6	P
48	Golden retriever	7	mast cell	n/r	3m	3	8	S dec
49	boxer	4	lymphoma	poor	1m	5	8	P
50	Samoyed	13	nasal	v guarded	8m	2	5	S
51	cross bred lurcher	7	spindle cell sarcoma	guarded	10m	5	9	S
52	whippet	11	spindle cell sarcoma	n/r	3m	3	8	S
53	GS Dalmation	10	spindle cell sarcoma	poor	14m	2	9	R
				MEAN	7.4	3.6	7.5	

n/r=not recorded

Table 2 Duration of treatment

mths	1	2	3	4	5	6	7	8	9	10	12	13	14	16	17	20	22	30
total	7	5	5	3	1	2	8	5	3	3	3	2	1	1	1	1	1	1

Primary Response Variable

The primary response variable was quality of life. Using the investigators grading system detailed above, then a comparison of the scores on entry into the study, with the final scores for each dog showed the following:

A score was recorded for 48 animals at the start of the study and 50 upon completion at 6 months, or earlier if the dog was withdrawn. The mean scores are tabulated above in table 1. Based upon the independent observations no dog had a lower score for quality of life upon completion or termination. The observations also considered that no change was recorded for 15 (28%) animals; whilst 38 (72%) dogs showed an improvement in quality of life, with 29 (55%) having an increased score of 4 or more. There was no clear trend for response according to cancer type, though more dogs with carcinomas had a change of 4 or more in the quality of life score, compared to animals with other cancers.

Secondary Response Variables and tabulation of individual responses

Tumour regression was measured, so far as was possible by either using calipers for external tumours, palpation for internal ones and/or by symptom description. The results are tabulated in the table below

Table 3. Tabulated tumour regression data as assessed by independent review

West Highland terrier 12 years Started 2/3/02 Case1	Suspected Mammary carcinoma confirmed by x-ray at Queens Veterinary school Cambridge. Poor QoL improved in first period of treatment as excessive thirst abated. Tumour size of 3.5cm remained constant. QoL was poor throughout the 1 month period of treatment
X bred Terrier 10 years Started 8/4/02 Case 2	Melanoma and Squamous cell carcinoma. Right Fore leg. Excised by local vet and confirmed by IDEXX Prognosis – regional lymph node spread and lung mets possible. Below average QoL had improved to very good by end of study period. Animal went without treatment and returned after 1 year still without showing any tumour re-growth and with very good QoL. Animal re-located after two years from start.

<p>Cavalier KCS 9years Started 27/4/02 Case 3</p>	<p>Mammary carcinoma confirmed by histology by IDEXX labs Apparent local spread in mammary tissue & ducts. Above average QoL was maintained during the study but the tumour grew from 1.8x3mm to 4.0x4.2mm. Condition maintained for total period of 17mths but the next three months showed a decline in QoL to below average and the animal died in January 2004 after 20mths of treatment</p>
<p>German Pointer 6 years Started 22/6/02 Case 4</p>	<p>Adenocarcinoma prescapular lymph node confirmed by x-ray and histology by Finn labs. Poor prognosis. Dog in poor and distressed condition chronic cough, panting with poor exercise tolerance. QoL improved to above average and animal with good exercise tolerance within the first month of treatment and maintained throughout the study period. LN size reduced initially from 5cm dia to 3.8cm but later returned to 5cm dia. February 03 owner confirms dog's progress when collecting medicine. In June 2003 owner reports dog involved in accident and was p.t.s.</p>
<p>Bearded Collie 12 years Started 22/6/02 Case 5</p>	<p>Nasal carcinoma confirmed by histology by AXIOM Labs. Nasal bleeding occurred 3 months before diagnosis and starting treatment with CV 247. Above average QoL improved to very good in the first two months treatment. Periods of nasal bleeding became intermittent and then occasional despite frequent sneezing. Owner reports pleased with dog's condition on 22/7/02 and again on 28/9/02, stated dog's condition better than 7/8 months ago. Debris snorted from nose improved breathing Dogs appetite, drinking and exercise tolerance normal. Blockage of Nasal passages and slight bleeding returned. In November (last visit) dog had visibly lost weight nasal tumour growing and had suffered with Pneumonia, treated locally. Owner reported dog pts by local vet 21/12/02.</p>
<p>Labrador 10 years started 2/8/03 Case 6</p>	<p>Malignant melanoma diagnosed by IDEX laboratories. Commented that it is "aggressive neoplasm with a poor long term prognosis." First presented on 2/8/03. Dog in good condition and enjoyed good QoL from the outset of treatment to well past the 6 month study period (February 04). Dog remained on treatment and was last seen on 24/7/04 when dog was in good condition and no sign of tumour re-growth. Dog put to sleep as a result of the melanoma.</p>
<p>Bearded Collie 13.5 years started 27/10/02 Case 7</p>	<p>High grade hepatoid (Rectal) tumour doubt expressed over complete removal. IDEXX gave guarded prognosis in Dec 01. Tumour recurred in Sept 02, 4cm dia QoL below average. treatment in first month interrupted by pneumonia - treated with antibiotics. . At 2 month point QoL improved to well above average & tumour reduced to 2.5mm dia. Other ailments gone. Tumour reduction continued to 1.5mm at the end of the study period when the dog was enjoying a good QoL. Animal last examined on 7/6/03 Dog died in July 2003 but enjoyed good QoL until the end</p>

