Randomised, double-blind, placebo-controlled study to assess the ocular safety of mirabegron in normotensive IOP research subjects

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INTRODUCTION & OBJECTIVES: Urologic drugs in development are often studied for ocular safety to ensure an acceptable safety profile when used in clinical practice. In overactive bladder (OAB), the mainstay of pharmacological treatment is currently antimuscarinic therapy. However, these agents are not recommended in OAB patients with uncontrolled narrow angle glaucoma (in which ocular fluid drainage is disrupted) due to the potential for increased intraocular pressure (IOP) and risk of a medical emergency that could lead to vision loss. Mirabegron, a potent and selective β3-adrenoceptor agonist, is a first in a new class of agents for OAB with a distinct mechanism of action. This study assessed the effect of mirabegron on

IOP and ocular safety in research subjects.

MATERIAL & METHODS: In this phase I non-inferiority study, consenting males or females aged ⩾ 18 years with normal IOP (⩾ 10 to ⩽ 21 mmHg) were randomised 1:1 to oral mirabegron 100 mg or placebo once daily for 56 days. Notable exclusion criteria consisted of a history of glaucoma or ocular hypertension, abnormal visual field or any ophthalmic condition that could interfere with study assessments. Primary and secondary outcome variables were change from baseline to day 56 and day 10 in subject-average IOP, respectively. IOP was measured in each eye between 9 and 11 am under rigorous conditions for standardisation. Treatment differences between mirabegron and placebo on the primary IOP variable were assessed using analysis of covariance (ANCOVA) with treatment as fixed factor and baseline IOP as covariate. From the ANCOVA model, non-inferiority was accepted if the upper limit of the 2-sided 95% CI for the adjusted mean treatment difference was less than 1.5 mmHg. Pre- and post-dose ocular evaluations, adverse event (AE) collection, and standard safety assessments were performed.

RESULTS: In total, 321 subjects were randomised and 305 completed the study. Mean (SE) IOP at baseline was 15.3 (0.16) mmHg for mirabegron and 15.4 (0.16) mmHg for placebo; values at day 56 were 15.0 (0.16) mmHg and 15.2 (0.17) mmHg. Adjusted mean IOP change from baseline to day 56 was -0.3 mmHg for mirabegron and -0.2 mmHg for placebo (-0.1 mmHg difference [95% CI -0.4 to 0.3]). For the primary endpoint, mirabegron was non-inferior to placebo, based on the prespecified limit of 1.5 mmHg. IOP data from day 10 were consistent with those at day 56. No subject discontinued due to increased IOP. Clinically significant increases from baseline in IOP occurred rarely and only with placebo. Visual acuity and biomicroscopy data were unremarkable. No treatment-emergent AE of glaucoma was reported.

CONCLUSIONS: Mirabegron was non-inferior to placebo with regard to effect on IOP. Clinically, these results demonstrate that mirabegron did not increase or decrease IOP with chronic treatment and support the ocular safety of mirabegron.