	Human trials			
	Study description	Patients	Outcomes	Notes
1	CV247-2. Pilot phase II study to investigate if dietary advice combined CV247 supplementation has tumour static properties. (Addenbrook and Bedford Hospitals, patients recruited March-November 2001, study ran to September 2004). Design: all patients received active drug and dietary advice. Doses: Mn gluconate 20mg, Cu gluconate 20mg, Na salicylate 350mg, and 400mg of ascorbic acid once daily for patients under 50kg body weight, 2 and 3 times daily for patients 50-75 and over 75kg respectively. Endpoints: tumour markers progression, radiological lesions measured in n2 dimensions, quality of life (QoL) questionnaire (Rotterdam Symptom Checklist).	Total: 37 Age: 53-82 Males: 28 Females: 9 Tumours: Prostate -14 Colorectal -12 Ovarian -2 Breast – 2 Lung -2 Unknown primary -2 Sarcoma-1 Renal cell -1 Thyroid -1	Treatment was well tolerated. Abdominal complaints in 6 patients were resolved with ranitidine (H2 antagonist that reduce acid production in the stomach – a common side-effect of salicylic acid); 2 patients had slightly elevated serum Cu, 1 patient – Mn. No significant response, including QoL, was noted in patients with advanced cancers, including metastatic prostate cancer (one patient with aggressive non-metastatic cancer was withdrawn). 2 ovarian carcinoma and 6 early prostate cancer patients had significant (p=0.0238, 2-tailed paired t-test) reduction in tumour growth rate (increase tumour doubling time in weeks), one ovarian cancer ceased growing. Asymptomatic patients (n=7) at the entry to the study had no change in QoL; ovarian cancer patients (n=2) had stabilised QoL for the duration of the study with subsequent deterioration consistent with disease progression.	Published as "Dietary Advice combined with a salicylate, mineral and vitamin supplement (CV247) has some tumour static properties. Nutrition and Food Science vol 35, 436-451, 2005. Presented at: -European Society of Medical Oncology Conference in October 2003; -The British Oncology Association Conference, Cambridge 2003
2	CV247-3. Compare safety and efficacy of CV247 and Sodium salicylate (SS) for treatment of early stage progressive prostate cancer. (Bedford and Addenbroke Hospitals, October 2003 – November 2007). Design: randomised, double blind, phase II study, comparing the effectiveness of sodium salicylate plus dietary advice, versus CV247 plus dietary advice, in a cohort of 110 men with early stage progressive prostate cancer. Doses: as before – study (1) Inclusion criteria: PSA progression >20% over 6 months. No other medical conditions or concurrent medication Endpoints: 1) Change in mean PSA from baseline to 12 months; 2) %patients still taking medication after 12months. Patients were withdrawn if PSA was growing faster than at baseline, or total PSA increase was greater than 20% from the baseline.	Males: 110 Age: 61-87 60 men had previous radiotherapy +/- adjuvant hormones, 10 had PSA relapse after radical surgery.	There was no statistical difference in PSA change from baseline or number of patients stabilised with the treatment between CV247 and SS groups. 40 out of 110 (36.4%) patients remained on either intervention. 14 out 40 patients had decreased PSA from baseline. The remaining 26 patients continued PSA progression albeit at reduced rate from baseline. Adverse events (AE) were similar in both groups; total 183 mild to moderate and 26 severe AEs were reported by 76 patients; 25 mild-moderate and 1 severe AEs were most likely treatment related (dyspepsia and nausea being the most common). One and 4 patients were withdrawn because of increased Mn levels in CV247 and SS groups respectively.	Publication: "A randomised double blind phase II study of lifestyle counselling and salicylate compounds in patients with progressive prostate cancer". Nutrition and Food Science vol 39,295-305; 2009)
3	CV247-4. Effectiveness and tolerability of CV247, combined with an optional reduced salt and reduced sugar diet, in 36 patients with advanced malignant disease who had either completed or opted for no further	36 advanced cancer patients. Cancer types: breast,	12 of 25 patients who continued beyond the 1st month of the study had no change in QoL scores or total global health, 3 patients had decreased scores and 10 had improvement.	

	conventional treatment. (Dr. R Taylor, Hospice of St Francis, Berkhamsted and private clinic in Harrow, Middlesex). Design: open label; treatment received for 6 months. Endpoints: monthly QoL: self-scored validated (EORTC) questionnaire; monthly clinical assessments.	prostate, mesothelioma, ovarian, NH lymphoma, thymoma and other cancer types.	11 out of 36 patients withdrew after first assessment, mostly due to choice of an alternative treatment. 12 out of 25 remaining patients completed 6 months treatment; 7 out of 12 patients continued treatment beyond 12 months. GI tract disturbances were most commonly reported AEs, however no serious AEs were reported.	