Rottweiler Started 26/4/03 Case 8	Heart based tumour diagnosed by RVC. No treatment available, advised to keep dog comfortable at home. Animal tired and listless poor exercise tolerance. CV 247 treatment over 5 month period appetite returned, tiredness disappeared and good exercise tolerance restored. QoL was restored to Good. Animal last examined on 19/8/03. Owner reported dog died of Heart attach in late September
GSD X 10 years Started 5/6/04 Case 9	Spindle cell tumour confirmed by Finn Pathologists. History of swellings from 20/9/03 one removed from under throat. One on head larger. Swelling removed re-grew rapidly. Biopsy 10/5/04 confirmed spindle cell tumour. When first seen in May, dog had poor Qol and rapidly growing tumour above right eye (small orange size). Tumour reduced to half original size and QoL improved to good after two months treatment. No sign of tumour after 4 mth treatment and dog's QoL very good at end of study. Last treated 16/7/05
Labrador 9 years. Started 15/10/03 Case 10	Suspected Malignant Melanoma. Tumour re-grew CV247 started 15/10/03. Initially swelling on gum continued to grow. After 2 mths treatment the mass smoothed (in Dec). Animal has progressed well in following 6 months QoL good. Animal last examined on 17/5/04 as part of the study but continues with CV 247 treatment. Animal alive and well
Whippet 8 years Started October 03. Case 11 PG	Suspected Lung Cancer diagnosed by X Ray (dense tissue) Attended regularly over 7 month period. QoL changed from 4 to 10 as dog regained health. Owner noted in April dog laid out flat for first time and in may reported the dog was breathing normally and "back to normal" last exam 23/4/04. Dog continuing treatment and is alive an well
Collie X 13 years Started October 03 Case 12	Suspected Round cell tumour by ARK Veterinary centre. During pre treatment biopsy taken from the tumour (on right side of neck) by own vet during treatment which lasted 2 months. CV 247 treatment administered for 1 month the animal's QoL improved from Poor, not eating or drinking, to Good with good appetite. Owner telephoned 2 months after start of CV 247 and reported dog had died 30 December 03
GSD X 12 years Started 23 October 03 Case 13	Suspected Splenic tumour diagnosed by palpation, first seen by emergency Vet after collapse. Animal too weak to subject to biopsy. Animal had a history of loose faeces. Treatment improved quality of life when it was noted that the animal was doing well enjoying exercise in December. The animal's faeces was improving in January. Vet surgeon reported that the dog had died and Post Mortem confirmed vets originals diagnosis of tumour. The tumour had spread to liver
Golden Retriever 10 years started 27/10/03 Case 14	Mast Cell Tumour excised with histology. Pathology suggests possibility of metastasis. When first seen large mass growing rapidly 3mm dia metastasis expected. After 2 months treatment with CV247 no sign of tumour returning and no other signs on body. Last examined 10/3/05 no sign of tumour. QoL good throughout.

