Atacicept Reduces Serum Gd-IgA1 by Quartiles in IgAN Patients

Jonathan Barratt[1], James A. Tumlin[2], Celia J.F. Lin[3], Yusuke Suzuki[4], Marshall W. Fordyce[3], Gerald B. Appel[5]

Institutions:
1. University of Leicester, Leicester, Leicestershire, United Kingdom.
2. Emory University, Atlanta, GA, United States.
3. Vera Therapeutics, Inc., South San Francisco, CA, United States.
4. Juntendo Daigaku, Bunkyo-ku, Tokyo, Japan.
5. Columbia University Irving Medical Center, New York, NY, United States.

Disclosures

- Jonathan Barratt: Received consultancy payments and research funding from Vera Therapeutics
- James A. Tumlin: Received consultancy payments and research funding from Vera Therapeutics
- Celia J.F. Lin: Employee of Vera Therapeutics
- Yusuke Suzuki: Received consultancy payments and research funding from Vera Therapeutics
- Marshall W. Fordyce: Employee of Vera Therapeutics
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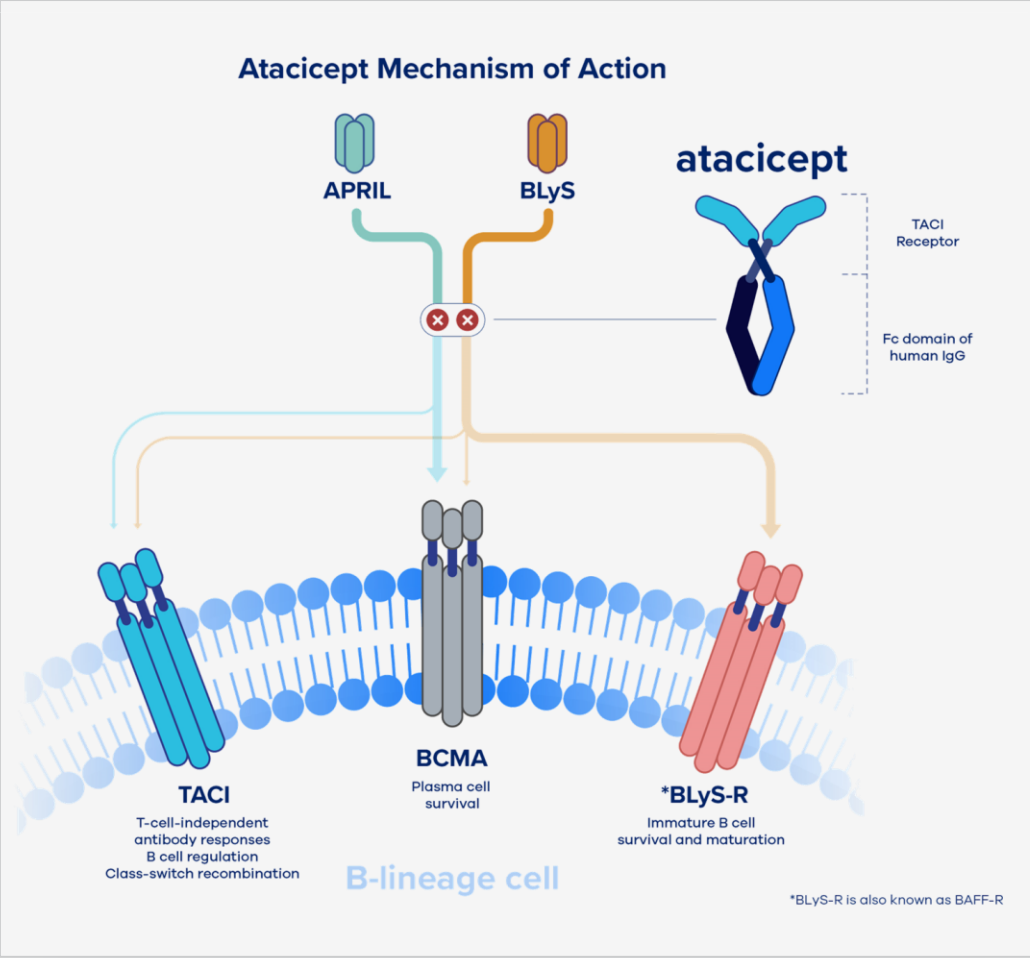
Atacicept is a Dual Inhibitor (BLyS and APRIL) of Plasma Cells and B Cells

