EVER001 Phase 1b/2a pMN Trial Interim Analysis

December 2024

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Today's Speakers

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Chief Business Officer

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Chief Scientific Officer

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Chief Medical Officer

Everest Medicines' Strategic Focus on Renal Diseases

Indication	IgA Nephropathy (IgAN)	Primary Membranous Nephropathy (pMN)	Minimal Change Disease (MCD)	Focal Segmental Glomerulosclerosis (FSGS)	Lupus Nephritis (LN)
Prevalence in China	4-5M	~2M	1-2M	500K-1M	400-600K
Prevalence in US	130-150K	80-100K	20K	40K	40K
Prevalence in EU & Japan	~360K[1]	~120K	The prevalence data for EU and Japan are similar to US.		
Pipeline	Launched NEFECON® budesonide delayed release capsules		No approved therapy globally		
	EVER001				

Note: IgAN=IgA nephropathy; pMN =primary membranous nephropathy; LN=lupus nephritis; MCD=minimal change disease; FSGS=focal segmental glomerulosclerosis

Source for prevalence: KOL and company internal estimate.

1: Willey, C.J., et al. NDT (2023) Nephrology Dialysis Transplantation; Nephrology. 2024;29(Suppl. 2):65–67.

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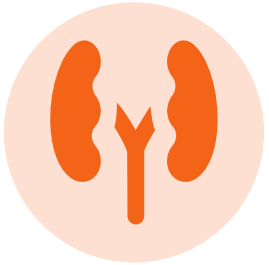
Disease Overview – Primary Membranous Nephropathy



- **Membranous nephropathy** (MN) is among the **more common nephrotic syndromes** in adults without diabetes with an idiopathic **primary form (~80% cases)** and a secondary form (~20% cases) associated with an underlying disorder (e.g. infections, drugs, cancers, etc).[1]

- **~80% patients show nephrotic syndrome**, symptoms include **high proteinuria (common range 3.5g-20g/24h), decrease in serum albumin levels causing severe swelling**
- Mean diagnosis age between 40-60

- **Half of the patients continue to have nephrotic syndrome** despite treatment
- **One-third of patients progress to end-stage renal disease (ESRD)** with current treatment options

Note:

1. Guggenheim Securities, LLC research and analysis
2. Clin J Am Soc Nephrol 12: 983–997, 2017.
3. Am J Kidney Dis 2021. 77(3):440-453

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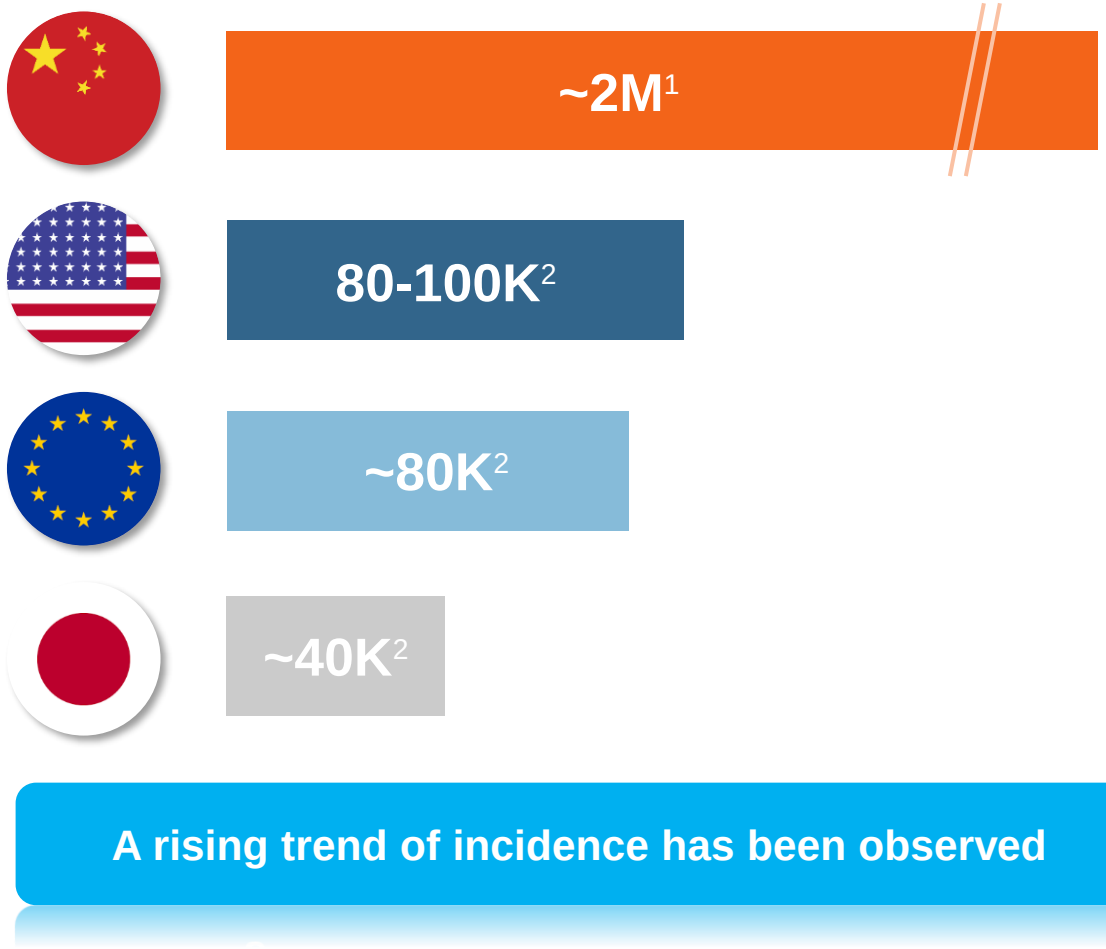
Significant Unmet Medical Needs in Primary Membranous Nephropathy Globally

