Abstract:

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Efficacy and safety of various doses of the new dual endothelin receptor antagonist aprocitentan in the treatment of hypertension

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Background: Endothelin Receptor Antagonists (ERAs) have been investigated for the treatment of a variety of cardiovascular conditions because of their potent vasodilating properties. However, until now, ERAs have only been registered for the treatment of pulmonary arterial hypertension and scleroderma-induced digital ulcers. This class of drugs may also be useful in the treatment of difficult to control hypertension with a medical need.

Purpose: To investigate the efficacy and safety of various doses of the new dual ERA, aprocitentan, in the treatment of hypertension in order to determine the most appropriate dose(s) for further clinical development using an unattended, automated office BP (AOBP) device (BpTRU). This Phase 2 trial was registered at ClinicalTrials.gov [NCT02603809].

Methods: Eligible patients with hypertension (mean sitting systolic/diastolic BP 149.7/97.6 mmHg) received aprocitentan 5, 10, 25 or 50 mg, matching placebo or lisinopril 20 mg as a positive control, once daily for 8 weeks using a randomised, double-blind, parallel-group study design. AOBP was assessed at baseline and weeks 2, 4, 8, and 10 (withdrawal) by recording multiple BP readings with the patient resting quietly. Additionally, 24 h ambulatory BP monitoring was performed at baseline and week 8.

Results: A total of 490 eligible patients were randomised to the double-blind phase with 430 subjects successfully completing 8 weeks of treatment. Decreases in sitting systolic/diastolic AOBP, from baseline to week 8 were 10.3/6.3, 15.0/9.9, 18.5/12.0 and 15.1/10.0 mmHg for aprocitentan 5, 10, 25, and 50 mg, respectively vs. 7.7/4.9 mmHg for placebo and 12.8/8.4 mmHg for lisinopril. No changes in heart rate or body weight were observed for any dose of aprocitentan.

Modelling the dose-response suggested that the maximal effect of aprocitentan is achieved at a dose of approximately 25 mg and that 70% of this effect is already observed at a dose of 10 mg. Aprocitentan treatment was associated with decreases in haemoglobin, haematocrit, and albumin which exhibited a monotonic dose-response relationship, in line with its known vasodilating effects. Estimated increases in plasma volume were 3.0%, 5.1%, 6.9%, and 9.5% for aprocitentan 5, 10, 25, and 50 mg, respectively, vs. 7.7/4.9 mmHg for placebo and 12.8/8.4 mmHg for lisinopril. No changes in heart rate or body weight were observed for any dose of aprocitentan.

The overall incidence of adverse events observed in the aprocitentan groups (ranging from 22.0% to 40.2%) was similar to that seen in the placebo group (36.6%). Overall, the most common events were hypertension, headache, and nasopharyngitis.

Conclusions: These findings support the use of aprocitentan at doses between 10 and 25 mg for further
investigation as a potential treatment for hypertension.