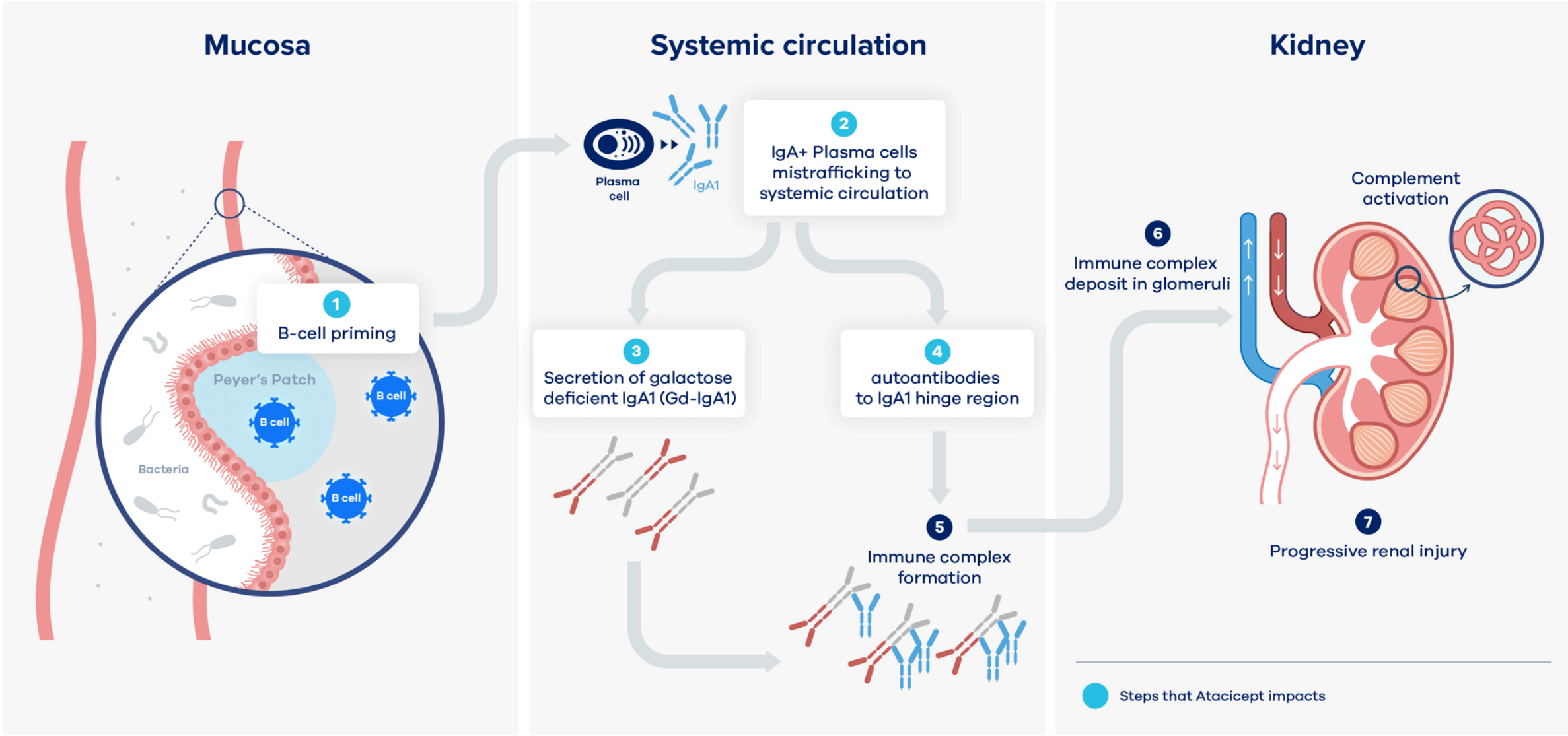


Key Considerations

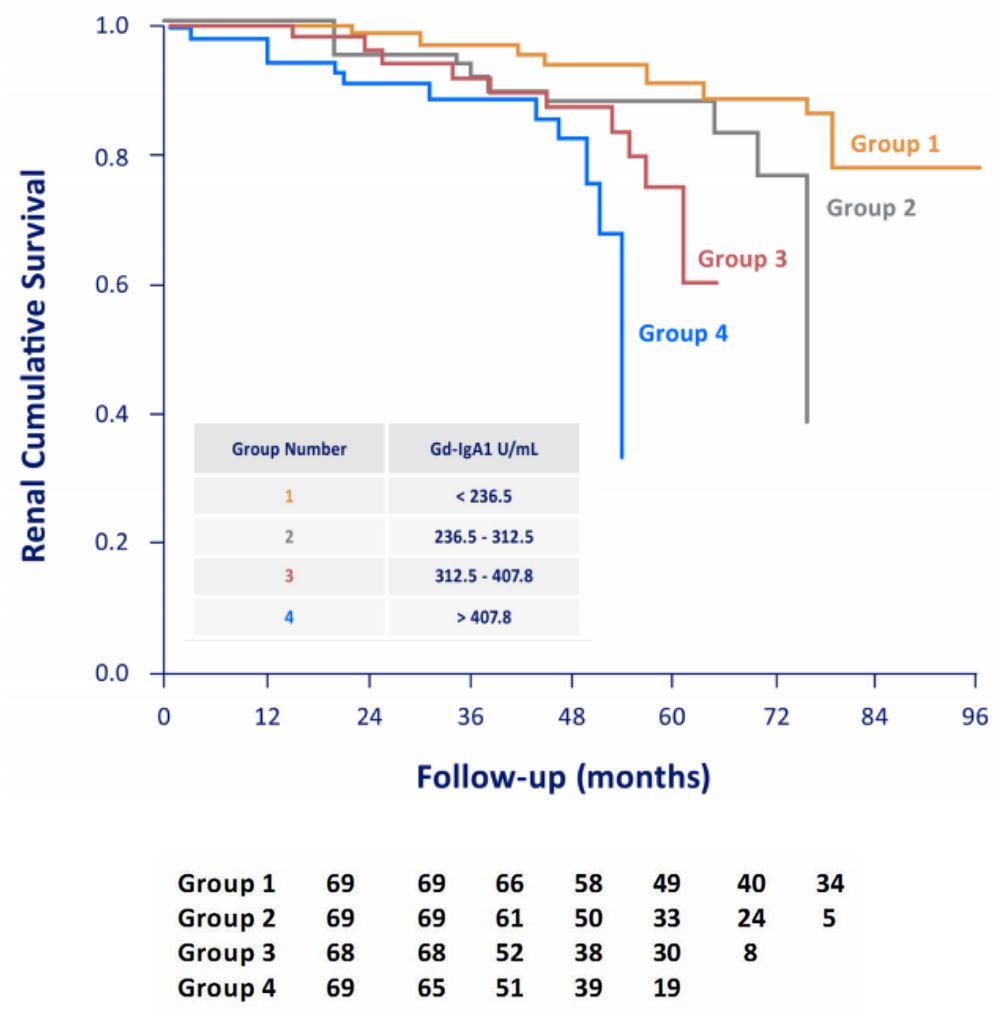
- Fully humanized fusion protein, subcutaneously administered weekly
- Dual blockade by TACI-Ig shown to be more potent than blocking BLyS alone or APRIL alone[1] and has benefit of targeting long-lived plasma cells[2], in addition to B cells, thus reducing autoantibody production[3]

1Haselmayer P et al. Eur J Immunol 2017;00:1–11. 2Hiepe F et al. Nat Rev Rheumatol 2011;3:170-178. 3Gordon et al. 2017 Arthritis & Rheumatology 69(1): 122-130.