Primary Membranous Nephropathy (pMN) Prevalence



Significant Unmet Medical Needs

- **No treatment** has been approved for pMN. **Current treatment options** (e.g. cyclophosphamide, calcineurin inhibitor, rituximab) **are used off label**
- **More than 30%** of patients **do not respond to current treatment options**, and around **30%** patients who achieve remission will **relapse**
- Current treatment options are associated with **substantial side effects** and there is need for safer treatment.

Note:
1. China Insights Consultancy estimates
2. Company market research

EVER001: A Potent Covalent Reversible BTK inhibitor Suitable for Autoimmune Renal Indications

Compared with covalent and irreversible BTK inhibitors, EVER001 is potentially BIC with high selectivity and high potency

1. Reversible covalency
2. Excellent selectivity
3. Potent target binding
4. Potential lower toxicity

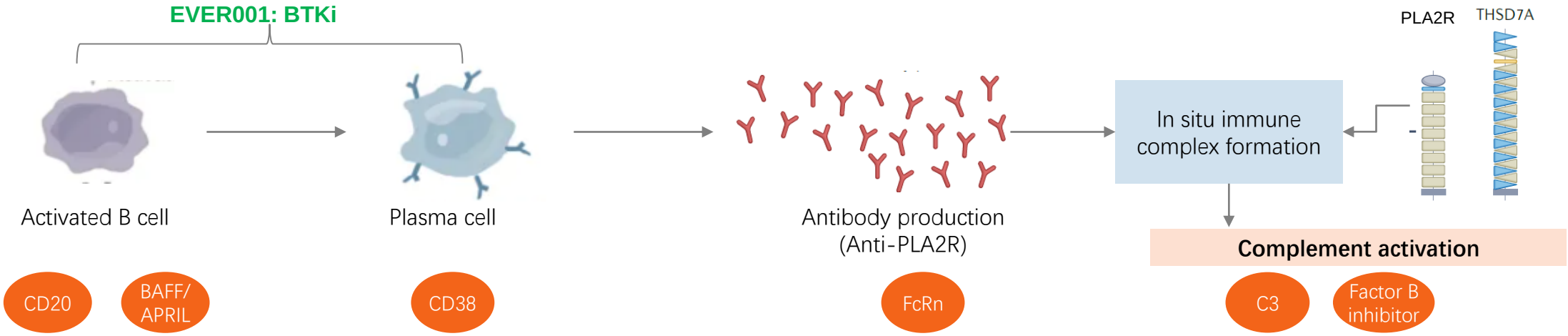
Compound	IC50 nM	Kinase IC50/BTK IC50 (fold)						
	BTK	LCK	SRC	LYN	EGFR	ITK	TEC	JAK3
EVER001	1.8	3668x	4853x	1125x	714x	5178x	6x	>10000x
Ibrutinib	1.5	4x	17x	17x	4x	3x	5x	21x

Kinase inhibition of EVER001 is highly selective over EGFR, ITK and TEC family kinases, which are thought to be associated with undesirable safety profile

BTKi	Selectivity (IC50 fold)		
	EGFR	ITK	TEC
EVER001	714x	5178x	6.6x
Ibrutinib	4x	3x	5x
Zanubrutinib	8.7x	187x	6.7x
PRN1008	400x	338x	0.6x
Acalabrutinib	>200x	>200x	18x

BTK Inhibitor Targets Multiple Key Nodes in the Pathogenesis of Membranous Nephropathy

