Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst214P.pdf

Analysis of safety, pharmacokinetic and pharmacodynamic data derived from a single ascending dose Phase 1 study involving a promising non-cytotoxic anti-cancer agent Sulforadex®

J Taubel[1], U Lorch[1], J Singh[1], D Howat[2]. [1]Richmond Pharmacology Ltd., St George's University of London, Cranmer Terrace, London, UK, [2]Evgen Ltd., Liverpool Science Park, Innovation Centre 2 - 146 Brownlow Hill, Liverpool, UK

Literature evidence suggests that consumption of cruciform vegetables such as broccoli contain specific compounds that are capable of suppressing the initial phase of carcinogenesis or the progression of neoplastic cells to cancer. In animal models of prostate cancer one such compound sulforaphane, a derivative of glucoraphanin, has been shown to inhibit tumour formation and metastases (Singh *et al*., 2009). It is well documented that sulforaphane inhibits histone deacetylase (HDAC), which is up-regulated in certain types of cancer including prostate cancer (Myzak *et al*., 2006). Sulforadex® is a new pharmaceutical product composed of synthetic sulforaphane and α-cyclodextrin. While the initial indication is the prevention of progression of early prostate cancer, Sulforadex® is a promising non-cytotoxic product with low toxicity and anticipated to have few side effects in healthy individuals or cancer patients. Although there are many clinical studies in progress with sulforaphane derived from botanical sources (Shapiro *et al*., 2006), to date there is no clinical experience with Sulforadex®. In this double blind, placebo controlled single ascending dose Phase 1 study, 29 healthy male subjects received single oral doses (50 mg, 100 mg, 300 mg, 500 mg or 700 mg) of Sulforadex® or placebo to assess its safety, pharmacokinetics (PK) and pharmacodynamics (PD) in healthy male volunteers.

Subjects' eligibility was evaluated during screening 21 days prior to first drug administration with safety monitoring and serial blood samples for PK evaluation throughout the period of admission. Subjects attended for one in-house period to the unit and remained in-house until discharge on Day 3 with a follow-up visit performed 7-14 days after discharge. Samples for HDAC in peripheral blood mononuclear cells were taken for PD analysis and safety assessments included adverse event (AE) recording, standard clinical laboratory safety tests (haematology, biochemistry, and urinalysis) and vital signs (blood pressure, heart rate and tympanic temperature).

In doses up to 300 mg oral Sulforadex® no adverse events were detected. However, oral doses of 500 mg and 700 mg Sulforadex® were associated with an increasing frequency of vomiting in subjects. The majority of the AEs were of mild intensity and there were no serious adverse events and no subject withdrawals due to AEs. The safety findings also showed that there were were no clinically significant changes in clinical laboratory tests, physical examinations, vital signs, Holter ECGs, telemetry and 12-lead ECG parameters. PK data showed that the mean plasma concentrations of sulforaphane following administration of single doses of Sulforadex® (50 mg, 100 mg, 300 mg, 500 mg and 700 mg) in subjects appeared to be dose linear. The PK analysis also revealed that dose proportionality was not established for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. The PD findings showed that there was no significant difference in

HDAC activity following placebo treatment in comparison to HDAC activity following 500 mg and 700 mg Sulforadex® treatment. Interpretation of these results is difficult due to the large variability of this data.