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Baseline characteristics of the ALIGN trial: a Phase 3 randomized, double-blind, placebo-controlled clinical trial of atrasentan in patients with IgAN

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SUMMARY

- ALIGN is designed to assess the effect of atrasentan, compared with placebo, in reducing proteinuria and eGFR decline in adult patients with IgAN receiving an optimized dose of an ACEi or ARB
- Baseline demographics and patient characteristics show that ALIGN has enrolled a globally representative population of patients with IgAN
  - Most patients were recruited in Asia, where the prevalence of IgAN and other glomerular disease is higher than in the rest of the world
  - Women are well represented in ALIGN with a participation rate >40%
- ALIGN is anticipated to provide unique insights into a potential new treatment option for patients with IgAN

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INTRODUCTION

- Lifestyle modification and either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) are the current treatment options for IgA nephropathy (IgAN)[1]
  - While this approach slows the rate of kidney function loss in most patients, residual kidney function loss exceeds the target needed to avoid a lifetime risk of kidney failure[2]
- In patients with IgAN, upregulation of endothelin-1 exerts deleterious effects through binding to the endothelin A receptor[3]
- Atrasentan is a potent and selective endothelin A receptor antagonist
- Interim results from the Phase 2 AFFINITY trial show that atrasentan plus optimized ACEi or ARB treatment was well tolerated and resulted in clinically meaningful proteinuria reductions at 12 and 24 weeks[4]
- ALIGN is a Phase 3, randomized, double blind, placebo-controlled study to assess the efficacy and safety of atrasentan vs placebo in adult patients with IgAN receiving optimized ACEi or ARB treatment
- The sodium-glucose co-transporter 2 inhibitor (SGLT2i), dapagliflozin, has been shown to reduce the risk of progression to chronic kidney disease in patients with IgAN[5]
  - ALIGN includes an exploratory cohort to address potential additive effects of atrasentan and SGLT2i

METHODS

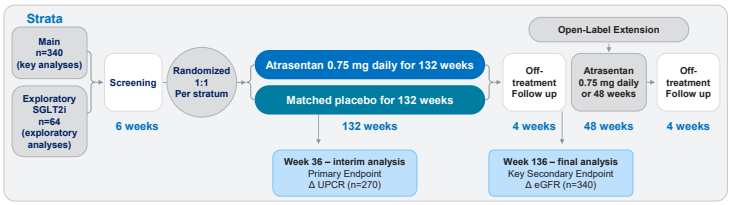
- **Key inclusion criteria**: men and women aged ≥18 years, with biopsy-proven IgAN receiving maximally tolerated and optimized dose of a RAS inhibitor (stable for at least 12 weeks before screening) with total urine protein ≥1 g/day and eGFR of at least 30 mL/min/1.73 m^2. *Exploratory SGLT2i stratum only*: on a stable dose of an SGLT2i plus maximally tolerated and optimized dose of a RAS inhibitor that have been stable for at least 12 weeks prior to screening
- **Key exclusion criteria**: concurrent diagnosis of another cause of chronic kidney disease; clinical suspicion of rapidly progressive glomerulonephritis or Henoch-Schonlein Purpura (IgA vasculitis); clinical diagnosis of nephrotic syndrome; brain natriuretic peptide of >200 pg/mL at screening; hemoglobin below 9 g/dL at screening or prior history of blood transfusion for anemia within 3 months of screening; or history of organ transplantation (apart from corneal transplant); received any investigational agent/approved IgAN treatment (other than a RAS inhibitor) including SGLT2i (except for subjects in the exploratory SGLT2i stratum) within 1 month (or 5 half-lives, whichever is longer) before screening
- **Primary endpoint**: change in proteinuria (urine protein–creatinine ratio [UPCR] based on 24-hour urine collection) from baseline to Week 36 in the main stratum
- **Key secondary endpoint**: change from baseline to Week 136 in eGFR in the main stratum
- **Safety endpoints**: type, incidence, severity, seriousness, and relatedness of treatment-emergent adverse events and incidence, severity, seriousness, and relatedness of adverse events of special interest

RESULTS

Patients

- Patients were enrolled at 133 clinical practice sites across 20 countries worldwide
- 340 patients with biopsy-proven IgAN were randomized to receive 0.75 mg atrasentan or placebo daily orally for 132 weeks (main stratum; **Figure 1**)
- 64 patients receiving a stable dose of SGLT2i were enrolled to an exploratory SGLT2i stratum
- Patients that were randomized and received at least one dose of the assigned treatment are reported here (n=339)

Figure 1



Baseline demographics

Main stratum

- Mean age (SD): 44.7 (12.0) years
- Sex distribution: 143 (42.2%) women; 196 (57.8%) men
- Race: 54.9% Asian; 35.4% white; 1.5% black/African American; 1.5% American Indian/Alaska Native
- Recruitment locations: Asia (45.4%); Latin America/Caribbean (20.6%); North America (15.6%); Europe (12.1%); Oceania (6.2%)

Exploratory SGLT2i stratum

- Participants randomized to this exploratory stratum generally had similar characteristics to those in the main stratum
- Patients in this stratum were slightly older, with more white than Asian people, and were more likely to be recruited in Europe/North America

Table 1. Baseline demographic characteristics (main stratum and exploratory SGLT2i stratum)

