AFFINITY Study: 1-Year Results of Atrasentan in IgA Nephropathy

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KEY FINDINGS & CONCLUSIONS

- Atrasentan, in addition to standard-of-care, was well tolerated and there were no serious treatment-related adverse events. One treatment-related adverse event of headache led to study drug discontinuation.
- Treatment with atrasentan resulted in a clinically meaningful, stable reduction in proteinuria over 1 year of treatment in patients with IgAN receiving optimized standard-of-care, supporting its therapeutic potential in IgAN.
- Further evaluation of the effect of atrasentan on clinical outcomes in patients with IgAN is ongoing in the global Phase 3 ALIGN study (NCT04573478).

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INTRODUCTION

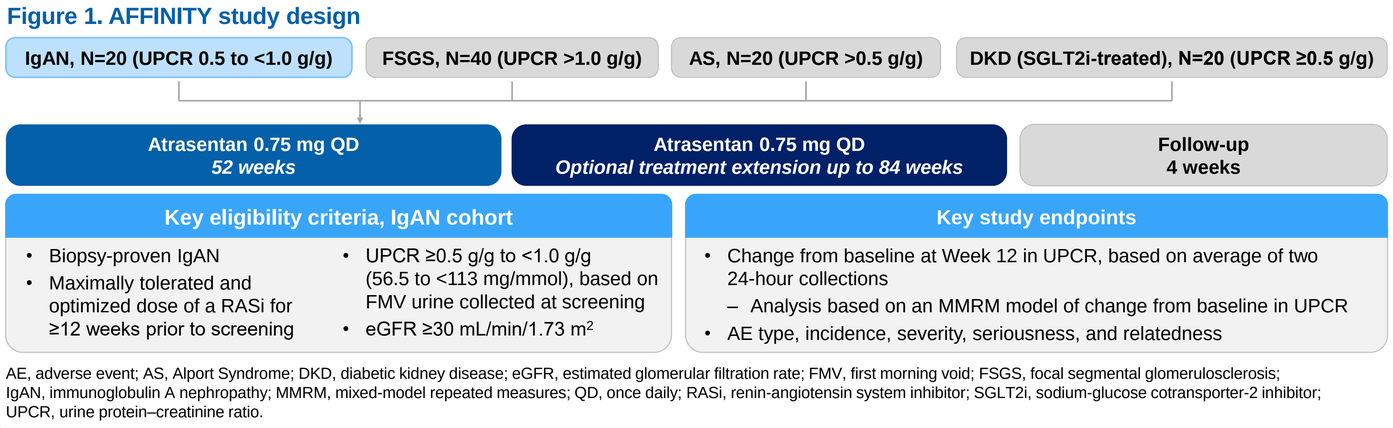
- IgA nephropathy (IgAN) is the leading cause of primary glomerulonephritis globally, with limited treatment options.[1,2]
- Endothelin pathway dysregulation is associated with IgAN pathophysiology.[3]
  - Endothelin A (ET_A) receptor activation drives mesangial cell activation, kidney inflammation and fibrosis, and proteinuria, all hallmarks of IgAN.[3]
- Atrasentan is a potent, highly selective ET_A receptor antagonist that has demonstrated clinically meaningful reduction in proteinuria with a favourable safety and tolerability profile in patients with IgAN.[4]

METHODS

Study design

- AFFINITY is a global, phase 2, open-label basket study evaluating the efficacy and safety of atrasentan in patients with proteinuric glomerular disease (NCT04573920; **Figure 1**).
- The IgAN cohort included adults with biopsy-proven IgAN:
  - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2
  - Urine protein–creatinine ratio (UPCR) ≥0.5 g/g and <1.0 g/g (first morning void), and
  - On maximum tolerated/stable renin-angiotensin system inhibitor (RASi) for ≥12 weeks.
- Patients took 0.75-mg oral atrasentan once daily (QD) for 52 weeks.
- The primary endpoint was change in 24-hour UPCR from baseline to Week 12.

Figure 1. AFFINITY study design



AE, adverse event; AS, Alport Syndrome; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FMV, first morning void; FSGS, focal segmental glomerulosclerosis; IgAN, immunoglobulin A nephropathy; MMRM, mixed-model repeated measures; QD, once daily; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UPCR, urine protein–creatinine ratio.

