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Introduction: Mavoglurant is a noncompetitive antagonist at the metabotropic glutamate receptor 5 (mGlur5) currently being investigated as oral treatment of Parkinson’s disease–associated levodopa-induced dyskinesia (PD-LID) and fragile X syndrome (FXS). This study evaluated the impact of single therapeutic and supratherapeutic intravenous (IV) doses of mavoglurant on the QTc interval duration in healthy subjects in compliance with the ICH E14 guideline.

Patients (or Materials) and Methods: In a pilot-phase, the safety and tolerability of single, ascending IV doses of 25 mg, 37.5 mg, and 50 mg of mavoglurant was assessed in 36 healthy subjects (n = 12 per dose level). Subsequently, a randomized, placebo- and active-controlled, 4-period, single-center, crossover thorough QTc study has been conducted in 76 healthy subjects with the following single-dose treatments: therapeutic and supratherapeutic dose of mavoglurant, 400-mg moxifloxacin, and placebo. Mavoglurant was administered intravenously in a double-blind fashion, while the positive control moxifloxacin was orally administered in an open-label fashion. Holter ECG monitoring was performed up to 24 hours postdosing, and QTc data were derived from triplicate ECGs extracted at 3 predose (=baseline) and 12 postdose time points.

Results: An acceptable safety and tolerability of mavoglurant was confirmed at single IV doses of 25 mg, 37.5 mg, and 50 mg according to predefined criteria. Hence, doses of 25-mg and 50-mg mavoglurant were selected as therapeutic and super-therapeutic dose for the core TQT study. The upper bound of the 90% 2-sided CI of the placebo and baseline-corrected QTcF (ΔQTcF) did not exceed 10 ms at any postdose time point for both doses of 25-mg and 50-mg mavoglurant. The maximum QTcF prolongation of 1.98 ms (90% CI, 0.58–3.38) on 25 mg and 1.49 ms (90% CI, 0.10–2.88) on 50 mg were observed 3 hours’ postdosing. The PK/PD analysis confirmed the lack of an association between AFQ056 plasma concentrations and ΔQTcF data over the entire range of Cmax data at 25-mg and 50-mg mavoglurant (r2 < 0.01). An outlier analysis showed no subjects with newly identified QTcF intervals >480 ms or any QTcF prolongation >60 ms compared with baseline in any treatment group. Study validity was confirmed given that the lower bound of the 90% CI of ΔQTcF for moxifloxacin was >5 ms at 4 predefined postdose time points (1, 2, 3, and 4 hours) (Bonferroni-adjusted P < 0.0125).

Conclusion: In this thorough QTc study, the lack of any clinically relevant QTc prolongation was demonstrated for both therapeutic and supratherapeutic single IV doses of 25-mg and 50-mg mavoglurant.

Disclosure of Interest: M. Ufer: Shareholder of Novartis Pharma, employee of Novartis Pharma.

PP248—MELITOR® – REGULATORY ISSUES AS PREREQUISITE FOR PUTTING DRUG ON THE MARKET

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Introduction: Melitor®/agomelatine is a melatonergic antidepressant developed by the pharmaceutical company Servier. It is marketed for the treatment of major depressive disorder and has been reported to have a reduced level of sexual side effects as well as discontinuation effects compared with some other antidepressants. Agomelatine may also have positive effects on sleep.

Patients (or Materials) and Methods: According to Serbian Law on Medicinal Products and Medical Devices, regulatory procedural steps taken for getting Marketing Authorisation Approval in Serbia, started on 2011 year. Assessment of submitted documentation/Module 1-5 Common Technical Document/ lasted longer, because of waiting additional regulatory data requested from the manufacturer.

Results: After evaluation submitted documentation by ALIMS’s Assessors, and re-evaluation the same documentation by the experts that are in Advising Working Group for medicinal products of Medicines and Medical Devices Agency of Serbia, the ALIMS requested again additional data related to efficacy and safety of this drug. The explanation of this action was: Mechanism of action of agomelatine does not support the pharmacotherapeutic principles of threatening major depression.

Results of submitted clinical trials did not prove the efficacy of this drug. After oral administration, pharmacokinetic results showed nonlinearity in wide dose range and rough proportionality inside the therapeutic dose range. As postmarketing follow-up reports, applicant for getting Marketing Authorization Approval submitted 4 Periodic Update Reports /PSURs/. On the basis of these PSURs, it could not be concluded that benefit/ risk assessment of agomelatine in the treatment of major depression is positive.

Conclusion: After several meetings, relevant ALIMS’ experts suggested refusal of Melitor® registration. The regulatory story is still lasting, because applicant lodged the complaint on ALIMS’ decision.

PP245—IN-VITRO BIOASSAY OF 1,5-DIMETHYL CITRATE MONOHYDRATE; A COMPOUND ISOLATED FROM THE FRUIT OF MANGIFERA INDICA (ANACARDIACEAE)

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Introduction: In this study, an in vitro bioassay of 1,5-dimethyl citrate monohydrate was carried out; 1,5-dimethyl citrate monohydrate is a hydrated citric acid derivative with molecular formula C9H12O7·H2O isolated from Mangifera indica fruit.

Patients (or Materials) and Methods: To support the hypothesis that the compound may have effect on smooth muscles, the activity of this pure compound on the longitudinal smooth muscles of isolated guinea pig ileum, rabbit jejunum, and guinea pig trachea was determined.

Results: Graded doses of the compound (0.5 mg/mL and 1 mg/mL) showed a dose-dependent increase in contraction of the longitudinal smooth muscle of the isolated guinea pig ileum similar to histamine, and this contraction was antagonized by mepyramine. The compound was thus speculated to be a histaminergic agonist, which acts on the H1 histamine receptors found on smooth muscles. Activation of these H1 receptors in smooth muscle cells causes an increase in phosphoinositol hydrolysis and increase in intracellular calcium which brings about contraction of intestinal smooth muscle. The compound, however, at a concentration of 1 mg/mL produced no remarkable effect on the rabbit jejunum. Because the compound did not produce any remarkable effect on the rabbit jejunum, it is possible to speculate that the compound 1,5-dimethyl citrate monohydrate at 1 mg/mL does not activate the cell specific receptors on the smooth muscles neither does it interact with voltage-operated Ca2+ channel. The compound also at a concentration of 5 mg/mL produced no appreciable response on guinea pig trachea.

Conclusion: This suggests that the compound may not interact with the receptors present to cause any remarkable response.

Disclosure of Interest: None declared.

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