Galactose-deficient IgA1 (Gd-IgA1) Plays a Central Role in IgAN Pathogenesis



Renal Survival Deteriorated by the Quartile of Serum Gd-IgA Level



Risks of composite end-point natural Log-transformed Gd-IgA1 and ascending quartiles

	Gd-IgA1,median (Range), U/ml	Hazard Ration (95% Confidence Interval) & p value			
		Unadjusted	Model 1 [a]	Model 2 [b]	Model 3 [c]
Composite endpoint					
Per 1SD lnGd-IgA1	312.5 (89.0–1442.0)	2.07 (1.53–2.78) 1.68×10^{-6}	1.51 (1.16–1.97) 0.002	1.50 (1.15–1.96) 0.003	1.44 (1.11–1.88) 0.006
Gd-IgA1 quartiles					
1	193.88 (89.0–237.0)	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
2	272.51 (239.0–312.0)	2.63 (0.94–7.36) 0.066	2.71 (0.99–7.39) 0.052	2.73 (0.99–7.45) 0.051	2.47 (0.91–6.72) 0.077
3	345.67 (313.0–406.0)	4.03(1.36–11.96) 0.012	3.74 (1.28–10.93) 0.016	3.72 (1.27–10.89) 0.016	3.86 (1.33–11.33) 0.013
4	487.36 (408.0–1442.0)	6.76 (2.23–20.19) 0.001	5.18 (1.75–15.34) 0.003	5.29 (1.78–15.73) 0.003	4.76 (1.61–14.09) 0.005

Composite endpoint was defined as 50% decline of eGFR(n=29), ESRD(n=3) or death(n=2). The 2 deaths also had 50% decline of eGFR.

Abbreviation: LnGd-IgA1, Natural Log-transformed galactose-deficient IgA1. Unadjusted Model analyzed Gd-IgA1 as continuous data.

[a] Model 1 adjusted for eGFR, proteinuria and hypertension (yes or no). Hypertension (yes or no) was analyzed as dichotomous data.

[b] Model 2 adjusted for covariates in model 1 plus histological grading (mild and severe lesion group).The latter variable was analyzed as categorical data.

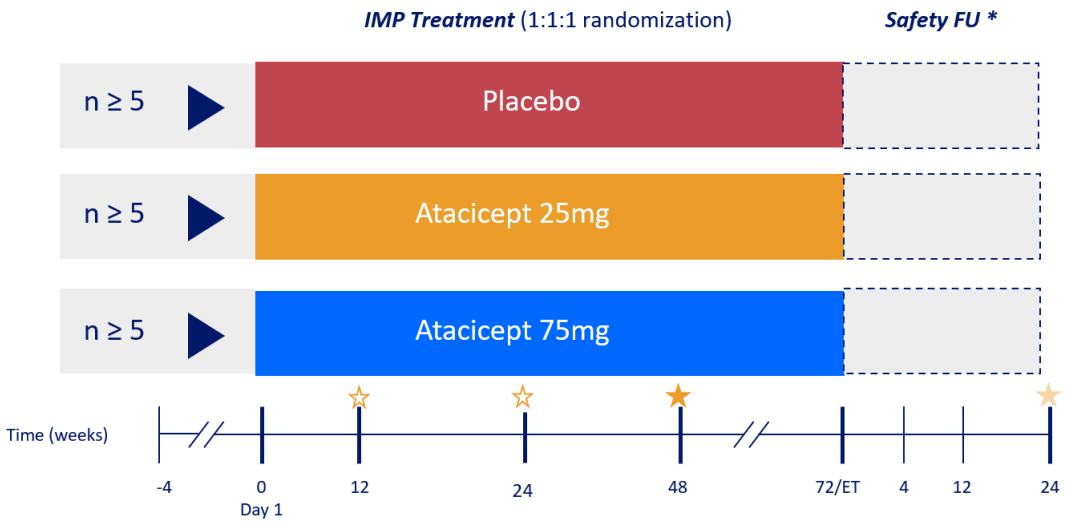
[c] Model 3 adjusted for covariates in model 2 plus steroid use (yes or no). The latter variable was analyzed as dichotomous data.