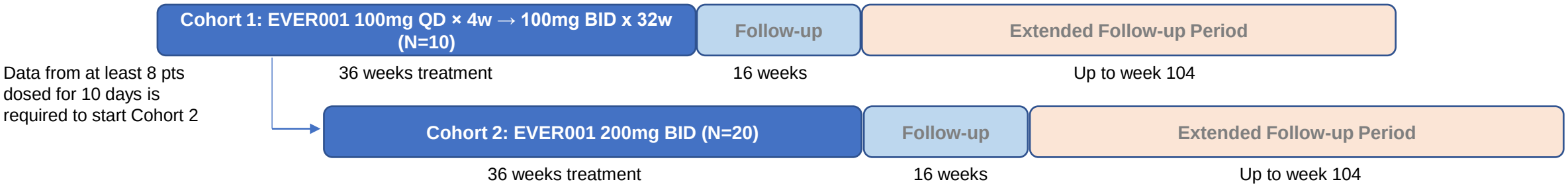
- BTK inhibitors target B-cell signaling to prevent maturation and proliferation of B cells, eventually preventing differentiation into autoantibody producing plasma cells.
- BTK inhibitors also have broad immunomodulatory effects on a variety of immune cells beyond B cells, which differs from the mechanism of B-cell depleting agents such as anti-CD20 antibodies
- Compared to anti-CD20 antibodies, the oral formulation of BTKi allows for more rapid recovery of B-cell function upon treatment withdrawal



EVER001: Phase 1b/2a Clinical Proof-of-Concept Trial Ongoing

Phase 1b/2a study in Chinese pMN patients with positive anti-PLA2R autoantibody

- Data cutoff date: Sep 13, 2024
- 31 subjects were enrolled in the study in total
- 11 subjects in Cohort 1 have completed 36 weeks of treatment. 7 subjects in Cohort 2 have completed 24 weeks of treatment



Eligible subjects were adults with biopsy proven pMN, anti-PLA2R autoantibody level > 20RU/mL and 24h, and proteinuria>3.5g/24h

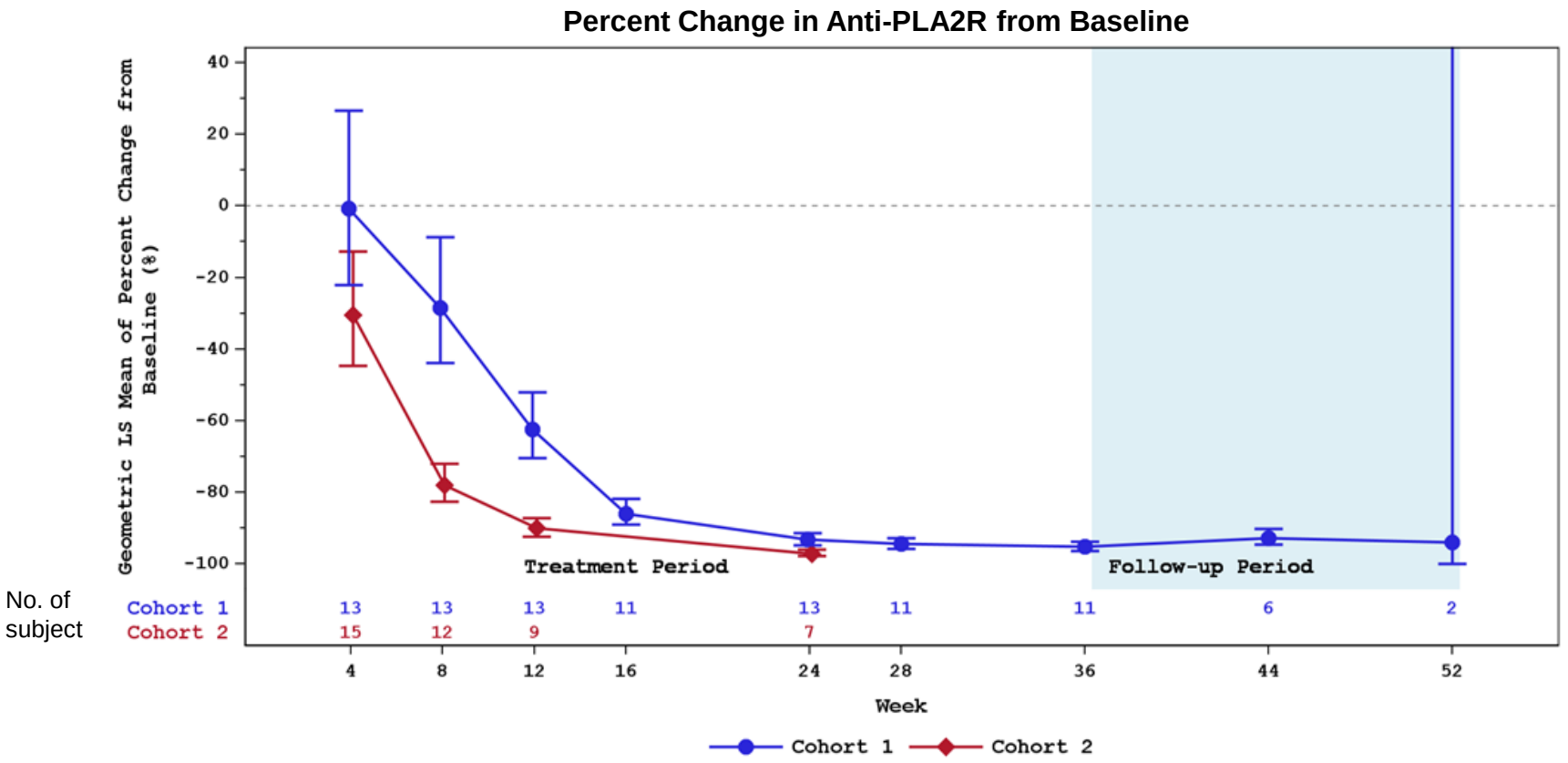
Primary endpoint

- Safety and tolerability

Secondary endpoints

- Percentage change from baseline of 24h proteinuria, anti-PLA2R autoantibody level, UPCR and eGFR
- Complete or partial remission of 24h proteinuria
- Remission of anti-PLA2R autoantibody

