FIRST INTO MAN ADMINISTRATION OF UR-63325, A FIRST IN CLASS H₄ RECEPTOR ANTAGONIST

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**Background:** UR-63325 is a new selective antagonist of the histamine H₄ receptor, discovered and developed at Palau Pharma for the oral treatment of allergic respiratory disease. UR-63325 has been thoroughly studied in non-clinical models of efficacy, safety, pharmacokinetics (PK) and toxicity. The present study is the first reported clinical administration to humans of an H₄ receptor antagonist. PK and pharmacodynamics (PD) modelling using PK, activity and receptor affinity data from animal studies was built to predict human parameters and to design this randomised double blind and placebo controlled single rising dose study. The primary objective of the study was to identify the maximum tolerated single dose (MTD) of UR-63325, and secondarily, to explore its PK and PD through measurements of an H₄ receptor dependent blood biomarker.

**Methods:** Eight increasing single doses (2 mg to 100 mg) were tested in 8 cohorts, each with 8 healthy volunteers (6 subjects treated with UR-63325 and 2 with placebo). Subjects were hospitalised for 4 days, and were medically monitored throughout their stay and up to 8 days post-dosing. To enhance volunteers’ safety, in each period a sentinel pair of subjects (1 placebo and 1 active) preceded by one day the rest of the cohort; dosing of subjects was separated by safe periods. The PK-PD human predicted model was reassessed by a Dose Escalation Safety Committee (DESC) after each cohort in order to check fitness with actual data and robustness of predictions, and to re-assess risk/benefit for next cohort.

**Results:** Treatment emergent Adverse Events reported were generally mild and did not differ from placebo. Fitness with the PK-PD model allowed full sequential dose escalation as per protocol up to 100 mg. No Minimum Intolerated Dose was reached, but both PK and PD objectives were met - thus no MTD was defined. PK results showed linearity with very low inter-individual variability. Half-life supports once daily administration. Positive biomarker results already in the low/medium range of doses suggest dose-dependent relevant and sustained activity and a wide safety margin.

**Conclusions:** PK and PD study objectives were met without observation of dose limiting adverse events; no MTD was identified. The observed data fitted well with a priori PK and PD predictions, showing small variability and half-life suitable for once daily dosing. A multiple ascending dose study is ongoing and a proof of concept in rhinitis is planned.