Clinical Therapeutics/Volume ▮, Number ▮, 2017

# Relationship Between Atrasentan Concentrations and Urinary Albumin to Creatinine Ratio in Western and Japanese Patients With Diabetic Nephropathy

Chih-Wei Lin, PhD; Nael M. Mostafa, PhD; Dennis L. Andress, MD; John J. Brennan, PhD; Cheri E. Klein, PhD; and Walid M. Awni, PhD

*AbbVie Inc, North Chicago, Illinois*

## ABSTRACT

**Purpose:** The objective of the current analyses was to characterize the pharmacokinetic properties of atrasentan and the exposure-response relationships for the efficacy end point, urinary albumin to creatinine ratio (UACR), and the treatment-emergent adverse event, peripheral edema, during 8 or 12 weeks of treatment.

**Methods:** Results from 3 Phase II, randomized, double-blind, placebo-controlled studies (N = 257) were used for the population pharmacokinetic and exposure-response models. Concentration-time and response data for efficacy and tolerability were analyzed using a nonlinear mixed-effects population analysis and logistic regression approaches.

**Findings:** The pharmacokinetic data were adequately described by a 2-compartment model with first-order absorption and elimination. After weight was accounted for, no clinically meaningful differences were found in CL/F or $V_d$/F of the central compartment between Western and Japanese patients. Exposure-response analyses confirmed the efficacy of atrasentan in reducing UACR, with an estimated decrease in UACR of ≥37% when the atrasentan dose was 0.75 mg or higher. No significant association between atrasentan exposure and the rate of edema was identified at atrasentan doses of 0.5, 0.75, and 1.25 mg. The rates of peripheral edema were comparable in patients receiving active treatment and placebo.

**Implications:** The exposure-response relationships for efficacy and tolerability were consistent between Western and Japanese patients. On the basis of these analyses, a dose of 0.75 mg/d was selected for the Phase III trial. ClinicalTrials.gov identifiers: NCT01356849, NCT01399580, and NCT01424319.

(*Clin Ther*. 2017;▮:▮▮▮–▮▮▮) 

**Key words:** atrasentan, diabetic nephropathy, exposure response, peripheral edema, pharmacokinetics, UACR.

## INTRODUCTION

Endothelins may play a significant role in pathophysiologic changes that occur in the vasculature in diabetes mellitus and lead to complications of retinopathy, neuropathy, and renal failure.[1] The role of endothelins in regulating renal function has been widely investigated, and it is clear that endothelins play a role in renal injury caused by metabolic diseases, including diabetes.[2,3] As a result, the endothelin system is being actively investigated as a therapeutic target for treatment of diabetic nephropathy.[2–5]

Atrasentan is an orally bioavailable, potent endothelin receptor antagonist with a high selectivity for the endothelin A receptor.[6] In a rat model of diabetic nephropathy, atrasentan treatment prevented albuminuria and glomerulosclerosis in association with reductions in glomerular permeability and urine transforming growth factor β.[7,8] In patients with type 2 diabetic nephropathy and residual albuminuria who were receiving stable doses of renin angiotensin system (RAS) inhibitors, treatment with atrasentan 0.75 mg and 1.75 mg once daily for 8 weeks significantly reduced the urinary albumin to creatinine ratio

*Accepted for publication July 11, 2017.*
http://dx.doi.org/10.1016/j.clinthera.2017.07.011
0149-2918/$ - see front matter

(UACR) by 42% and 35%, respectively, compared with placebo, with minimal fluid retention at the 0.75-mg dose.[9,10] At the higher dose of atrasentan, edema was observed in 46% to 58% of patients receiving atrasentan compared with 9% to 11% of patients receiving placebo.[9,10]

To confirm the results of the above study and to select an atrasentan dose for evaluation in a larger Phase III trial (NCT01858532), 3 Phase II studies were conducted to characterize the pharmacokinetic properties, efficacy, and tolerability of atrasentan in Western and Japanese patients with type 2 diabetes mellitus and nephropathy who had residual albuminuria while receiving a maximally tolerated labeled dose of a RAS inhibitor and a diuretic. The primary objective of each study was to evaluate the efficacy of atrasentan as measured by the change from baseline in logarithm-transformed UACR. Efficacy and tolerability results from 2 of the studies have been described previously and confirmed atrasentan's effect in reducing albuminuria in patients with diabetic nephropathy without increasing edema compared with placebo.[11] In the current report, we present a population pharmacokinetic model that was developed using data from these 3 studies to characterize the pharmacokinetic properties of atrasentan in patients with diabetic nephropathy. Exposure-response analyses were conducted to evaluate (1) the relationships between atrasentan plasma concentrations and changes in log-transformed UACR and (2) the correlation between atrasentan exposure and the incidence rate of peripheral edema. Possible differences in the pharmacokinetic properties of atrasentan and exposure-response relationships in Western patients compared with Japanese patients were also evaluated. Finally, the effects of covariates on the pharmacokinetic properties of atrasentan and exposure-response relationships were explored.

## PATIENTS AND METHODS

### Patients

Enrollment criteria were similar for each study and have been described in detail for studies 1 and 3.[11] Eligible patients were men and women at least 18 years of age (20 years of age in Japan) with type 2 diabetes with nephropathy who were receiving angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and who had an estimated glomerular filtration rate ≥30 and ≤75 mL/min/1.73 $m^2$ by the epidemiology collaboration formula, UACR ≥300 and ≤3500 mg/g, systolic blood pressure ≥110 and ≤180 mm Hg, serum albumin ≥3.0 g/dL, brain natriuretic peptide ≤200 pg/mL, and glycosylated hemoglobin $A_{1c}$ ≤12%. At the end of the screening period, a UACR ≥200 g/mg, stable and controlled systolic blood pressure (110–160 mm Hg), a diuretic at any dose unless medically contraindicated, serum potassium ≤5.5 mEq/L (5.5 mmol/L), and a RAS inhibitor at maximum tolerated labeled dose for the previous 4 weeks were required for entry into the treatment period.

### Study Designs

Each study was a Phase II, randomized, double-blind, parallel-arm, placebo-controlled, multicenter study that included a screening period, a run-in period, an 8- or 12-week treatment period, and a 30-day follow-up visit (Figure 1 and de Zeeuw et al[11] for studies 1 and 3). Patients who met the inclusion and exclusion criteria at the last run-in visit were randomized to receive placebo or atrasentan tablets at a low dose (0.5 or 0.75 mg/d) or high dose (1.25 mg/d). A stratified randomization scheme ensured balance among treatment groups with respect to UACR levels at run-in week −1 (≤1,000 and >1,000 mg/g). The studies were conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The protocols for these studies were approved by the institutional review boards, and written informed consent was obtained from each patient before any study-related procedures were performed.

### Pharmacokinetic Properties, UACR, and Peripheral Edema

Blood samples for determination of plasma atrasentan concentrations were obtained by venipuncture before study drug administration at the week 2 study visit and at the study visits every other week thereafter until the end of treatment or premature discontinuation. Plasma atrasentan concentrations were measured by the Bioanalysis Department at AbbVie using validated bioanalytical methods.[12]

Three consecutive first morning void urine samples were collected within 3 days before the run-in week −1 visit and all treatment period visits (except week 1) for