PP165—EVALUATION OF JNJ-26489112, A NOVEL ANTIEPILEPTIC DRUG: A PLACEBO-CONTROLLED, EXPLORATORY STUDY

D. Kasteleijn-Nolst Trenité[1*]; N.A. Diprospero[2]; J.A. Moyer[2]; J. Gambale[2]; G. Pandina[2]; L. Ford[2]; S. Girgis[2]; L. Xi[2]; and J. Nye[2]
[1]Neuroscience, Sapienza University, Rome, Italy; and [2]Research & Development, Johnson and Johnson, New Jersey

Introduction: JNJ-26489112 appeared in animal models as a centrally active, broad spectrum anticonvulsant. A Phase-IIa placebo-controlled, single-blind Proof of Concept study was performed to explore dose-related anticonvulsant effects in epilepsy patients.

Patients (or Materials) and Methods: Twelve adult Caucasian patients (3 men, 9 women; age, 18–40) with idiopathic photosensitive epilepsy underwent standardized photic stimulation during scalp EEG recording. Photosensitivity ranges (SPR) were determined before and at hourly intervals for up to 8 hours and at 12 hours after receiving a single oral dose of placebo on day 1, JNJ-26489112 on day 2, and a second dose of placebo on day 3. One patient withdrew after day 1. A positive response was defined as abolishment of the epileptogenic response or reduction in at least 3 out of 4 consecutive time points on either day 2 or day 3 compared with baseline day 1. The difference in SPR at each time point on day 2 and day 3 were calculated relative to matched time points on day 1 and plotted versus time for each patient. The type of response (ie, positive response or complete suppression) and number of responders were summarized by dose level. Cohorts of 4 patients were dosed 1000, 2000, or 3000 mg, respectively, and blood samples taken after each EEG photosensitivity measure. Safety was assessed by the reporting of adverse events, vital signs, 12-lead ECG, physical and neurological examinations, and laboratory assessments.

Results: Ten of 11 patients (91%) showed a clear pharmacodynamic effect starting on dosing day 2, with a dose-dependency for complete suppression.The median Tmax of JNJ-26489112 (range, 3.73–5.04 hours) in plasma was similar across all 3 dose groups and plasma exposure increased proportionally with dose; concentrations of other AEDs did not appear to be effected by coadministration of JNJ-26489112. Most frequent adverse events reported being mild headache, dizziness, and nausea.

Conclusion: Single oral doses of JNJ-26489112 were well tolerated and exhibited dose-related antiepileptic effects in patients with idiopathic, photosensitive epilepsy.

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PP166—EFFECT OF CARVEDILOL VERSUS CARVEDILOL/IVABRADINE COMBINATION ON HEART RATE, QUALITY OF LIFE, MORBIDITY AND MORTALITY IN PATIENTS WITH STABLE ISCHEMIC HEART FAILURE

T. Al Saadi[1]; M. Sallam[2]; K. Al Hashmi[3]; and A.M. Elhawary[1*]
[1]Phamacology and Clinical Pharmacy, College of Medicine and Health Sciences, Sultan Qaboos University; [2]Cardiology, Sultan Qaboos University Hospital; and [3]Physiology, College of Medicine and Health Sciences, Sultan Qaboos University, muscat, Oman

Introduction: Increased heart rate is a significant predictor of death and hospitalization in heart failure patients. Risk increases directly with increasing heart rate above 60 beats/min. These lead to the hypothesis that lowering heart rate with the If inhibitor, ivabradine, could be beneficial for cardiac function and clinical outcomes in heart failure patients.

Patients (or Materials) and Methods: A total of 309 stable IHF patients attending Sultan Qaboos University Hospital, Cardiology Clinic, were screened. Qualified patients were enrolled in the study and were randomly allocated to 2 groups: carvedilol up to 25 mg BID (group I) and carvedilol/ivabradine up to 25/7.5 mg BID (group II). The duration of follow-up was 6 months. The average daily dose of ivabradine was 5.8 mg. The average daily dose of carvedilol was 16.2 mg and 11.4 mg in group I and in group II respectively.

Results: Resting HR decreased in both groups from 82.6 (12) to 72.9 (12.7) beats/min in group 1 ($P = 0.05$); and from 85.3 (9.7) to 68.5 (9.4) beats/min in group II ($P = 0.05$). The reduction in HR was significantly higher in the combination group [(diff = 7.3 beats/min, $P = 0.03$)]. There was a significant increment in left ventricular ejection fraction (LVEF) in group II by 4.6 (5.9)% ($P = 0.01$), whereas no significant change was observed in group I. The reduction in HR due to ivabradine was associated with pronounced increment in health-related quality of life and reduction of incidence of admission events to hospital with worsening heart failure. Ivabradine in combination with carvedilol was associated with nonsignificant asymptomatic bradycardia ($P = 0.08$).

Conclusion: Combining ivabradine to carvedilol in stable ischemic heart failure patients with heart rate faster than 70 beats/min was associated with better heart rate reduction, improvement of quality of life, and reduced rehospitalization. Risk of bradycardia should be taken in consideration when ivabradine is used with carvedilol

Disclosure of Interest: None declared.

PP167—INTEGRATED 14C STUDY DESIGNS TO PROVIDE INTRAVENOUS PK AND HUMAN MASS BALANCE AND METABOLISM DATA FROM A SINGLE PROTOCOL AND A SINGLE REGULATORY SUBMISSION

L. Stevens[*]; and I. Shaw
Quotient Clinical, Nottingham, United Kingdom

Introduction: Combining the regulatory requirement to obtain human mass balance and metabolism data along with determining absolute oral bioavailability and clearance data for new drugs requires an ability to formulate and manufacture both intravenous and oral drug products at microtracer and therapeutic doses, respectively, along with the ability to correctly implement accelerator mass spectrometry (AMS) to provide the differential analysis required for 14C intravenous drug product.

Patients (or Materials) and Methods: We will describe variations of integrated study design, combining intravenous microtracer doses with the conventional human mass balance study either as a crossover study in the same subjects or as a parallel group study in separate cohorts of subjects to deliver a material, time and cost efficient study that is rich in PK and metabolism data to support regulatory submission. In the microtracer part of the study, intravenous levels of 14C parent drug are generated by AMS analysis and absolute bioavailability data is generated by comparison against conventional liquid chromatography-mass spectrometry (LC-MS/MS) analysis of unlabeled orally administered drug. Mass balance data are generated after administration of a 14C labeled oral dose in a second period of the study utilizing liquid scintillation counting to determine 14C recovery from excreta. Metabolite profiling and identification is also performed from the samples collected at this part of the study.

Results: A variety of study designs and summary data from completed studies will be reviewed, and the benefits and merits of the design over conventional approaches to generate such data will be discussed. This will include evaluation of time and dose-dependent