

# Atrasentan Exhibits a Consistent, Predictable Pharmacokinetic Profile Among Healthy Asian Adults

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# Author Disclosures

- Dr. Rastogi has received consultation payments from Chinook Therapeutics
- Dr. Lv has received consultation payments from Chinook Therapeutics and KBP Bioscience
- Drs. Catanzaro & Tong are employees of Chinook Therapeutics
- Dr. Suzuki has received consultation payments and research funding from Chinook Therapeutics

# Introduction: IgA Nephropathy

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis (GN) globally

Approximately 30-45% of IgAN patients will develop end-stage kidney disease (ESKD) over a period of 20-25 years<sup>1,2</sup>

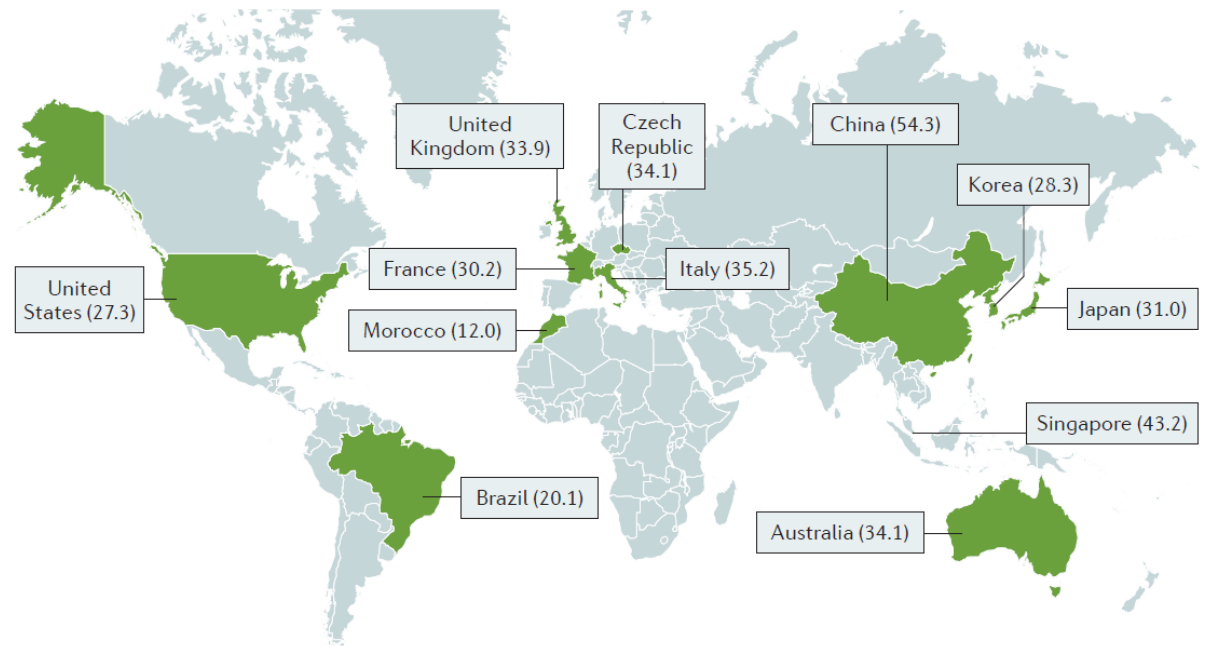
No approved treatments and limited options for high-risk patients<sup>1,2</sup>

- RAS inhibition (ACEi/ARB) is frontline (KDIGO 1B)
- Steroids & immunosuppressive agents provide inconsistent therapeutic benefit and are accompanied by significant side effects (KDIGO 2B)

