

## **008. Multiple-Ascending-Dose Study of IW-1973, a Soluble Guanylate Cyclase Stimulator**

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### **Purpose**

Soluble guanylate cyclase (sGC), an enzyme that catalyzes the formation of cyclic guanosine monophosphate (cGMP) in response to nitric oxide (NO) binding, is a key mediator of local blood flow, inflammation, and fibrosis. IW 1973 is an orally available sGC stimulator that enhances NO sGC-cGMP signaling and reduces blood pressure (BP) in animal models of hypertension, both alone and in combination with other antihypertensive agents.

### **Methods**

A Phase 1b placebo-controlled, randomized, multiple-ascending-dose study was conducted to assess safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (BP, heart rate, platelet function, and plasma biomarkers) of IW-1973 in healthy subjects. Four successive cohorts of 11 subjects each (8 active and 3 placebo) were enrolled. Subjects received a starting dose once daily (QD) for 14 days followed by an up-titrated QD dose for 7 days.

### **Results**

IW-1973 doses ranging from 15 to 40 mg were tolerated. There were no serious adverse events (AEs), severe AEs, or discontinuations due to AEs. Among the 32 subjects who received IW-1973, the most common AEs (which occurred mainly at doses  $\geq 30$  mg) were headache (15 subjects), dizziness/postural dizziness (6) and orthostatic hypotension/BP decreased (4). AEs tended to resolve with continued dosing. The AE profile of higher doses was not clearly improved by up titration from a lower starting dose. PK was dose proportional, both for C<sub>max</sub> and AUC, with a T<sub>max</sub> of 2-4 hours and an effective half-life of 24-37 hours. After 14 days of treatment, least squares mean change from baseline in 24-h ambulatory systolic BP ( $\pm$ SE) was 0.85 $\pm$ 1.32 (placebo), 7.29 $\pm$ 1.62 (15 mg), 3.27 $\pm$ 1.61 (20 mg), 6.75 $\pm$ 1.62 (30 mg), and 5.23 $\pm$ 1.61 mmHg ( $\leq 40$  mg,  $\leq 0.5$  mg/kg). After 21 days, the change from baseline was 4.81 $\pm$ 1.19 (placebo), 8.21 $\pm$ 1.46 (15 to 30 mg), 6.29 $\pm$ 1.45 (20 to 40 mg), 9.05 $\pm$ 1.56 (30 to 40 mg), and 6.58 $\pm$ 1.45 mmHg ( $\leq 40$  to  $\geq 40$  mg). IW-1973 produced a dose-related increase in plasma cGMP indicating target engagement. There was no clear effect of IW-1973 administration on platelet function as assessed by the PFA 100<sup>®</sup> system.

### **Conclusions**

Further clinical investigation of IW-1973 is ongoing or planned in multiple indications, including hypertension.