



Rapid Clinical Responses in Phase 2 Trial of HLX79 (E-602), a First-in-Class Human Sialidase-Fc Fusion Protein, Plus HLX01 (Biosimilar Rituximab) in Membranous Nephropathy

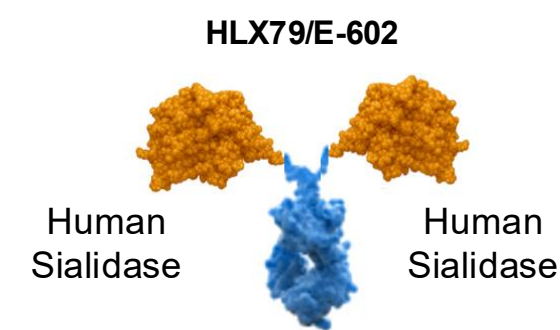
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Background

Primary membranous nephropathy (pMN) is a leading cause of nephrotic syndrome in adults; without remission, 30–40% of patients progress to kidney failure. Anti-CD20 therapy is a KDIGO-recommended first-line treatment, but clinical remission lags B cell depletion by months, and response plateaus at ~50–60% at 24 months even with the deeper depletion achieved by obinutuzumab (MENTOR, MAJESTY). The lag carries clinical cost: sustained nephrotic proteinuria drives nephron loss, and thromboembolic risk is concentrated in the first months of disease.

CD163+ macrophages persist in glomerular disease and are associated with chronic injury and fibrosis and may sustain disease after the autoimmune trigger is controlled. HLX79/E-602 (efgitasialase alfa) is a human sialidase–Fc fusion protein that removes terminal sialic acid from hypersialylated cell surfaces, disrupting sialoglycan-mediated immune functions. In a Phase 1 oncology study, E-602 reduced tissue CD163+ macrophages in 8 of 10 paired biopsies without systemic macrophage depletion, and desialylation enhances macrophage phagocytosis (ADCP) of antibody-coated B cells preclinically. We hypothesized that adding E-602 to rituximab would shorten time to response and increase response rates in pMN.



Prior Clinical Development (Phase 1)

Phase 1 Data

HLX79/ E-602 was safe and well tolerated in a phase 1 safety study (NCT05259696) in patients with advanced solid cancers, with no dose-limiting toxicity at any dose levels evaluated. A total of 69 patients were treated, and average number of doses administered was 7 (range 1 to 44 doses).

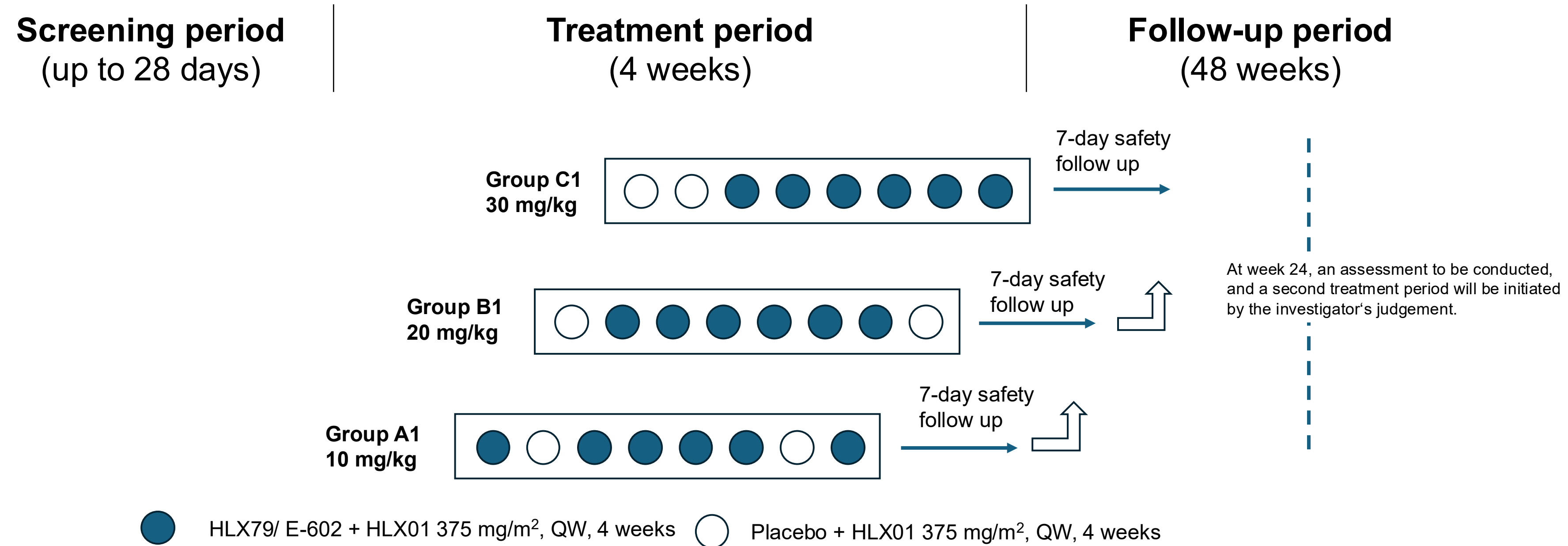
- Well-tolerated up to 30 mg/kg weekly with repeat dosing
- Therapeutically relevant levels of desialylation of B cells is achieved at 20 mg/kg and 30 mg/kg, with dose response
- Significant reduction of CD163+ macrophages in inflamed tissue demonstrated in humans at 20 mg/kg