West Highland Ter. 13years. started13/11/03 Case 15	Hepatoid Gland Adenoma Regrowth occurred after tumour was excised August 02. Observation – multi centre ulcerating tumour on right side of anus. Progress stable enjoying good QoL started losing weight March and Diabetes mellitus diagnosed from blood test result. Adenoma stabilised but animal begins urinating when at rest. Owner requests dog is put to sleep 14/6/04. Diabetic complications.
G Retriever 5 years started14/11/03 Case 16	Suspected Round cell lymphoma. Varying good and bad days throughout December but frequency of bad days reduced and the bright periods are brighter. Early January had relatively bad two weeks and had vomited. Has since steadily improved and mucous membranes and lymph nodes became normal. Animal last examined on 17/5/04 as part of the study but continues with CV 247 treatment. Animal alive and well
TerrierX 8 years Started 2/11/03 Case 17	Suspect Brain Tumour. Had been treated for epilepsy since May 02. Was euthanased during 2nd week of trial
GS Pointer 13.5 years Started 22/11/03 Case 18	Suspected haemangio-sarcoma with lung mets. Seen infrequently owner lives in Dorset. Owner treated the dog with CV247. When seen reported as being in good condition with good QoL. After 7mnts of treatment dog suffered haemorrhage (not unexpected because of cancer type) and became weak. Euthanased 23/6/04
Bearded Collie 8 Years Started 23/7/03 Case 19	Ovarian carcinoma. Diagnosed April 02 during spay operation. Very poor quality of life when first referred very thin and panting, fluid in abdomen. Satisfactory QoL achieved in first month moving to above average at 4 months and restored to good QoL at 6 mths. Fluid in abdomen drained, lymph nodes reduced in size and dog was eating well. Last recorded examination 20/3/04 Dog died 9 months after first treatment and experienced Good QoL.
Labrador 12 years Started 12/12/03 Case 20	Mast cell tumour effecting spleen suspected but result of biopsy was in determinant. Symptoms included oedema at face and brisket with chronic cough. Quality of life improved from poor to satisfactory in first three months of treatment and last report recorded dog was "Happy" until complications (fluid) became apparent and QoL reduced. Dog put to sleep on 29/3/04
Labrador 7years Started 29/11/04 Case 21	Surgical examination confirmed large pancreatic mass and histopathology confirmed disease to be primary and metastatic pancreatic islet cell tumour. Prognosis is that tumour will progress and glycaemic control will become impossible and euthanasia would need to be considered. Dog improved over two month period below average to satisfactory. Coat demonstrably improved, eating well. Dog deteriorated over two week period in June 05 and died in July.

<p>Cocker Spaniel 12 years Started 28/12/03 Case 22</p>	<p>Surgical examination confirmed large mass in bladder, too large to remove. Miserable dull looking with difficulty in passing urine. During the 6 months of treatment the quality of life of the animal improved from poor (2/3) at the beginning to very good score (9) when last seen. Last examined in May 04 dog normal has no difficulty in passing urine. No mass detected, QoL restored & good. Owner has not presented animal for treatment (Burton on Trent) but sent X ray from own vet showing mass had been eliminated. Animal alive and well Owner collects medicine at intervals</p>
<p>Bearded Collie 12 years Started 23/10/04 Case 23</p>	<p>Haemangio sarcoma Heart found by echocardiography Dog experiencing very poor QoL on admission to the study this improved to average in the first few days of treatment. Comment from the referral clinic said tumour had shrunk to half original size, as measured by echocardiograph. Following death of other family dog (sister) the patient suddenly deteriorated and died after two weeks of treatment.</p>
<p>Rough Collie 8 years Started 29 11 03 Case 24</p>	<p>Squamous cell carcinoma of buccal oral mucosa left upper jaw, first noticed April 2002. Initial eruption slow but with increasing speed Diagnosed in Sept 02 started cv 247 treatment 27/11/03. When first seen the QoL was assessed as poor. Under treatment for 1 month when noticed tumour had shrank and dog could retrieve objects without obvious pain. This was impossible before. At the 6 month point the swelling over upper lip very small and the lymph nodes normal. Animal appears well and is rated as having a QoL of Very Good 9.. Dog remains at this level of health. The dog is resident in Dorsetshire and was last examined in December 2004. Contact has been maintained (13/4/05)</p>
<p>Cocker Spaniel 10 years Started 31/1/04 Case 25</p>	<p>Analsac carcinoma diagnosed and treated by RVC. 5 nodes removed 3 chemotherapy given. Second operation to remove further nodules aborted because X Ray under anaesthetic showed tumour had metastasised to lung. Dog In poor condition when first presented. Poor QoL. Muffled lung sound. 2mths later dog eating well with very good QoL appears normal, lively clear lung no lumps. Dog remains in good health for the six month study period when there was no indication of the tumour. Dog dies suddenly in September of unrelated cause</p>