4	Compassionate use of CV247 over 5 year period in advanced cancer patients (Dr R. Taylor, Harrow, Middlesex. 2000-2005). Design: open label. Doses: as in (1) Endpoints: global health assessment; scored scale used: O –medication for less than 3 month, 1 –serious AE, 2- mild AE, treatment ceased, 3- rapid disease progression, 4 slow deterioration, 5 symptoms stabilisation, 6 –improved symptom load up to 6months, 7- persistent improvement beyond 6 months, 8 – evidence of disease stabilisation, 9 – evidence of disease improvement, 10 – disappearance of original disease.	(109) Assessment performed in 78 patients. Age range: 14-85	Of 78 patients who were treated for 3 or more months, 21 (27%) showed marked improvement, with disease stabilised, regressed or disappeared (scores 8-10). 60 patients had reduced symptoms burden (scores 6). In several cases of lung cancers, where the untreated prognosis was 6-9 month, several patients lived more than 2 years and enjoyed excellent quality of life. Most improved symptoms over the course of the study were pain and increased energy levels.	

	Animal Trials		
	Study	Methods	Results
1	The effect of CV247 on induced lymphoma in mice as a model of human cancer (Prof P Beverley, Middlesex Hospital, 1996) Animals used: male C57Bl mice, n=50 Doses: 0.1ml CV247 contained: Mn gluconate – 0.2mg (0.025 Mn) Cu gluconate – 0.2mg (0.028mg Cu) Ascorbid acid (Vit. C) – 4.0mg Na Salicylate – 3.5mg Endpoint: tumour diameters, weights and multiple tumour appearance cases.	Mice injected s/c with RMA lymphoma cells and treated once daily with 0.1ml of CV247 (n=24) or water (n=26) by oral gavage. CV247 groups also received CV247 in drinking water at 3 time points each day. Tumour diameters were measured daily. Statistics: RM ANOVA and Mann-Whitney U test for number of tumours developed.	After day17 post tumour injection, there was significant difference in size (p=0.012) and weight (p=0.0025) of the excised tumours. Number of tumours grown along the tumour injection tract was significantly more frequent in control group (n=10) vs treatment (n=1). No side-effects attributable to CV247 were noted.
2	An open label study of CV247 in 51 dogs diagnosed with a variety of cancers (Carter and Sebasteny in private veterinary practices, completed 1999. Part published in Veterinary Practice, Feb 1999) Treatment: 1ml of CV247 contained: Mn gluconate – 2mg (=0.25mg Mn) Cu gluconate – 2mg (=0.28 Cu) Na salicylate – 35mg Ascorbic acid - 40mg Volumes received depended on body weight (range 1.5 – 9ml) Inclusion criteria: confirmed cancer diagnosis Endpoints: tumour regression, extension of life beyond forecast, QoL score.	51 dogs were treated and monitored between 0.5 and 25 months QoL scores: 1-2 poor, 3/4 - below average but eating and drinking, 5 – satisfactory, good appetite, 6/7 – as in 5, animal is alert, 8 – good, animal is active, 9 – very good, 10 – excellent, health exceeding that before illness.	Regression was observed in 17 tumours (sarcoma, carcinoma, lymphoma, and melanoma). 74.5% dogs were considered to increase their life expectancy, however extended life is deemed a qualitative subjective determination. Most commonly QoL improved by 8 points. Qualified success of treatment was 35.3%; failed or inconclusive results were 27.5%. No adverse event connected with treatment were reported.
3	An open label study of CV247 in 53 dogs with uncontrolled progressive malignant disease over a 6 month period (Carter, Grant and Sebasteny in private vet practices, completed 2004). Treatment and doses as above. Inclusion criteria: as above, +prognosis older than 28 days. Endpoints: as above	53 dos (25 females, 26 males, 2 not recorded). Age: 3-17 year Assessments similar as in 1st study.	72% (38) animals responded to treatment, mostly showed improved QoL, with 55% (29) increased QoL score of ≥4; disease regressed in 25% of cases (13 animals) and stabilised in 47%. 28% (15) animals showed no change (worsened) in disease progression. No clear trend was observed when responses were stratified based on cancer type; however more dogs with carcinomas had ≥4 QoL score increase. No adverse event connected with treatment were reported.