Close to 100% Reduction in Anti-PLA2R in Both Cohorts



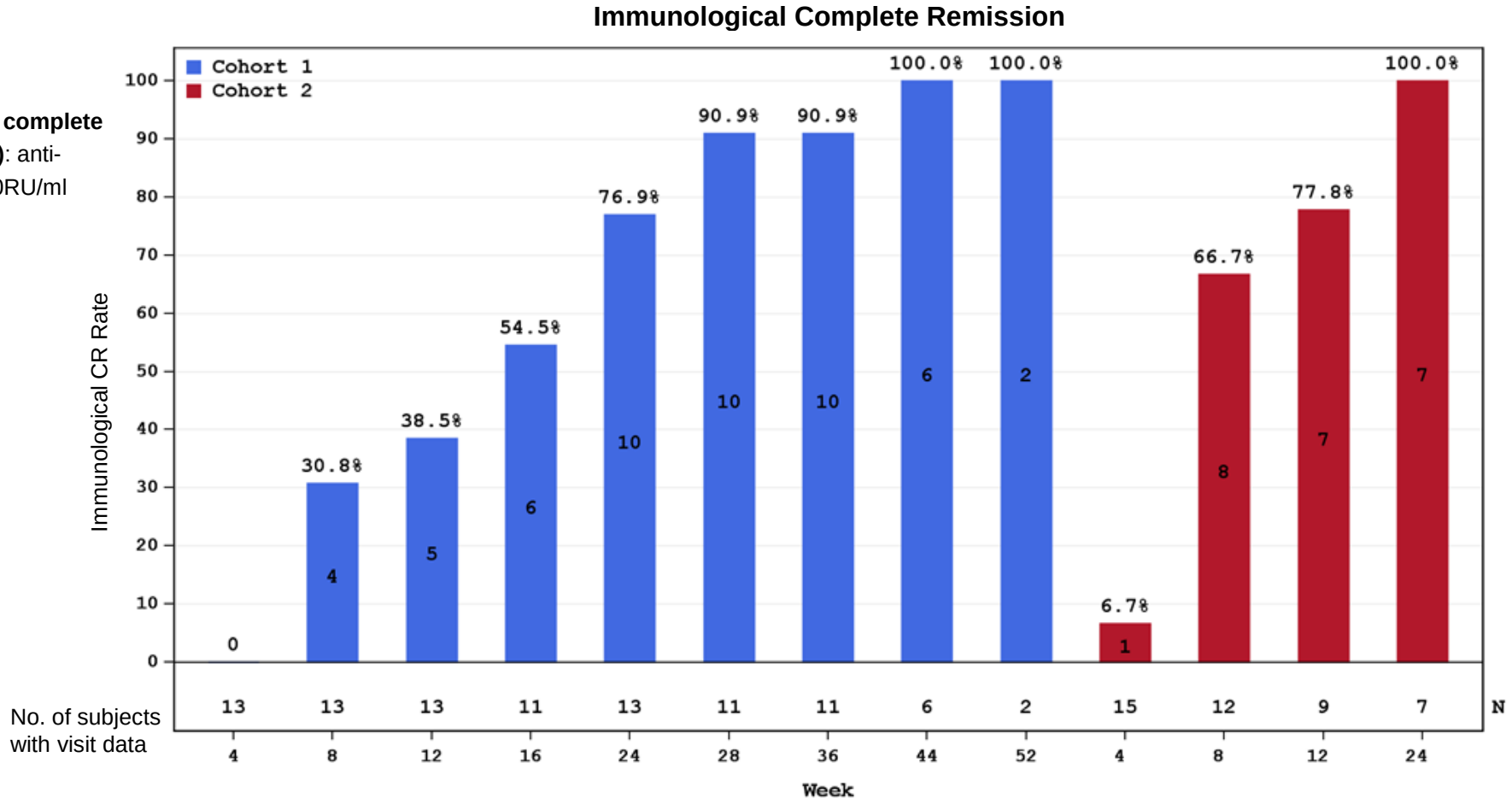
- By the cutoff date, EVER001 induced close to 100% anti-PLA2R autoantibody reduction in both cohorts. Reduced anti-PLA2R autoantibody levels were maintained up to 52 weeks during off-treatment follow up period in cohort 1.
- >90% reductions in anti-PLA2R autoantibody were observed as early as Week 24 in Cohort 1 and Week12 in Cohort 2.