Renal deterioration composite endpoint:
50% decline in eGFR, ESRD, or death

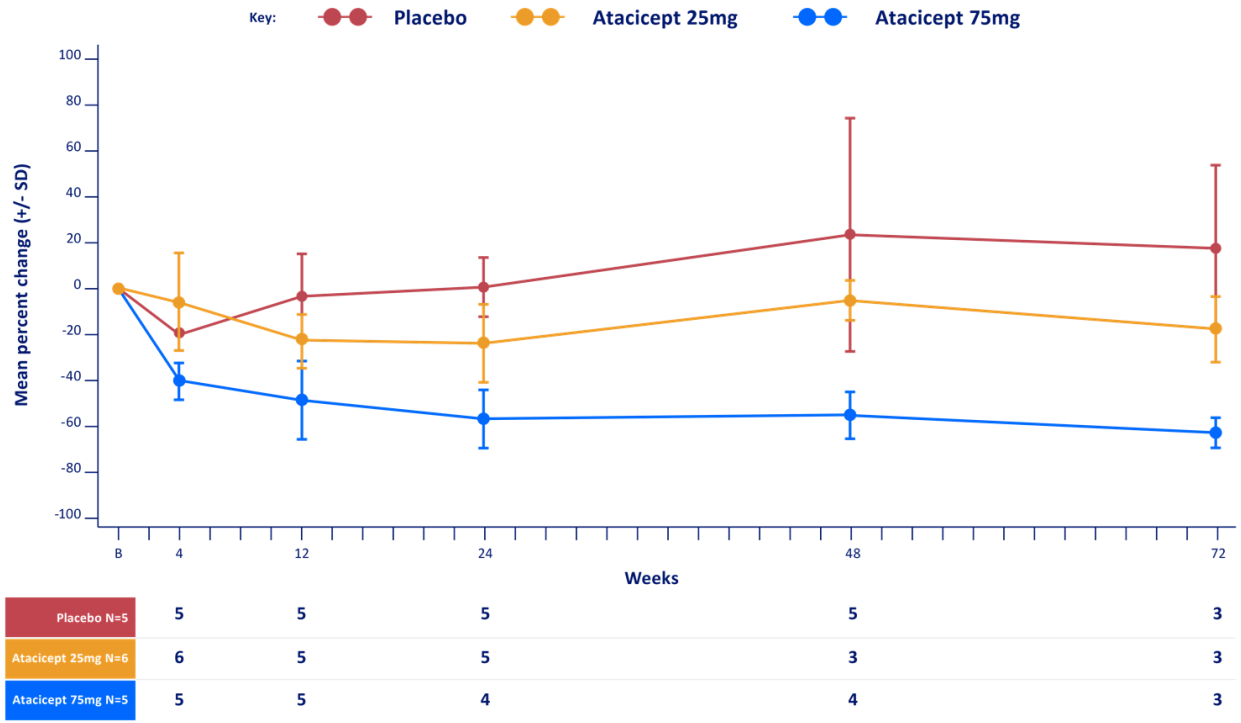
Zhao N et al. Kidney Int 2012;82(7):790-6

The Ph2a JANUS trial was the first to show substantial Gd-IgA1 reduction with atacicept in IgAN patients

Ph2a JANUS Study Design



Dose-dependent reductions in Gd-IgA1 were observed for up to 72 wks with atacicept



Methods

In the JANUS study, serum Gd-IgA1 was assessed at baseline (BL), wks 4, 12, 24, 48, and 72

At BL, pts were divided into 4 equal groups according to the quartiles of serum Gd-IgA1 distribution and quartile level was assessed at each timepoint

A separate cohort of ~150 IgAN pts from the Univ of Leicester was used as a reference population for quartile determination