Geographical differences in IgAN prevalence<sup>2</sup>

- Appears more common with potentially accelerated progression in Asia

## Global Prevalence of IgAN (% of biopsy-proven primary GN)



There remains an urgent need globally for new IgAN treatments

# Introduction: Atrasentan

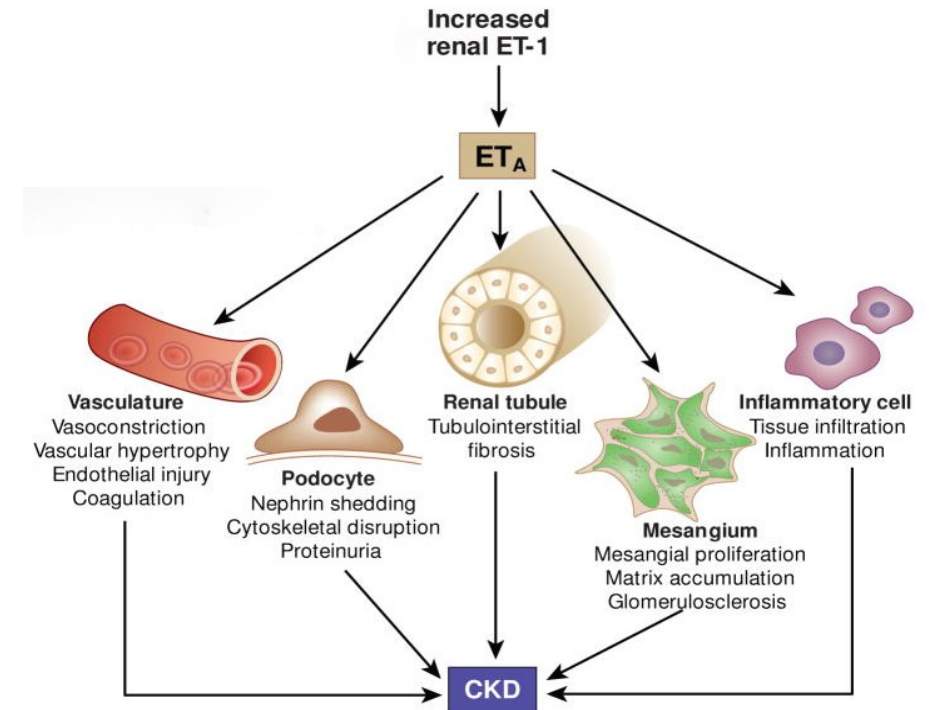
Atrasentan is a potent and selective endothelin A (ET<sub>A</sub>) receptor blocker

Intra-renal endothelin (ET) system activation has been reported to predict clinical progression of IgAN<sup>1</sup>

ET<sub>A</sub> activation has potential to drive IgAN progression through multiple mechanisms including:<sup>2</sup>

- Mesangial cell activation
- Proteinuria
- Kidney inflammation and fibrosis

Atrasentan has been previously shown to decrease proteinuria and improve kidney outcomes in diabetic kidney disease patients<sup>3,4</sup>



The global Phase 3 ALIGN trial is assessing the efficacy, safety and tolerability of atrasentan in IgAN patients at risk of progressive kidney function loss, despite optimized RAS blockade (NCT04573478)

# Objective & Study Designs

The objective of this study was to compare the safety, tolerability, and pharmacokinetics (PK) of atrasentan in healthy Chinese, Japanese and North American adults

## Chinese Study

- Open label, randomized
- 0.5 mg, **0.75 mg**, **1.25 mg**

## Japanese Study

- Double-blind, randomized, placebo-controlled
- 0.5 mg, **0.75 mg**, **1.25 mg**, placebo

## North American Study

- Open label, randomized, 3-period, crossover
- 0.35 mg, **0.75 mg**, **1.25 mg**

Three separate, single-dose, randomized studies were conducted in healthy Chinese, Japanese and North American adults of non-Asian descent.

PK profiles were characterized from plasma samples following dosing under fasted conditions. PK parameters were estimated using noncompartmental methods. Relevant common dose levels (0.75 mg and 1.25 mg) were compared between groups.

Safety and tolerability were evaluated in each study based on assessments of adverse events, physical examinations, vital signs, electrocardiograms and clinical laboratory tests.