Note:
1. Immunological complete remission (ICR): anti-PLA2R autoantibody titer < 20RU/ml (negative).
2. Baseline median anti-PLA2R autoantibody titer was 85.4 RU/mL

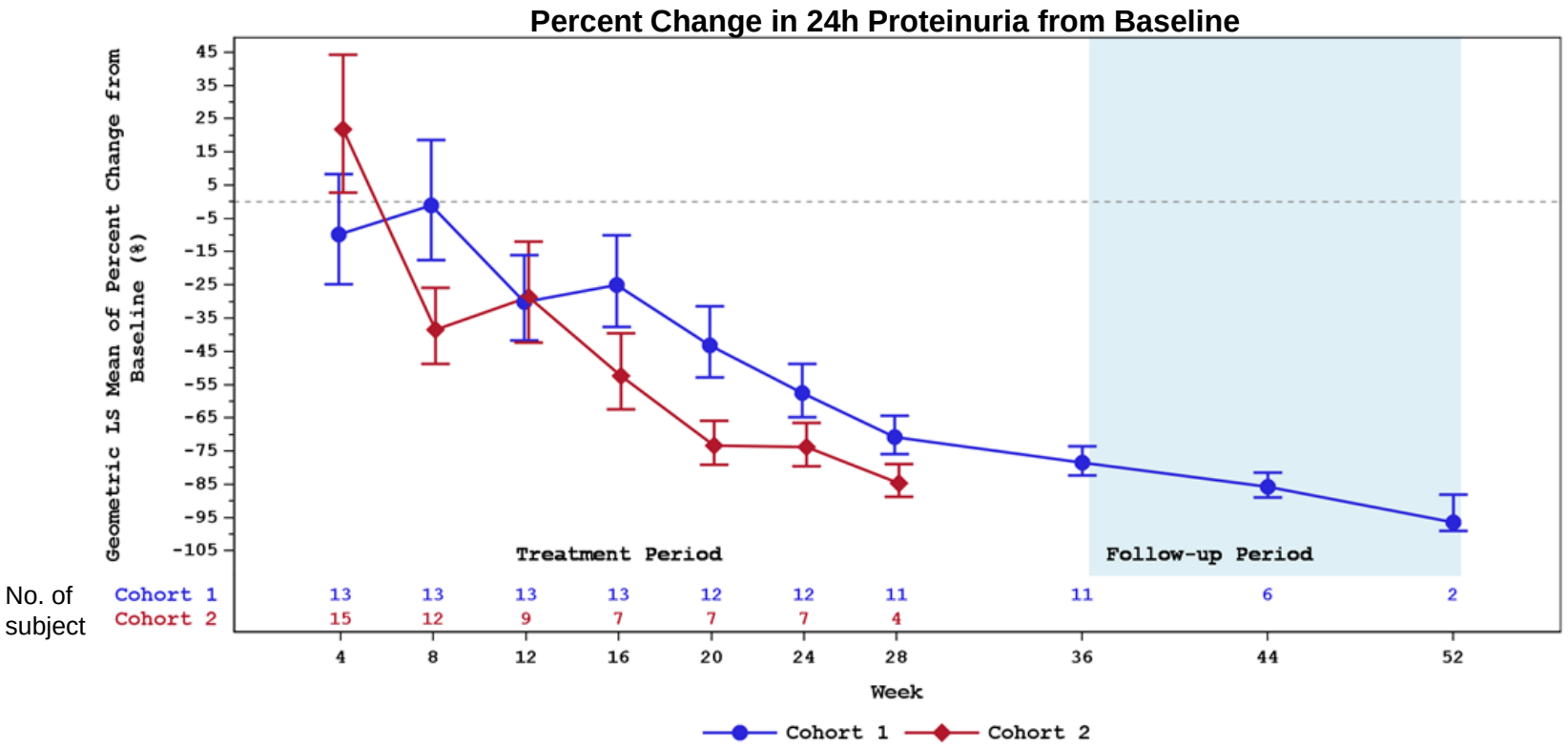
Most Subjects Experienced Immunological Complete Remission by 8-16 Weeks

- Observed immunological complete remission (ICR) rate increased with treatment in both cohorts. As early as week 4-8, ICR was observed.
- In Cohort 1, 6 of 11 (54.5%) subjects experienced ICR at week 16, and as high as 90.9% (10/11) of subjects achieved ICR at week 28
- In Cohort 2, 8 of 12 (66.7%) subjects experienced ICR at week 8, and all the subjects (7/7) reached ICR at week 24

Immunological complete remission (ICR): anti-PLA2R titer < 20RU/ml (negative).