4	A target animal safety study by oral administration of CV247 to Beagle dogs for 26 weeks (Huntingdon Life Sciences, 2003) GLP study. Doses: 0.44 and 0.88 ml/kg/day for 2 weeks. Endpoints: overall safety and tolerability of CV247.	9 male and 9 female dogs, aged 5 months and weight range 7.8-9.9 kg at the start, dosed daily orally onto the back of the tongue. From week6, higher dose was changed to oral gavage due to profuse salivation. Treatment groups: Control, 0.44 and 0.88 ml/kg/day, 3 males and females per group.	Treatment was overall well tolerated; no effect on body weight, food consumption and biochemical changes was observed. Several clinical signs were associated with the taste of the test material. Haematology findings were increased haematocrit, RBC and reticulocytes in females; reduction in mean corpuscular haemoglobin concentration (MCHC) was observed in both males and females. The effects were considered treatment-related but not toxic. Reduction in thymus size was reported. Systemic exposure had linear kinetics over the dose range 15.4-30.8mg/kg/day.
5	Study to investigate the anti-cancer potential of CV 247 and its constituents dosed to C57Bl mice bearing a syngenic tumour. Animals: 110 female C57Bl mice. Doses and groups: CV247 – 3, 10, 20 ml/kg CV247 components: Soldium Salicilate (SS) – 35 mg/kg Ascorbic acid (AA) – 40mg/kg Mn gluconate (MG) – 2mg/kg Cu gluconate (CG) – 2mg/kg were tested in the following combinations: SS, SS+AA, SS+AA+CG, SS+AA+MG; Gemcitabine – 120mg/kg Endpoints: Tumour weight, volume and visual examination (qualitative characterisation) and scoring for signs of inflammation and necrosis.	All mice were s/c injected with LL2/LLc1 tumours. Group 1-3: 3, 10 and 20ml/kg CV247 was started on day7 after tumour inoculation for 14 days. Group4: 10ml/kg CV247 treatment was commenced on the same day of tumour inoculation for 21 days. Groups 5-8: SS, SS+AA, SS+AA+CG, SS+AA+MG for 14 days daily. Group9: Gemcitabine every 3rd day. Group10: untreated. All treatments were administered by orally, apart from gemcitabine, which was given ip.	The dosing regimens were well tolerated. Neither treatment produced clinically significant tumour-static effects (tumour weight and volume). Tumours from CV247 treated animals (all doses) were soft (97.5%), with empty tumour core (27.5%), whereas in all other groups the tumours were solid and no empty core was observed. CV247 tumours appeared to ulcerate more readily compared to untreated counterparts. No effect was observed on tumour volume, but the tumour weights appeared to be reduced in CV247 treated animals (not in dose dependant manner), however more so in gemcitabine treated group.
6	Oral examinations with CV247 in rats. (Semmelweiss University, Budapest. The study is published as "Protective effect of CV247 against cisplatin nephrotoxicity in rats" in Human and Experimental Toxicology, 2013) Animals: 40 males 8 week old Wistar rats, 175-190g body weight. Design: 4 groups (n=10 per group): CV247 dose: Ascorbic acid -2 x 120 mg/kg/day sodium salicylate – 2 x 105 mg/kg/day, Cu gluconate – 2 x 6 mg/kg/day, Mn gluconate - and 2 x 6 mg/kg/day.	Groups 1 and 2 received CDPP vehicle (10ml/kg body weight) or CV247 3ml/kg bodyweight) twice daily by gastric gavage for 14 days. Groups 3 and 4 had single i.p. injection of CDPP 6.5mg/kg followed by CV247 or vehicle 30minutes after CDPP injection. Blood samples were taken at day12 and day14 for renal function assessment; kidneys were removed at day14. Metal concentrations were measured by inductively coupled plasma optical emission spectrometry (ICP-OEC).	Plasma CV attenuated the CDDP-induced elevation in plasma Fe and reactive oxidant levels. Kidney Co-administration of CV with CDDP - restored Fe, Zn and Mo concentrations to control levels, - significantly increased renal Cu and Mn concentrations (although Cu and Mn remained below the control levels), - kidney Pt concentration was reduced by 30% ($p < 0.05$). Kidney histology. CV247 reduced severity score of cisplatin-induced kidney injury. CV administration after treatment with CDPP offered some protection against nephrotoxicity at 2 weeks in rats.