# Methods & Study Participants

## Methods

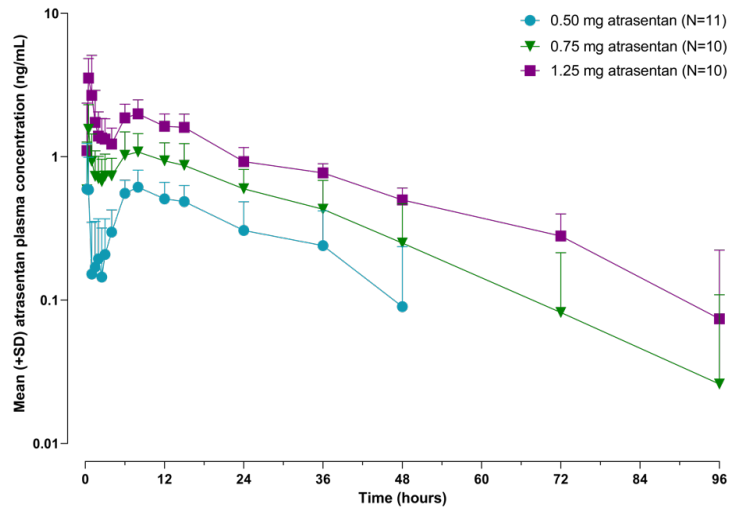
- Dose proportionality with respect to  $AUC_{0-inf}$  and  $C_{max}$  were analyzed using analysis of covariance (ANCOVA; Chinese and Japanese studies)
- Statistical comparisons of  $AUC_{0-inf}$ ,  $C_{max}$ ,  $t_{max}$  and  $t_{1/2}$  following a single dose of atrasentan in Chinese, Japanese, and North American adults were performed using one-way ANOVA for the 0.75 mg and 1.25 mg dose cohorts

## Demographics and Baseline Characteristics

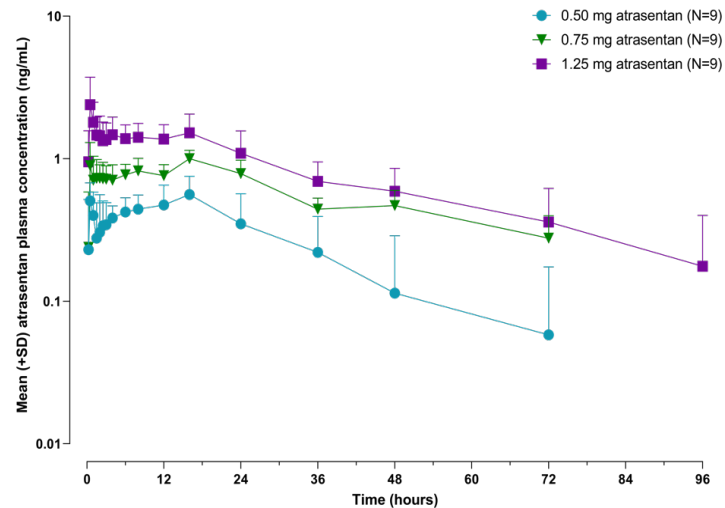
	Chinese N=31	Japanese N=36	N. American N=12
<b>Sex, n (%)</b>			
Female	0	9 (25)	3 (25)
Male	31 (100)	27 (75)	9 (75)
<b>Age, yrs., mean (SD)</b>	27.2 (2.6)	41.9 (11.2)	41 (8.4)
<b>Weight, kg, mean (SD)</b>	66.9 (7.9)	64 (9.8)	75.7 (12.6)

# Pharmacokinetic Profiles

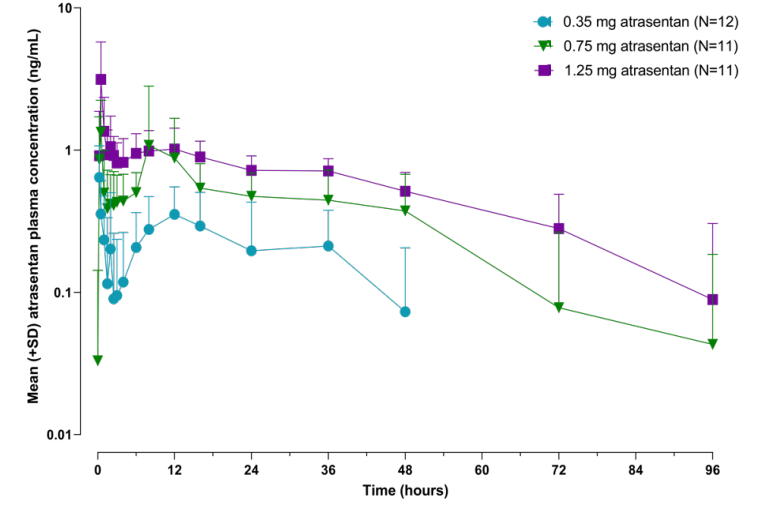
## A. Chinese Study



## B. Japanese Study<sup>a</sup>



## C. North American Study<sup>b</sup>



### Mean (SD) for 0.75 mg dose

$C_{max}$ (ng/mL)	1.64 (0.71)	1.11 (0.33)	1.76 (1.74)
$AUC_{0-inf}$ (ng*h/mL)	46.5 (17.2)	57.7 (12.7)	57.2 (25.3)