<p>Boxer 2 Years Started 22 11 03</p> <p>Case 26</p>	<p>Suspected cutaneous lymphosarcoma following numerous biopsies taken and examined by Royal Veterinary School and finally from Post Mortem examination analysis reported in September 2004.</p> <p>Dog had history of skin tumours which failed to heal. Treated with CV 247 for 9 mths where the persistent major tumour in dorsal region reduced from 7cm to nil in three months. QoL improved from satisfactory to Good until the end of the 6 month study period. Dog continued treatment with CV 247 at home for 3 further months. Owner decided to have dog put to sleep on 31 August 2004 because mucous membranes worsened</p> <p>Photographs of skin lesions, ultra-sound scans, clinical & post mortem reports enclosed with clinical evidence.</p>
<p>Labrador 10 years Started 29/10/03</p> <p>Case 27</p>	<p>Adenocarcinoma. Spleen excised by own vet on 15/9/03 showed secondary tumour. Primary source unknown. Suspected enlarged prostate. Prognosis poor. CV247 started late October . After 6 weeks no evidence of abdominal mass or diarrhoea and prostate enlargement reduced. QoL improved from satisfactory to very good after 6 weeks treatment. Own vet begins treating dog for hair loss. Animal demands moderate exercise. After 5 months of treatment signs of deterioration begin and at 6 months scan reveals secondaries. Dog is subsequently put to sleep due to spinal secondary</p>
<p>Collie X 12 years Started 30/11/01</p> <p>Case 28</p>	<p>Tumour excised Nov 01 shown to be Haemangio-pericytoma by histology. Amputation offered but rejected. Small swelling arose inside left leg shortly after. Biopsy of this and a mass taken from eyelid, diagnosed as benign lipoma and meibomian adenoma respectively. Good QoL this continued for period of treatment 9 mths.</p> <p>Dog, now 15 re-presented after 3 years from treatment start. QoL satisfactory. Lipomatous tumour is still present dog maintains energy.</p>
<p>Pomeranian 11 yaers</p> <p>Started 22/9/01</p> <p>Case 29</p>	<p>An unusual case. Seizure of unknown origin (possibly brain considered) Dog under treatment for c 3 years by own vet for frequent seizures. Following extensive examination by RVC resulting in in-conclusive summary stated on CV 247 with immediate result. Seizures eliminated from 2 per day within 5 days of starting treatment. QoL maintained /improved throughout treatment. Now treated with CV247 for c2.5 years.</p>
<p>Golden Retriever 16.5years Started 28/2/04</p> <p>Case 30</p>	<p>Peri-anal-adenoma Tumour 2.5cm dia adjacent anus regrew at site of tumour excised October 2003 Dog dull and panting with poor QoL when presented. Dog stopped panting brighter after 1 month. And tumour shrunk to 2cm after two months treatment & with QoL improved to above average. Dog maintained this condition throughout remainder of study when the dog became 17 years. Owner pleased with dog's health</p> <p>Owner had dog put to sleep when the animal became unwell in September, 7 months after starting CV 247 treatment.</p>

<p>X Breed 11 years Started 19/6/04 Case31</p>	<p>Mast cell Tumour cranial left ear diagnosed by RVC who advised wide margin excision and aspiration of lymph nodes. Surgery declined. When presented dog had below average QoL and tumour measured 1.5cm dia. QoL improved to Very Good in two months and tumour reduced in size 0.8cm then to 0.3cm at the end of the study period. Last examined August 2005 owner pleased with outcome.</p>
<p>Patterdale Terrier 15 years Started 26/1/04 Case 32</p>	<p>Suspected spindle cell tumour of front leg. Animal was treated for two months with no material effect. Animal lost weight and became progressively worse. Owner requested the dog be put to sleep.</p>
<p>Boxer 10.5 years Started 7/1/04 Case 33</p>	<p>Suspected Prostate Cancer started treatment but was put to sleep almost immediately after condition worsened and dog deteriorated.</p>
<p>Labrador 7 Years Started 27/01/04 Case 34</p>	<p>Nasal carcinoma excised January 2003 re-grew January 2004. Initial treatment own Vet was Synlux tabs and again was debulked. Tumour not visible but dog is depressed with poor QoL, breathing noisily. Lymph nodes in the neck enlarged. After first month dog appears normal enjoying good QoL breathing less noisy and lymph nodes reduced in size. When seen on 16/4/04 Dog is in good health no lymph node enlargement and breathing un- troubled. Owner lives in Manchester and failed to continue treatment.</p>
<p>Airedale 10 years Started 9/8/04 Case 35</p>	<p>Suspected melanoma excised in June histology showing some evidence but not definite. Started treatment in August. CV247 taken regularly as prescribed. Animal was lethargic pre-treatment with considerable thirst. Rated as 4 below average QoL. Restored to full health with very good QoL(10). Owner reports animal in good health and “hip problems” overcome. Maintenance treatment continues</p>
<p>Lurcher x Greyhound Started 9/3/04 Case 36</p>	<p>Suspected Liver Cancer. Dog said to have been doing well in the early weeks following the start of treatment. Heart was beating faster and the dog keen on going on short walks. Dog put to sleep after 1 months treatment</p>
<p>Labrador 9 years Started 6/3/04 Case 37</p>	<p>Carcinoma of the lung confirmed by X ray and histology. Treated with CV 247 for 1 year. QoL improved from poor to a very good score of 9. Coughing ceased after first month, no return of this symptom.</p>
<p>Collie X 13 years started 14/2/04 Case 38</p>	<p>Suspected carcinoma of the mammary gland. Tumour was palpable measuring 5.5 x 6.5 cm. Following treatment QoL returned to good and tumour no longer attached to body wall. Last examined 15/5/04</p>