Atacicept 75 mg decreased serum Gd-IgA1 levels by up to two quartiles

Gd-IgA1 level (ng/ml)	Quartile
< 3.13	1ST
3.13-5.01	2ND
5.01-7.75	3RD
> 7.75	4TH

Quartiles determined by JANUS population

SUBJECT	ALLOCATION	Baseline	WEEK 4	WEEK 12	WEEK 24	WEEK 48	WEEK 72
1	Placebo	4TH	4TH	4TH	4TH	4TH	4TH
2	Placebo	4TH	3RD	4TH	4TH	4TH	4TH
3	Placebo	2ND	2ND	2ND	2ND	3RD	3RD
4	Placebo	2ND	1ST	2ND	2ND	2ND	
5	Placebo	4TH	3RD	4TH	4TH	4TH	
6	Atacicept 25mg	4TH	4TH	3RD	3RD	3RD	3RD
7	Atacicept 25mg	3RD	3RD	3RD	3RD	3RD	3RD
8	Atacicept 25mg	4TH	3RD	3RD	3RD		
9	Atacicept 25mg	2ND	2ND				
10	Atacicept 25mg	1ST	1ST	1ST	1ST		
11	Atacicept 25mg	2ND	2ND	1ST	2ND	2ND	2ND
12	Atacicept 75mg	3RD	1ST	1ST	2ND	1ST	
13	Atacicept 75mg	4TH	3RD	2ND	1ST	2ND	2ND
14	Atacicept 75mg	1ST	1ST	1ST	1ST	1ST	1ST
15	Atacicept 75mg	2ND	1ST	1ST		1ST	1ST
16	Atacicept 75mg	4TH	3RD	3RD	2ND		

After 24 Weeks, all subjects receiving atacicept 75mg had reductions in serum Gd-IgA1 to the lowest risk quartiles

Results generally consistent when using quartiles determined by the larger reference Univ of Leicester population

Gd-IgA1 level (ng/ml)	Quartile
< 5.26	1ST
5.26-8.13	2ND
8.14-11.67	3RD
> 11.67	4TH

Quartiles determined by Univ or Leicester population

SUBJECT	ALLOCATION	Baseline	WEEK 4	WEEK 12	WEEK 24	WEEK 48	WEEK 72
1	Placebo	4TH	3RD	3RD	4TH	3RD	3RD
2	Placebo	3RD	3RD	3RD	3RD	3RD	3RD
3	Placebo	1ST	1ST	1ST	1ST	2ND	2ND
4	Placebo	1ST	1ST	1ST	1ST	1ST	
5	Placebo	2ND	2ND	3RD	3RD	4TH	
6	Atacicept 25mg	3RD	3RD	2ND	2ND	2ND	2ND
7	Atacicept 25mg	2ND	2ND	2ND	2ND	2ND	1ST
8	Atacicept 25mg	3RD	2ND	2ND	2ND		
9	Atacicept 25mg	1ST	1ST				
10	Atacicept 25mg	1ST	1ST	1ST	1ST		
11	Atacicept 25mg	1ST	1ST	1ST	1ST	1ST	1ST
12	Atacicept 75mg	2ND	1ST	1ST	1ST	1ST	
13	Atacicept 75mg	3RD	2ND	1ST	1ST	1ST	1ST
14	Atacicept 75mg	1ST	1ST	1ST	1ST	1ST	1ST
15	Atacicept 75mg	1ST	1ST	1ST		1ST	1ST
16	Atacicept 75mg	3RD	2ND	2ND	1ST		

After 24 Weeks, all subjects receiving atacicept 75mg had reductions in serum Gd-IgA1 to the lowest risk quartile

Conclusion

In this randomized, placebo controlled trial in IgAN patients, atacicept, administered subcutaneously once weekly, demonstrated a substantial reduction in serum Gd-IgA1 in a dose dependent manner that was durable through 72 weeks.

The largest effect was seen in the atacicept 75mg arm, where after 24 weeks all subjects had reductions in serum Gd-IgA1 to the lowest quartiles, which is associated with the most favorable renal survival.

These results represent the first randomized controlled trial evidence for normalization of Gd-IgA1 with an investigational therapeutic for IgAN patients.

The ongoing Ph2b ORIGIN trial evaluating up to atacicept 150 mg in IgAN patients will help determine how these robust reductions in Gd-IgA1 translate to measures of renal function, including proteinuria and GFR.

Back-up

Demographics and Baseline Characteristics of JANUS and Univ of Leicester Populations

	JANUS (n=16)	Univ of Leicester (n=150)
Age, mean±SD	43 ±11	39 ±7
Male	50.0%	65%
Caucasian	69%	94%
Asian	19%	4%
Other	13%	2%
eGFR (mL/min/1.73 m^2), mean±SD	60 ±20.6	62 ±5.7
UPCR by 24 hr urine, mean±SD	1.7 ±0.8	1.4 ±0.6
History of systemic corticosteroids	25%	6%
Patients on ACEi and/or ARB	100%	100%