- Atrasentan exhibited bi-phasic kinetics characterized by a  $T_{max}$  of 0.5 to 1 hour, followed by a secondary peak between 9 and 18 hours post-dose that is consistent with enterohepatic recirculation of the glucuronide metabolite
- The apparent clearance ranged from 13 to 20 L/h and the terminal  $t_{1/2}$  was 24 to 39 hours after a single dose

# Pharmacokinetic Results

Overall PK parameters were consistent in healthy adults of Chinese, Japanese and North Americans of non-Asian descent at the optimized clinical dose of 0.75 mg

PK Parameters (Mean ± SD)	North American (n=11)	Chinese (n=10)	Japanese (n=9)	One-way ANOVA P value
<b>AUC<sub>0-inf</sub> (ng-hr/mL)</b>	57.1 ± 25.3	46.5 ± 17.2	57.7 ± 12.7	0.376
<b>C<sub>max</sub> (ng/mL)</b>	1.37 ± 0.909	1.64 ± 0.706	0.950 ± 0.384	0.129
<b>t<sub>max</sub><sup>a</sup> (hr)</b>	0.50 [0.25 - 0.50]	0.50 [0.5 - 8]	0.67 [0.25 - 2]	0.199
<b>t<sub>1/2</sub><sup>b</sup> (hr)</b>	39.2 ± 43.4 <sup>c</sup>	24.6 ± 10.3	33.9 ± 15.1	0.019

<sup>a</sup> For t<sub>max</sub> (time at which C<sub>max</sub> was observed) values are median and range [min - max].

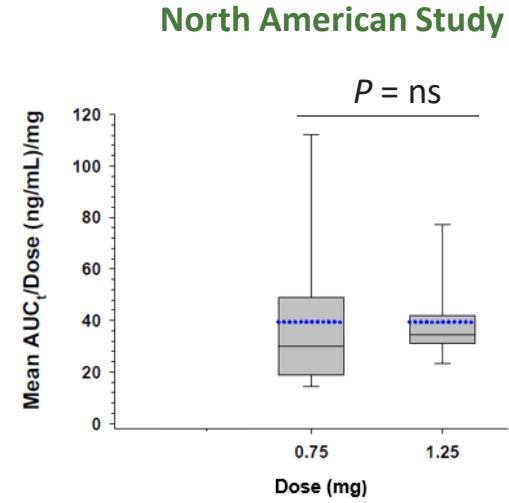
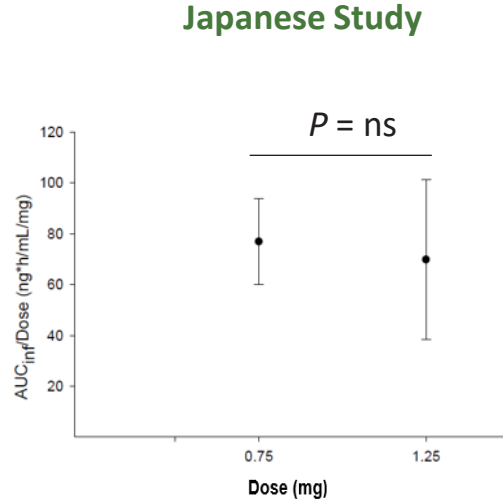
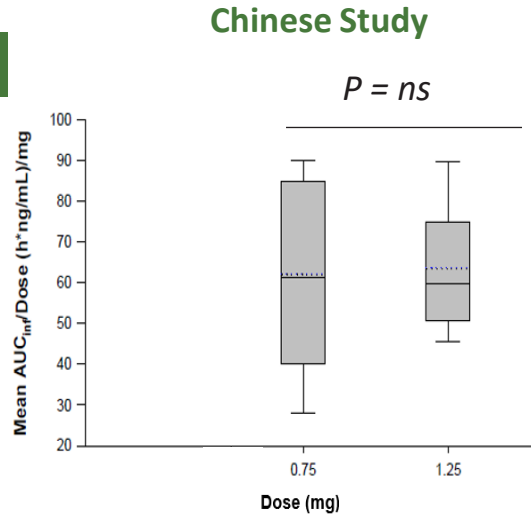
<sup>b</sup> For t<sub>1/2</sub> the mean is the harmonic mean and the SD is the pseudo-SD.