<p>Springer Spaniel 11 years Started 14/2/04</p> <p>Case 39</p>	<p>Suspected osteo-sarcoma of the zygomatic arch with lung metastases discovered on X ray. Animal experiencing a below average QoL at beginning and was returned to good QoL after 1 month treatment. Appetite restored. Last examination record April 04</p>
<p>Bernese Mountain Dog 8 years Started 15/11/04</p> <p>Case 40</p>	<p>Suspected Lymphoma of the eye. Tumour visible and eye removed. Histology taken but result indefinite. QoL maintained no deterioration in animal. No definite conclusion but dog continuing treatment. Result inconclusive.</p>
<p>Yorkshire Terrier 9 Years Started 20/8/04</p> <p>Case 41</p>	<p>Suspected lung cancer. following treatment for a chronic cough also being treated for heart condition. No improvement in cough or breathing but symptoms have not worsened. Dog not of robust health but remains happy good QoL after 7 months treatment. Owner reports dog died at home after 8 months treatment</p>
<p>Golden Retriever 10 years Started 27/10/03</p> <p>Case 42</p>	<p>Suspected tumour of the spleen confirmed during exploratory and terminal operation when dog was pts. CV 247 administered for c 2 months. QoL maintained at above average good appetite and energy returned but tumour continued to grow. QoL reduced to satisfactorily at time of final operation.</p>
<p>WH Terrier 10 years Started 21/2/04</p> <p>Case 43</p>	<p>Hepatoid gland carcinoma excised with histology. When first presented small swelling from anus tumour re-growing. Dog appeared unwell with below average QoL Dog progressed rapidly QoL improved by the 4 mths point. No evidence of tumour at end of study period and animal displayed a Good QoL Animal still attends for treatment 13 months after first presentation.</p>
<p>Yorkshire Terrier 12 Years Started 2/10/04</p> <p>Case 44</p>	<p>Pancreatic Cancer Observed during explorative operation. Large tumour adherent to right abdominal wall. Tumour not excised and owner is advised to have animal p.t.s. When first seen dog had very low QoL, which had been improved to above average with the dog eating well and taking exercise. All within the first month of treatment. QoL fully restored to very good after 4 months of treatment. This QoL was maintained at end of study period and when last seen. Coincident with improved QoL Lymph node enlargement eliminated and mucous membranes returned to normal pink colour.</p>