Substantial Reduction in Proteinuria During Treatment Period , which Continued to Decline During Off-treatment Period Up To 52 weeks



- 24h proteinuria decreased during the treatment period in both cohorts with further reductions up to 52 weeks during off-treatment follow up period in cohort 1.
- >50% reduction was seen as early as week 16 in cohort 2
- Reduction in proteinuria from baseline were 78.3% in cohort 1 at week 36 and 73.8% in cohort 2 at week 24

Note:

24h proteinuria complete remission: 24h proteinuria < 0.3g/24 h;

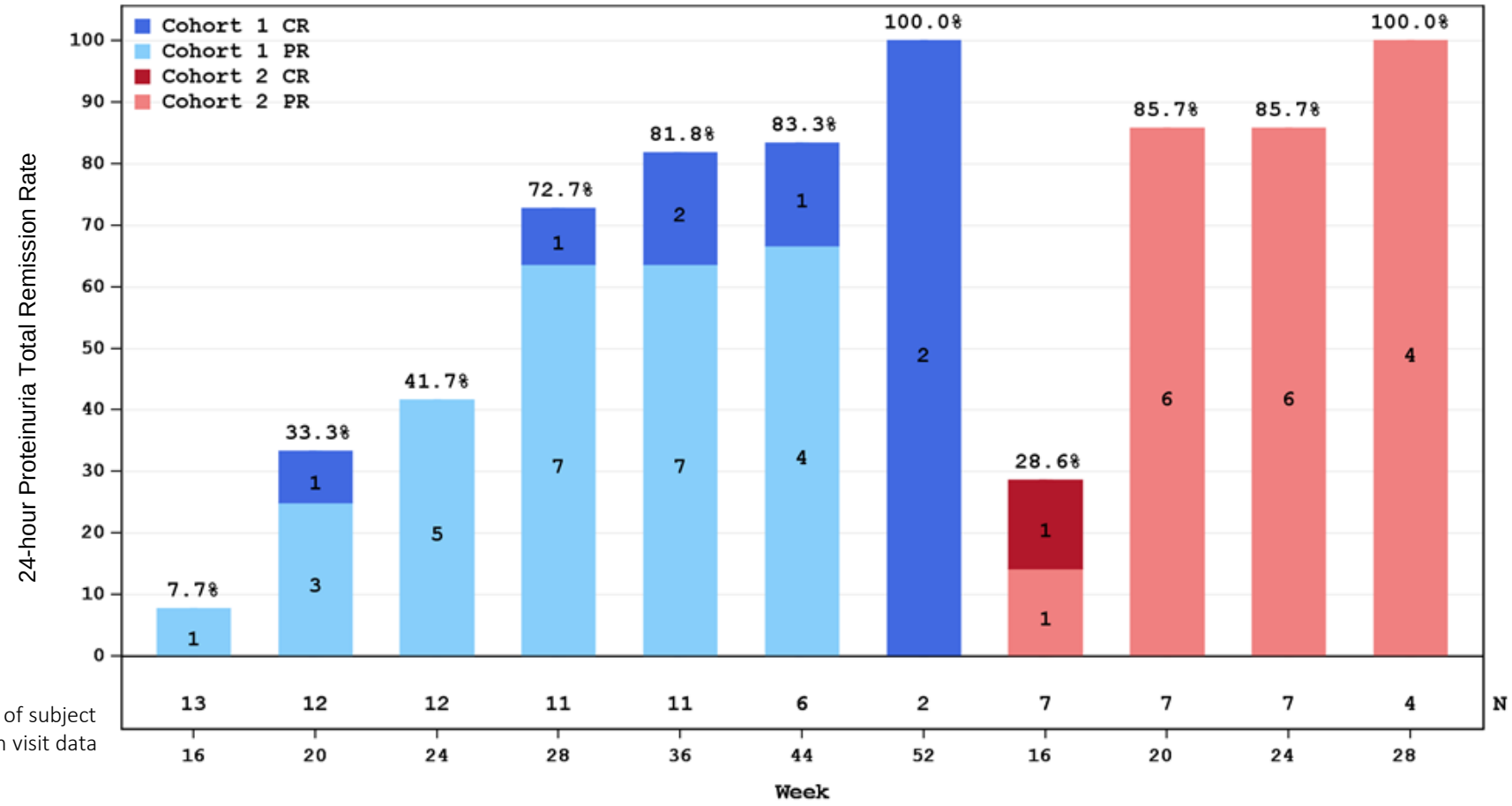
24h proteinuria partial remission: 24h proteinuria < 3.5g/24h, but ≥0.3g/24 h, and reduction > 50%, regardless of eGFR or the serum albumin level from baseline.

1. Baseline median anti-PLA2R antibody titer was 85.4 RU/mL

Proteinuria Remission Achieved in Most Subjects Within 24~28 weeks

- In Cohort 1, 72.7% of subjects experienced proteinuria remission at week 28 with 1 subject (9.1%) achieved complete remission (CR); then 81.8% of subjects experienced proteinuria remission at week 36 with 2 subjects (18.2%) achieved CR. The median time to proteinuria remission was 19.7 weeks
- In Cohort 2, as early as week 20, 85.7% of subjects experienced proteinuria partial remission (PR); then all 4 subjects achieved 100% proteinuria PR at week 28. The median time to proteinuria remission was 16.1 weeks

24-hour Proteinuria Total Remission (CR and PR)



No. of subject with visit data

24h proteinuria complete remission (CR): 24h proteinuria < 0.3g/24 h;
24h proteinuria partial remission (PR): 24h proteinuria < 3.5g/24h, but ≥0.3g/24 h, and reduction > 50%, regardless of eGFR or the serum albumin level from baseline.