Demographic	Total main stratum final analysis (n=339[2])	Total SGLT2i stratum (n=64)
Age, years, mean (SD)	44.7 (12.0)	47.2 (12.0)
Sex, n (%)		
Male	196 (57.8)	38 (59.4)
Female	143 (42.2)	26 (40.6)
Ethnicity, n (%)		
Hispanic or Latino	75 (22.1)	6 (9.4)
Not Hispanic or Latino	255 (75.2)	55 (85.9)
Not Reported	9 (2.7)	3 (4.7)
Race, n (%)		
American Indian/Alaska Native	5 (1.5)	0
Asian	186 (54.9)	26 (40.6)
Black or African American	5 (1.5)	1 (1.6)
Native Hawaiian/Other Pacific Islander	0	0
White	120 (35.4)	34 (53.1)
Not Reported	4 (1.2)	3 (4.7)
Other[1]	19 (5.6)	0
Geographic Region, n (%)		
Asia	154 (45.4)	16 (25.0)
Europe	41 (12.1)	21 (32.8)
North America	53 (15.6)	21 (32.8)
Latin America and the Caribbean	70 (20.6)	2 (3.1)
Oceania	21 (6.2)	4 (6.3)

[1]Includes patients with multiple races reported
[2]One randomized participant did not start study medication and was withdrawn

Patient characteristics

Main stratum

- Mean duration of IgAN (SD): 5.5 (5.9) years
- Baseline UPCR:
  - Median UPCR g/g (interquartile range): 1.4 (1.1, 2.0)
  - UPCR <1500 mg/g: 54%; UPCR ≥1500 mg/g: 46%
- Baseline eGFR, mean (SD):
  - eGFR: 58.7 (23.8) mL/min/1.73 m^2
- eGFR category, n (%):
  - eGFR ≤45 mL/min/1.73 m^2: 132 (38.9%)
  - eGFR >45 and <60 mL/min/1.73 m^2: 71 (20.9%)
  - eGFR >60 mL/min/1.73 m^2: 136 (40.1%)
- RAS inhibitor use at baseline:
  - 100 (29.5%) patients were on an ACEi
  - 236 (69.6%) were on an ARB
- 8 (2.4%) patients were taking SGLT2i

Exploratory SGLT2i stratum

- Baseline characteristics were broadly similar to the main stratum
- Exception of a slightly lower mean (SD) eGFR: 53.0 (22.2) mL/min/1.73 m^2

Table 2. Baseline clinical characteristics (main stratum and exploratory SGLT2i stratum)

Characteristic	Total main stratum (n=339)[1]	Total SGLT2i stratum (n=64)
BMI, kg/m^2	27.3 (6.0)	28.2 (7.1)
Duration of disease, years	5.5 (5.9)	5.7 (5.5)
Blood pressure		
SBP, mmHg Mean (SD)	124.1 (12.7)	125.8 (12.9)
DBP, mmHg Mean (SD)	79.2 (9.2)	81.2 (9.7)
24-hr UPCR, g/g Median (Q1, Q3)	1.4 (1.1, 2.0)	1.4 (1.0, 2.0)
Baseline 24-hr UPCR category, n (%)		
< 1500 mg/g	183 (54.0)	37 (57.8)
≥ 1500 mg/g	156 (46.0)	27 (42.2)
eGFR, mL/min/1.73 m^2		
Mean (SD)	58.7 (23.8)	53.0 (22.2)
Median (Q1, Q3)	52.5 (39.0, 74.0)	45.0 (35.0, 68.5)
eGFR category, n (%)		
≤ 45 mL/min/1.73 m^2	132 (38.9)	33 (51.6)
> 45 and ≤ 60 mL/min/1.73 m^2	71 (20.9)	9 (14.1)
> 60 mL/min/1.73 m^2	136 (40.1)	22 (34.4)
Hemoglobin, g/dL, mean (SD)	13.7 (1.7)	14.4 (1.6)
RAS inhibitor usage at baseline, n (%)		
None[2]	3 (0.9)	0
ACE inhibitor use only	100 (29.5)	19 (29.7)
ARB use only	236 (69.6)	44 (68.8)
Both ACE inhibitor and ARB use	0	1 (1.6)
RAS inhibitor tolerance, n (%)		
Tolerant	336 (99.1)	64 (100)
Intolerant	3 (0.9)	0
Baseline SGLT2i medication n (%)		
Any baseline SGLT2i medication	8 (2.4)	60 (93.8)
Dapagliflozin	7 (2.1)	54 (84.4)
Empagliflozin	1 (0.3)	4 (6.3)
Canagliflozin	0	2 (3.1)

[1]One randomized participant did not start study medication and was withdrawn. [2]Per protocol, patients who were intolerant to RAS inhibitors were eligible; however, the total percentage could not exceed ~5% of total population randomized in the main stratum. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure; SD: standard deviation; SGLT2i: sodium-glucose co-transporter 2 inhibitor; UPCR: urine protein–creatinine ratio

CONCLUSIONS

- ALIGN has enrolled a globally representative range of patients with IgAN
  - Most patients were recruited in Asia, where the prevalence of IgAN is higher than in the rest of the world
  - Women are well represented in the trial with a participation rate of >40%
- Baseline characteristics in the exploratory SGLT2i stratum are broadly similar to the main stratum
  - Importantly, the median UPCR is the same as the main stratum
- ALIGN will explore the potential benefits and risks of adding the endothelin A receptor antagonist, atrasentan, to evidence-based therapy including RAS inhibition, in patients with IgAN and severe proteinuria who are at high risk of kidney failure

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