RESULTS

- The IgAN cohort enrolled 20 patients with UPCR ≥0.5 g/g and <1.0 g/g; median age was 44.5 years, 50% were women, 45% were White, and 45% were Asian (**Table 1**).
- Nineteen patients completed 52 weeks of treatment.
- Median follow-up was 52.2 weeks (range: 18–55 weeks).

Table 1. Baseline demographics and characteristics

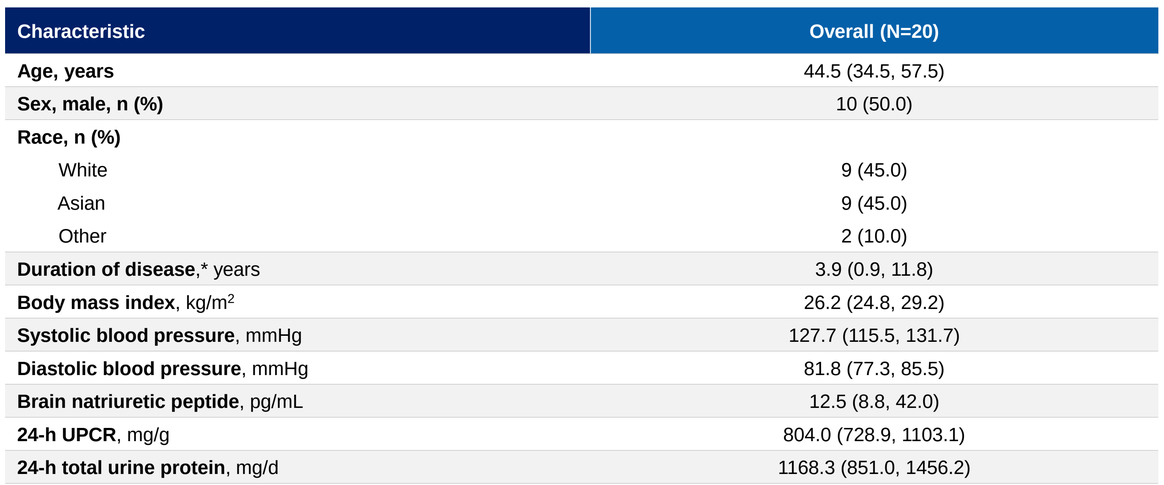
Characteristic	Overall (N=20)
Age, years	44.5 (34.5, 57.5)
Sex, male, n (%)	10 (50.0)
Race, n (%)	
White	9 (45.0)
Asian	9 (45.0)
Other	2 (10.0)
Duration of disease,* years	3.9 (0.9, 11.8)
Body mass index, kg/m^2	26.2 (24.8, 29.2)
Systolic blood pressure, mmHg	127.7 (115.5, 131.7)
Diastolic blood pressure, mmHg	81.8 (77.3, 85.5)
Brain natriuretic peptide, pg/mL	12.5 (8.8, 42.0)
24-h UPCR, mg/g	804.0 (728.9, 1103.1)
24-h total urine protein, mg/d	1168.3 (851.0, 1456.2)
24-h total urine protein ≥1 g/d, n (%)	14 (70.0)
eGFR, mL/min/1.73 m^2	45.8 (36.8, 73.8)
Concurrent RASi, n (%)	
Angiotensin-converting enzyme inhibitor only	8 (40.0)
Angiotensin receptor blocker only	12 (60.0)

*Duration was calculated as number of years between the date of biopsy and first dose date. If no biopsy, date of diagnosis was used.
Values are median (Q1, Q3) unless otherwise stated.
eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitor; UPCR, urine protein–creatinine ratio.

Efficacy

- Reduction in 24-hour UPCR was evident by Week 6 and sustained through Week 52 (**Figure 2**).
- The primary efficacy analysis using mixed-model repeated measures (MMRM) modeling for the change from baseline in natural log UPCR demonstrated a −48.4% (95% confidence interval: −56.4%, −39.0%) mean percent change from baseline to Week 12, representing a clinically meaningful reduction in proteinuria.