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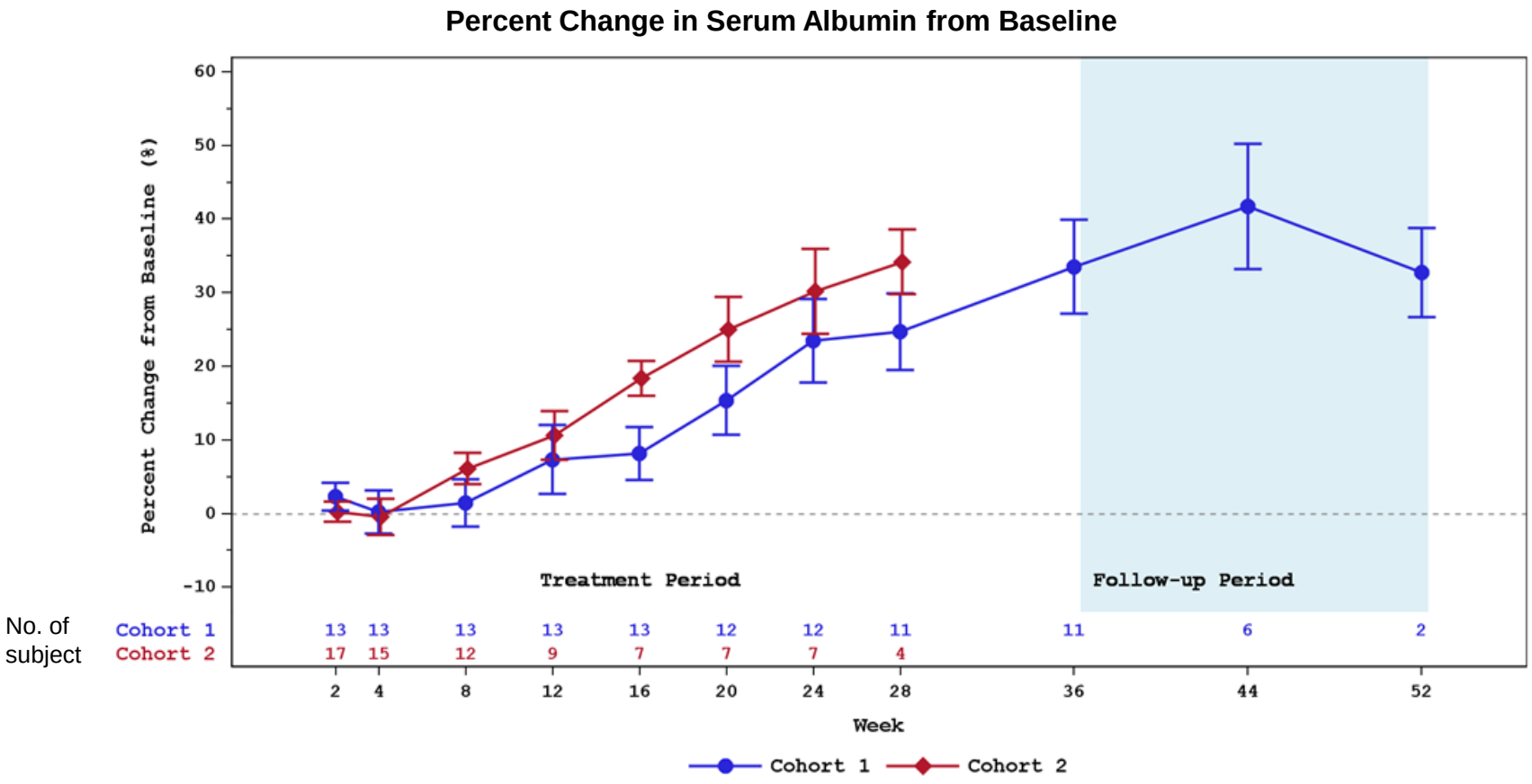
Serum Albumin Increased to Normal or Near Normal Range



- With reduction of 24h proteinuria, the serum albumin increased gradually by 33.6% at week 36 and 30.2% at week 24 in cohort 1 and cohort 2, respectively.
- Serum albumin levels returned to normal or near normal range at week 36 in cohort 1 and at week 24 in cohort 2.
- At the cutoff date, eGFR was stable.