Lurcher 9 years Started 18/9/04 Case 45	Infiltrative Lipoma diagnosed by histology swelling on R leg c1cm dia fluctuating in size. Excised May 04. CV247 started 18/9/04. When presented dog had poor QoL and swelling - size 10cm. Tumour reduced in size, QoL improved progressively over 3 month period. QoL remained at very good throughout period of study.
Boxer 7.5 Years Started 28/5/05 Case 46	Round Cell Tumour or poorly differentiated carcinoma suspected after fine needle aspirates were examined at RVC. . Further exploratory ops offered but refused. Dog had history of round cell tumours these were removed in 2003 & 04. Exam showed dog is rather dull with diarrhoea two masses in abdomen palpable also swelling on elbow. Poor QoL on entry but restored to Good after first month of treatment. Diarrhoea eliminated mass softer and smaller. Improvement continues mass not palpable good appetite and energetic.
Alsation 10 years started 1/10/03 Case 47	Nodules throughout lung fields neoplasia elsewhere suspected by RCV based on examination of x-ray. Dog very dull not eating when first seen. QoL below average. Treated for 1 month Eating improves panting ceases. QoL is above average. Owners (from Tunbridge Wells) fail to attend further clinics.
Golden Ret 7 year Started 7/2/04 Case 48	Mast cell tumour grew July 2003 and excised by own vet. Others then grew. Own Vet agreed the alternative therapy favoured by owner. CV 247 first given in Feb 04 when tumour measured 10x8cm. QoL below average. Over 3 mths period of treatment tumour measured only 6x4cm and QoL improved to good. Owner failed to continue treatment. Own vets notes recorded that Vet noted general progress of tumour and its reduction in size. Notes reveal dog pts September 04
Boxer 4 Years Started 23/2/04 Case 49	Lymphoma diagnosed by own vet from result of biopsy. Started on chemotherapy 13/2/04 which gave some improvement. When first treated with CV247 the lymph nodes were slightly enlarged but returned to normal in first week. QoL changed from average to good in 1 month.
Samoyed 13 years Started 18/12/04 Case 50	Nasal squamous cell carcinoma confirmed by QMVSH. Animal has long history of ill health viz: diabetes, hypothyroidism, testicular cancer (removed May 2004) dental disease, hind leg weakness. Observation at start of study showed dog is weak on back legs, has intermittent nasal bleeding and poor appetite. V poor QoL. After 1 month of treatment with CV247, dog is stronger on legs, eating better and less nasal bleeding. QoL improved to satisfactory. Dog continues in this manner QoL remains satisfactory dog now enjoys walks and owner is pleased with progress.

X bred Lurcher 5 years Started 20/10/04 Case 51	Spindle cell sarcoma affecting the head confirmed by Finn Pathologists. Tumour excised on 15/10/04. Initial QoL average. Progressed to V good QoL in three months and maintained throughout remainder of the study. No evidence of tumour recurrence.
Whippet 11 years Started 18/6/05 Case 52	Spindle cell sarcoma excised in June 2000 and again in June 2004. Both operations performed by own but different individuals. Amputation was discussed but rejected by owner. CV247 treatment started 18/6/05 examination showed mass was dull with several smaller swellings. Not eating well, below average QoL. After two months treatment with no signs of improvement swellings become softer and dog eating better and improves quickly QoL good. Dog alive. Last seen August 2005

The combined data from the primary and secondary end-points was assessed by the investigators and subsequently independently examined and verified by an expert veterinary surgeon, who assigned an overall disease response to CV247, as detailed in Table 1.

Disease Response

P=disease progressed (worsened) **15 (28%)**
S=disease stabilised **25 (47%)**
R=disease regressed (improved) **13 (25%)**

Efficacy Conclusions

This study was designed to see if treatment with a novel combination therapy, CV247, would be of benefit in dogs with a variety of different cancers. The primary objective was to assess the effect on quality of life. The great majority of the dogs included in the study had cancers with a guarded or poor prognosis following diagnosis of the cancer, and on entry into the study had quality of life scores, which reflected the severity of the disease.

From the change in quality of life scores almost 72% of the dogs recruited were independently assessed as gaining some benefit from the test medication, even if the period of benefit was quite short. Life expectancy was not estimated at the start of the study for most of the animals, but the duration of treatment for some dogs was possibly longer than expected, being in excess of 12 months for 11 (21%) of them.

When the secondary endpoints of tumour regression were also taken into account, then, following independent assessment, it was concluded that disease was stabilised or regressed in 38 dogs. There was no clear trend with regards to the cancer type, or dog variety that responded best to CV247. It might have been expected that those animals given a grave or very poor prognosis would be the animals to have been response

failures. This appears not the case, as in the majority of such animals, disease seemed to either stabilize or even regress.

The recommended diet was followed closely by the owners of all the dogs in the study but was not observed in the context of this study to affect the outcome of treatment.

Safety Evaluation

Extent of Exposure

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The total duration of dosing with CV247 varied between 1 and 30 months in a total of 53 dogs with a mean duration of 7.4 months per animal.

Adverse Events

No adverse events were recorded and the investigators confirmed that no owner reported any such events

Safety Conclusions

There were no reported adverse events during the course of the study.