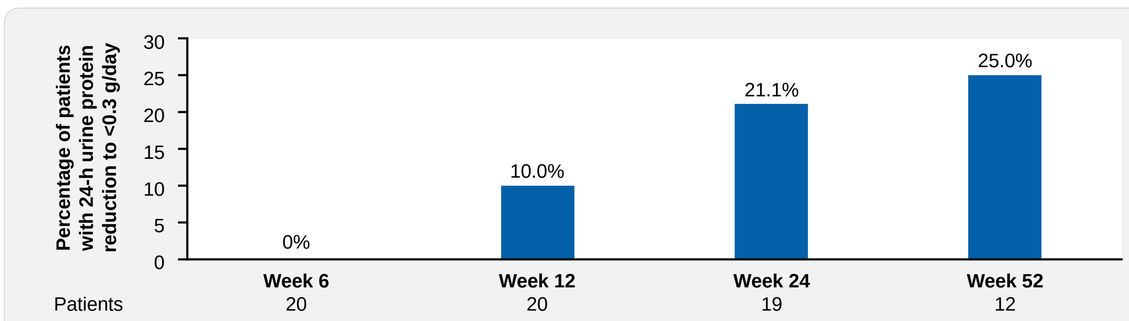
Figure 2. Least-squares mean percentage change from baseline in UPCR



Efficacy analysis set (N=20). LS mean percent change and 95% CI were calculated by transforming the results on the natural log scale and used an MMRM model with unstructured variance-covariance.
CI, confidence interval; LS, least squares; MMRM, mixed-model repeated measures; SE, standard error; UPCR, urine protein–creatinine ratio.

- In an exploratory analysis, 6 patients (30%) had a 24-hour total urine protein reduction to <0.3 g/day at any post-baseline timepoint.
  - At Week 52, 3/12 (25%) patients had 24-hour total urine protein reduction to <0.3 g/day (**Figure 3**).
  - Of 19 patients with a baseline 24-h total urine protein >0.5 g/day, 11 patients (58%) had a post-baseline 24-h total urine protein value <0.5 g/day.
  - Of 14 patients with baseline 24-h total urine protein >1 g/day, 13 patients (93%) had a post-baseline 24-h total urine protein value <1 g/day.

Figure 3. Patients with 24-hour total urine protein reduction to <0.3 g/day



Efficacy analysis set (N=20).

Safety and tolerability

- Atrasentan was well tolerated with no treatment-related serious adverse events (AEs) or deaths (**Table 2**).
  - AEs were seen in 18 (90.0%) patients, of which the most common was COVID-19; one patient discontinued treatment at Week 13 due to an AE of headache considered treatment related.

Table 2. Treatment-emergent adverse events (TEAEs)

IgAN cohort (N=20)	n (%)
Any TEAE	18 (90.0)
TEAEs reported in ≥10% patients	
COVID-19	8 (40.0)
Dizziness	3 (15.0)
Constipation	2 (10.0)
Headache	2 (10.0)
Edema peripheral	2 (10.0)
Any treatment-related TEAE	5 (25.0)
Any serious TEAE	1 (5.0)
Any treatment-related serious TEAE	0
Any TEAE leading to death	0
Any TEAE leading to study drug discontinuation	1 (5.0)*

*One patient discontinued treatment due to a related TEAE of headache at Week 13.
IgAN, IgA nephropathy; TEAE, treatment-emergent adverse event.

Table 3. Clinical and physical evaluations

IgAN cohort (N=20)	Week	n	Mean (SD) change from baseline
Body weight, kg	52	19	0.23 (3.24)
Systolic blood pressure, mmHg	52	19	0.11 (11.55)
Diastolic blood pressure, mmHg	52	19	−4.18 (7.42)
Brain natriuretic peptide,* pg/mL	24	18	8.36 (24.93)

*The mean (SD) BNP level at baseline was 22.22 (16.99) pg/mL (range 2.1 to 48.8 pg/mL). Generally, BNP levels <100 pg/mL suggest the absence of fluid retention in patients without kidney failure.[5] Safety analysis set (N=20).
BNP, brain natriuretic peptide; IgAN, IgA nephropathy; SD, standard deviation.

- There were no clinically meaningful mean changes from baseline in body weight, brain natriuretic peptide, or blood pressure (**Table 3**).

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Disclosures

This study is sponsored by Novartis Pharma AG.