Note:
1. Baseline median serum albumin was 31.2 g/L

Highlights from Ongoing Phase 1b/2a Study

EVER001 induced early onset and high rates of immunological and clinical responses

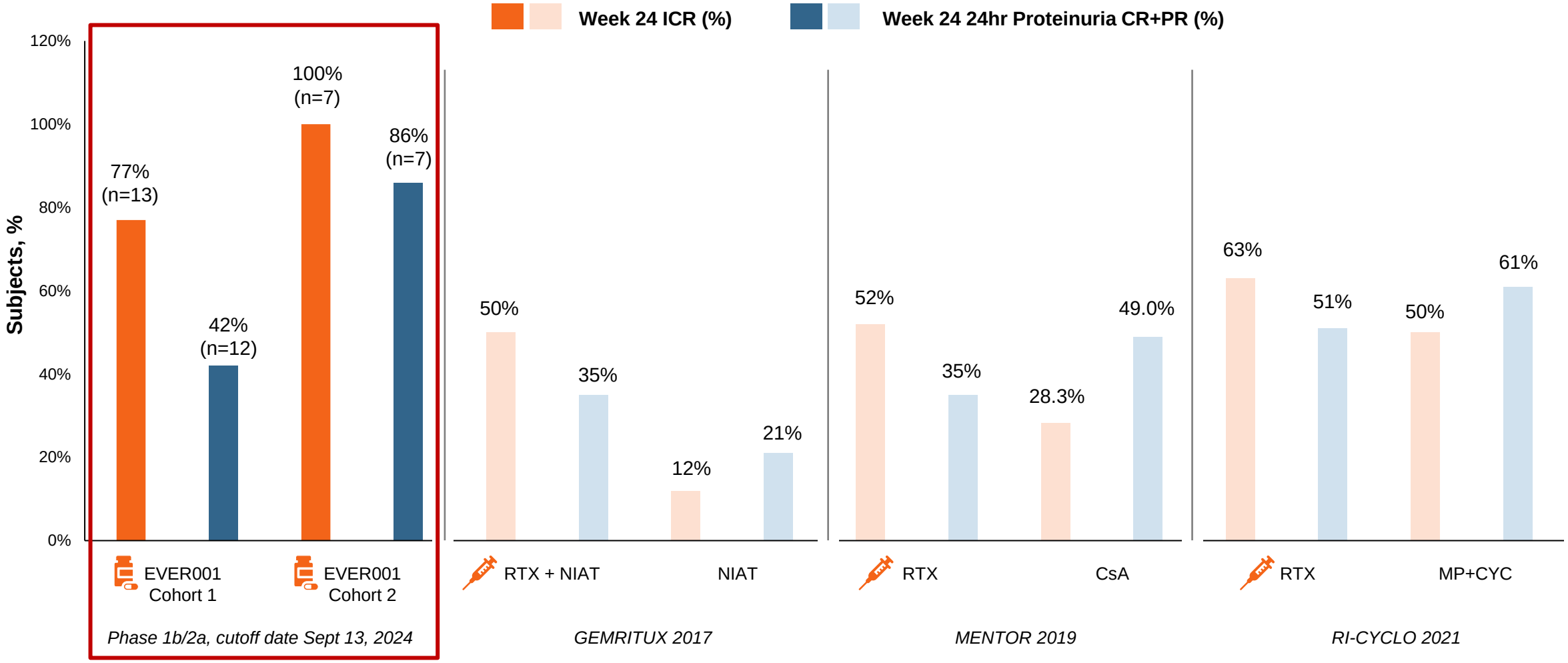
- ✓ Immunological response
  - In Cohort 1, as high as 90.9% (10/11) of the subjects achieved ICR at week 36
  - In Cohort 2, all (7/7) of the subjects reached ICR at week 24
  - Close to 100% reductions in both cohorts by the data cutoff date
- ✓ Clinical response
  - In Cohort 1, 81.8% of subjects experienced proteinuria remission at week 36
  - In Cohort 2, 85.7% of subjects experienced proteinuria remission at week 24
- ✓ Serum albumin levels returned to normal or near normal range at week 36 in cohort 1 and at week 24 in cohort 2

EVER001 treatment at both dose levels were well-tolerated and safe

- ✓ 58% of the subjects experienced treatment-related AEs. **Most were of Grade 1 or 2** and transient.
- ✓ **No clinically meaningful AEs** typically associated with BTK inhibitors, such as neutropenia, hemorrhage, cardiac arrythmia, have been observed.

Phase 1b/2a Clinical Data Comparison Versus Historical Data

Clinical Efficacy Data*



* Note: This analysis is the aggregation of results across independent studies with potential difference in baseline characteristics. There are risks inherent in conducting cross-trial comparisons.
CR: 24h proteinuria complete remission; PR: 24h proteinuria partial remission. RTX: rituximab, NIAT: nonimmunosuppressive antiproteinuric treatment, CsA: cyclosporin, MP: methylprednisolone , CYC: cyclophosphamide
Source: N Engl J Med. 2019 Jul 4;381(1):36-46. ; J Am Soc Nephrol. 2017 Jan;28(1):348-358.; J Am Soc Nephrol. 2021 Apr;32(4):972-982.

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Q&A

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