The summary presented is based upon independent examination and these data should not be construed as demonstrating efficacy and safety of CV 247 since the product has not yet received regulatory approval.

Study CV247-3

A study to compare the safety and efficacy of CV247 and Sodium salicylate for the treatment of early stage progressive prostate cancer

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The study was conducted over a 3 year period under the investigational directorship of Dr R Thomas, consultant oncologist, at Bedford General Hospital and Addenbrookes Hospital, Cambridge. The study enjoyed the distinction of being endorsed by the National Cancer Research Network (NCRN), and followed an earlier pilot study that found that previously untreated patients with early stage progressive cancer benefited from treatment with CV247.

CV247 is a combination product consisting of sodium salicylate, copper and manganese glutamates and ascorbic acid. The scientific rationale for the inclusion of the compounds is well documented with both copper and manganese being essential elements for life as components of superoxide dismutase, ascorbic acid being an essential vitamin with anti-oxidant properties, combined with the known anti-inflammatory properties of sodium salicylate. All these properties may well be of benefit in the treatment of certain aspects of cancer. Trace element deprivation, for example, could result in increased oxidative stress and altered or impaired immune function, whilst the benefits of ascorbic acid may well include enhancement of the immune system and activation of enzyme systems causing tumour cell death. Aspirin itself has been proposed as a treatment for certain types of cancer, but though sodium salicylate which is a close relative of acetyl salicylic acid, is known to be an effective anti-inflammatory agent with a lower propensity for gastrointestinal side effects, and might well inhibit the production of certain growth factors that promote angiogenesis and tumour progression. It has individual properties which are quite distinct, and its individual role as a treatment in early stage progressive prostate cancer would not be obvious and has consequently not previously been proposed or investigated.

CV247 has been found in open label studies to be of apparent benefit for the improvement of well being particularly in dogs with a wide variety of cancers, and possibly to improve quality of life in some human patients with terminal cancer. In addition as referred to earlier, it was observed in a pilot study to be of possible benefit to certain patients with early progressive prostate cancer

The objective of this study was to further investigate whether CV247 might be of benefit in the treatment of early stage progressive prostate cancer and to compare its safety and efficacy with sodium salicylate. According to the protocol all patients recruited into the study had evidence of progressive cancer as defined by histological examination, and PSA levels rising over 20% or more during the 6 month period prior to study entry (40% over 9 months). Such patients would normally be managed by a “watch and wait” programme and would, according to the investigator, be patients who he would usually expect to demonstrate continuing and often accelerating disease progression, with few

spontaneous remissions. The design of the study was to determine the period of disease stabilisation that patients would enjoy when treated with one or other of the 2 test medications assigned randomly. For the purposes of the study stabilisation was defined as an increase of less than 20% in serum PSA levels between any 2 clinic visits spaced 3 months apart. The duration of the study was set at 12 months though patients who were adequately stabilised at the end of this period were entitled to continue with the randomised medication indefinitely.

A total of 110 patients were recruited into the study, the great majority from Bedford general Hospital. The study was terminated on 30/11/06 at the end of which 38 patients (34.5%) had been stabilised for between 12 and 34 months in the double blind phase. 21 (55%) of these patients had been randomised to sodium salicylate and 17 (45%) to CV247. A further 10 patients were stabilised for 10 months (6 on CV247 and 4 on sodium salicylate). At the end of the study 10 patients were still being treated in the double blind phase, 3 of whom had been recruited less than 12 months prior to study completion. It is known that 2 of these patients were also stabilised for 12 or more months, both of whom had also been randomised to sodium salicylate. A total of 13 of the 38 patients stabilised for 12 months or more had an overall decrease in PSA levels during the period of stabilisation (8 on sodium salicylate and 5 on CV247).

Examination of the treatment "failures" found that 42 patients (38%) were withdrawn after only 4 months or less in the study. However the majority of these (78.6%) had been pre-treated at an earlier stage following diagnosis of prostate cancer including radiotherapy and chemotherapy. Further examination of the difference in periods of stabilisation when comparing pre-treated with non pre-treated patients revealed that the mean treatment period for all patients on CV247 was 7.4 and 11.3 months respectively, whilst the figures were 6.4 and 12.9 months for those patients randomised to sodium salicylate.

The adverse event (AE) profile was similar for both treatments. A total of 39 patients reported 97 AEs whilst being treated with CV247, compared with 37 patients reporting 112 events on sodium salicylate. The majority were mild or moderate in severity (76% of AEs reported by patients on CV247 and 75% for those on sodium salicylate). Only 13 AEs were considered to be probably or definitely related to CV247, and 12 to sodium salicylate. An AE was the cause for patient discontinuation for 4 patients on CV247 and for 7 on sodium salicylate.. Dyspepsia and nausea were the most common AEs for both treatments. Increased manganese levels were recorded for 6 patients on CV247 and for 9 on sodium salicylate, which resulted in 1 patient being withdrawn on CV247 and for 4 to be withdrawn on sodium salicylate. The reason for the increase whilst on sodium salicylate is not clear.

There were a total of 26 serious AEs, only one of which, an episode of acute pancreatitis, may have a possible relationship to the test medication.

The investigator had the option of putting any patient onto an "open" phase should the randomised treatment in the blinded phase fail to stabilise the disease progression. In every case this entailed the patient being treated with CV247 regardless of what treatment had been assigned during the blinded phase of the study. A total of 39 patients were entered into the open phase, 17 of whom were on CV247 in the blinded phase, and hence were effectively continuing with the same treatment. Analysis of the period of stabilisation revealed that a further 7 patients were stabilised for 12 or more months, 2 of

whom were switched from sodium salicylate but 5 of whom simply, and unbeknown to the investigator, were continuing with CV247.

It is not known whether the success rate of the 2 treatments would have been greater had the patients recruited all been previous treatment naïve, nor whether the trend would have been similar when comparing the 2 treatments. Nonetheless the evidence would strongly suggest that benefit was derived by a significant number of patients with early stage prostate cancer, and that within the limitations of this study design, that similar benefit was derived from both treatment options.