for moxifloxacin on day 1 and day 24. In treatment group B, placebo for ponesimod was administered once daily for 22 days (days 2–23). In addition, subjects received a single oral dose of moxifloxacin 400 mg either on day 1 or day 24. Replicate ECGs were to be extracted from the continuous digital 12-lead ECG recording over 12 hours. Primary end point was the baseline-adjusted, placebo-corrected effect of individual nonlinear corrected QT intervals (ΔΔQTcI) on day 12 (40 mg) and on day 23 (100 mg). The relationship between plasma concentrations of ponesimod and metabolites and ΔΔQTcI was assessed by applying a linear mixed effects modeling approach.
Results: Ponesimod caused a small QTc prolongation, with a mean peak effect on ΔΔQTcI of 6.9 ms (upper bound of the 2-sided 90% CI, 11.3 ms) on 40 mg and 9.1 ms (upper bound of the 2-sided 90% CI, 14.0 ms) on 100 mg. However, upon extrapolation to steady-state concentrations reached with 20-mg ponesimod, the upper bound of the 2-sided 90% CI would be below 10 ms, and should result in a negative study for doses of 20-mg ponesimod or lower. There was no relevant increased incidence of QTcI outliers, either as absolute or change from baseline, and QTcI >480 ms or QTcI increase >60 ms from baseline was not observed with ponesimod. Ponesimod did not affect the PR or QRS intervals. Assay sensitivity was demonstrated by moxifloxacin QTcI response with a mean peak effect on ΔΔQTcI of 11.8 ms (lower bound of the 2-sided 90% CI, 9.0 ms).
Conclusion: Ponesimod at doses of 40 mg and 100 mg causes a small QTc prolongation. However, based on the concentration-effect relationship no clinically relevant effect on QTc interval is expected for a dose of 20 mg, the highest selected dose for Phase 3.
Disclosure of Interest: M. Hoch: Shareholder of Actelion Pharmaceuticals Ltd, employee of Actelion Pharmaceuticals Ltd. A. Vaclavkova: Shareholder of Actelion Pharmaceuticals Ltd, employee of Actelion Pharmaceuticals Ltd. R. Stoltz: Employee of Covance Clinical Research Unit, Evansville. P. Brossard: Shareholder of Actelion Pharmaceuticals Ltd, employee of Actelion Pharmaceuticals Ltd. J. Dingemanse: Shareholder of Actelion Pharmaceuticals Ltd, employee of Actelion Pharmaceuticals Ltd.

PP163—PBMC INCREASE SIRTUIN3 PROTEIN EXPRESSION IN ACUTE ADAPTATION TO HYPOXIA IN HUMANS

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Introduction: Hypoxia is associated with pro-inflammatory conditions and increased risk of cardiovascular diseases. The transcription factors hypoxia-inducible factor (HIF)-1 and HIF-2 are known to have central roles in oxygen and energy homeostasis. Recent studies have shown that HIF-2α is deacetylated and activated by Sirtuin (Sirt)1, a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase, suggesting that Sirt1 may be involved in resistance to hypoxic stress. The aim of our pilot study is to investigate the acute role of Sirt in adaptation to hypoxic conditions.
Patients (or Materials) and Methods: Five healthy volunteers inhaled a gas mixture of 10% oxygen in nitrogen for 4 to 6 hours. Blood samples were taken 2, 4, 6 to 8, and 24 hours after start of inhalation. Erythropoietin levels were measured in plasma, and hemoxygenase 1 (HO-1), nicotinamide phosphoribosyltransferase (Nampt) and Sirt levels in peripheral blood mononuclear cells (PBMCs) by Western blot and qPCR.
Results: During inhalation of the 10% oxygen gas mixture, paO2 levels decreased from a mean of 90 mm Hg to 50 mm Hg. Mean erythropoietin levels increased from 6.6 to 11.7 mU/mL 6 to 8 hours after the start of inhalation. Western blot analysis showed increased expressions of HO-1 and Sirt3 after 6 hours. The expression of the Sirt substrate Nampt was also increased after 6 and 24 hours. In contrast, only a small increase in Sirt1 and Sirt3 mRNA was detected. Sirt2 mRNA or protein expression was not altered following hypoxia.
Conclusion: Systemic hypoxia increases Sirt3 protein expression in PBMC. This suggests that histone deacetylation of hypoxia-inducible factors are affected by changes in Sirt expression in diseases with intermittent hypoxia. Drugs targeting Sirt may thus influence adaptation to acute hypoxic episodes such as sleep apnea syndrome or chronic hypoxic conditions.
Disclosure of Interest: None declared.

PP164—DIPYRIDAMOLE DOES NOT LIMIT MYOCARDIAL ISCHEMIA-REPERFUSION INJURY AFTER CORONARY ARTERY BYPASS GRAFTING REGARDLESS AMPD1 GENOTYPE

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Introduction: In patients undergoing coronary artery bypass grafting (CABG), ischemia-reperfusion (IR) damages myocardial tissue. Postoperative plasma troponin is a biomarker of myocardial injury and is associated with an adverse outcome. In animals, dipyridamole reduces reperfusion injury by inhibition of the equilibrative nucleoside transporter (ENT) and subsequent increase in extracellular adenosine (an activator of intracellular prosurvival pathways). In humans, oral dipyridamole significantly inhibits ENT. Cellular uptake of adenosine is reduced in subjects with reduced adenosine monophosphate deaminase 1 (AMPD1) activity. We hypothesized that oral dipyridamole limits myocardial IR-injury in patients undergoing CABG surgery and that this protection is limited to those with normal AMPD1 activity.
Patients (or Materials) and Methods: In a double-blind trial, 94 patients undergoing elective CABG were randomized to pretreatment with either dipyridamole retard (200 mg BID for 3 days) or placebo. Patients abstained from caffeine for at least 24 hours. The primary end point: plasma troponin-I at 6, 12, and 24 hours after CABG (high sensitivity assay, Siemens). Secondary end points bleeding, arrhythmias 24 hours' postoperatively, the need for prolonged inotropic support, and prolonged ICU stay. In all patients, AMPD1 34C>T variants (CC: normal activity; CT and TT: reduced activity) was determined.
Results: Seventy-nine patients were included in the per-protocol analysis (46 placebo). Treatment arms did not differ with respect to age, gender, cardiovascular medication, cardiovascular risk factors, or aortic clamping time. Troponin concentrations increased from 0 (0–0) to maximally 3.4 (2.4–5.5) in placebo and 3.7 (2.7–6.1) μg/L at 6 hours after reperfusion (median with interquartile range; $P > 0.5$ for comparison between treatment arms, mixed model analysis after log transformation).This increase in troponin was correlated with aortic clamping time ($r = 0.3$, $P < 0.01$, Spearman). As for the primary end point, secondary end points did not significantly differ between the 2 study arms. Analysis restricted to the AMD1 CC variant provided similar results.
Conclusion: Dipyridamole before CABG does not prevent the rise in troponin, regardless of AMPD1 genotype. We confirmed a role for IR in this measure of cardiac injury. Therefore, dipyridamole does not seem an effective therapy to prevent ischemia-reperfusion injury in humans.
Disclosure of Interest: None declared.

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

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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

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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

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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