<sup>c</sup> Statistically significant by one-way ANOVA (P≤0.05).



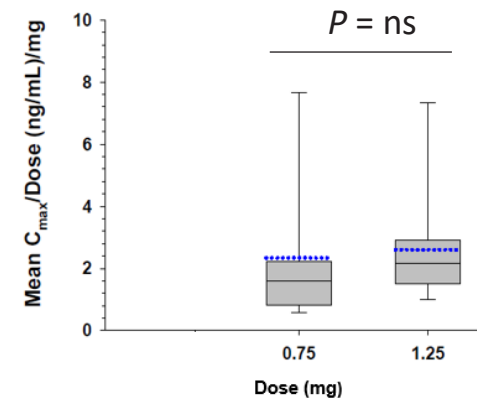
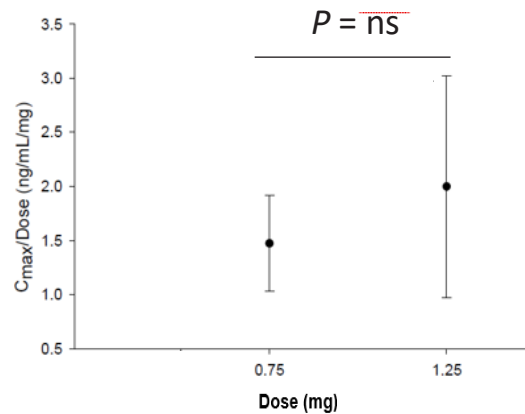
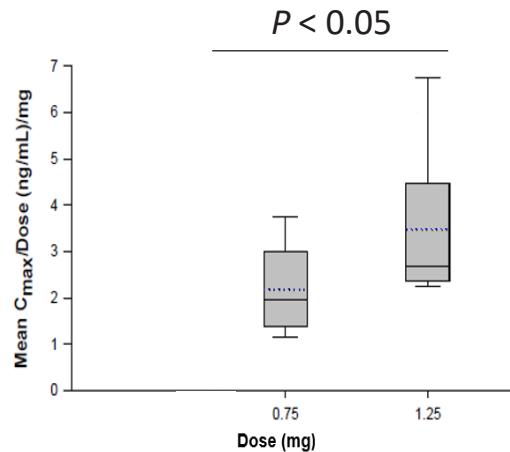
# Dose Proportional AUC Exposures Across the Common Efficacious Dose Range Tested (0.75 – 1.25 mg)

$AUC_{0-inf}/Dose$



- $AUC_{0-inf}$  was dose proportional across efficacious dose levels (0.75 - 1.25 mg) across ethnic groups

$C_{max}/Dose$



- $C_{max}$  was dose proportional across the efficacious dose levels (0.75 – 1.25mg) in North American and Japanese; however, greater than dose proportional in the Chinese ( $P < 0.05$ )

# Safety & Conclusions

## Safety

- Atrasentan was generally well-tolerated with no serious AEs or other significant AEs reported
- Treatment-emergent AEs assessed as possibly or probably related to the study drug were mild in severity
- No clinically significant changes in vital signs or laboratory measurements observed
- No new safety signals were identified and no significant differences among the groups with respect to safety

## Conclusions

- **Data from the three phase 1 studies of atrasentan demonstrated consistent and predictable safety, tolerability and linear dose-proportionality in healthy Chinese, Japanese and North American adults of non-Asian descent**
- **Atrasentan had similar PK parameters ( $C_{max}$ ,  $T_{max}$ , AUC) among the studied groups following administration of a single-dose of either 0.75 mg or 1.25 mg**
- **These data, along with previously published results, support the safety and tolerability of atrasentan in Asian adults as well as the use of the 0.75 mg dose in ongoing global studies in primary glomerular diseases**



*INFO35: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Atrasentan in Patients with IgA Nephropathy: The ALIGN Study*



*INFO36: Atrasentan in Patients with Proteinuric Glomerular Diseases: The AFFINITY Study*