PP201—AN OPEN-LABEL, RANDOMIZED, SINGLE-CENTRE, FOUR-WAY CROSSOVER STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE, ORAL DOSES OF RETIGABINE/EZOGABINE IN HEALTHY ADULT TAIWANESE SUBJECTS

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Introduction: Retigabine (RTG)/ezogabine, N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a novel antiepileptic compound. In 2011, RTG was approved by the FDA and European Commission as adjunctive treatment for partial onset seizures in adults aged ≥18 years. The global pivotal studies did not include Asian countries. The purpose of this study was to characterize the pharmacokinetics (PK) of single 50, 100, 200, and 400-mg doses of RTG and N-acetyl metabolites of RTG (NAMR) in healthy Taiwanese subjects.

Patients (or Materials) and Methods: Sixteen subjects were randomized to the study (ANE116798, NCT01462669), which comprised a screening visit, 4 treatment periods, and a follow-up visit. The following PK parameters were determined for RTG and NAMR: Cmax, AUC0–inf, Tmax, and t½. Safety and tolerability were measured using adverse event (AE) reports, vital signs, electrocardiograms, clinical laboratory measurements and Columbia Suicide Severity Rating Scale. Dose proportionality of RTG was assessed by fitting AUC0–inf and Cmax to a power model. A point estimate and 90% CI for the slope of the regression line obtained by regressing log(PK parameter) on log(dose) was calculated. As a secondary analysis, an analysis of variance was performed using loge-transformed dose-normalized AUC0–inf and Cmax by including periods and treatments as fixed effects and subjects as a random effect. All doses were compared with the 50 mg reference dose.

Results: Safety: No subject was withdrawn from the study owing to AEs and no serious AEs were reported. AEs reported most frequently in this population were somnolence, dizziness, and nausea, and the incidence of AEs increased with RTG dose. PK: Cmax value increases were approximately dose proportional from 50 to 100 mg, but less than dose proportional at 200 and 400 mg. AUC0–inf appeared to increase more than dose proportionally between 50 mg and the higher doses of 100, 200, and 400 mg. This was believed to be due to an underprediction of t½ at the 50-mg dose. AUC0–8, which represents the dosing interval of RTG with a 3-times-daily dosing regimen, was added as a post hoc PK parameter, since this truncated AUC is not confounded by determination of t½. AUC0–8 increased proportionally across the range of 50 to 400 mg.

Conclusion: Single oral doses of RTG (50–400 mg) were generally well tolerated in Taiwanese subjects. The PK parameters for RTG and NAMR in the current study in Taiwanese subjects are consistent with single-dose PK parameters obtained at these doses in healthy Western subjects.

Disclosure of Interest: M. Buraglio: Shareholder of share option, full-time employee.

PP202—CANCER CACHEXIA RAISES THE PLASMA CONCENTRATION OF OXYMORPHONE THROUGH THE REDUCTION OF CYP3A BUT NOT CYP2D6 IN OXYCODONE-TREATED PATIENTS

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Introduction: Cachexia decreases CYP3A metabolism of oxycodone, while its influence on CYP2D6 metabolism remains to be clarified in