Rationale for development in autoimmune glomerulonephritis, initially in membranous nephropathy (MN): MN is a well-characterized autoimmune kidney disease, driven by anti-PLA2R autoantibodies in ~70–80% of primary cases. B cell depletion is standard of care, but about two-thirds of patients do not achieve complete remission at 2 years (rituximab 35%, MENTOR; obinutuzumab 37%, MAJESTY). Responses take months to attain, and during that time persistent proteinuria drives fibrosis and irreversible loss of kidney function.

Phase 2A Study Design

A Randomized, Controlled, Multicenter Phase II Clinical Study to Evaluate the Efficacy, Safety, and Tolerability of HLX79/ E-602 (Human Sialidase-Fc Fusion Protein) in Combination with Rituximab Injection (HLX01, Anti-CD20 Antibody) Versus Placebo in Patients with Active Glomerulonephritis (primary membranous nephropathy and lupus nephritis). Part 2A of the study focused on primary MN. Clinical Trial ID: NCT07038382

Multiple Ascending Dose Phase 2A (n=24 planned)



Key inclusion criteria

- Male or female, 18 to 75 y.o.
- Primary MN diagnosed within 5 yrs biopsy confirmed or nephrotic syndrome and a positive anti-PLA2R
- Urine protein > 8g/24h or eGFR>60ml/ min/1.73m2 and urine protein >3.5g/24 h

Key exclusion criteria

- Secondary MN
- Malignancy
- Active, recurrent, or chronic infection
- Have received B cell depleting therapies within 1 year (eligible to participate if B cell numbers have recovered to normal range)

Phase 2A Results: Safety

Patient disposition and baseline characteristics

Characteristic	HLX79 Placebo (N=6)	10 mg/kg (N=6)	20 mg/kg (N=7)	30 mg/kg (N=7)	Total (N=26)
Age (years)					
Mean (SD)	54.8 (15.94)	53.3 (9.58)	56.1 (12.95)	55.7 (13.65)	55.1 (12.46)
Median (Q1, Q3)	58.0 (44.0, 68.0)	50.0 (45.0, 63.0)	57.0 (52.0, 66.0)	56.0 (54.0, 68.0)	56.0 (47.0, 67.0)
Sex, n (%)					
Male	4 (66.7)	5 (83.3)	5 (71.4)	3 (42.9)	17 (65.4)
Female	2 (33.3)	1 (16.7)	2 (28.6)	4 (57.1)	9 (34.6)
Anti-PLA2R antibody qualitative result, n (%)					
Positive	2 (33.3)	6 (100)	5 (71.4)	3 (42.9)	16 (61.5)
Negative	4 (66.7)	0	2 (28.6)	4 (57.1)	10 (38.5)
Anti-PLA2R antibody quantitative result (RU/mL)					
Mean (SD)	375.933 (851.7281)	76.890 (75.3341)	73.194 (73.6310)	15.781 (20.4029)	128.453 (409.1101)
Median (Q1, Q3)	8.505 (6.160, 118.310)	37.980 (27.000, 125.770)	65.290 (1.720, 153.390)	10.630 (1.720, 17.590)	25.135 (6.160, 67.900)
24-hour urine protein (g/24h)					
Mean (SD)	9.0733 (5.9745)	12.2105 (5.3904)	8.0723 (4.3690)	6.4977 (3.4359)	8.8343 (4.9805)
Median (Q1, Q3)	6.5600 (4.4500, 14.3600)	11.0065 (8.4800, 12.7200)	8.5500 (3.7950, 11.3690)	4.7300 (4.2200, 8.1000)	8.0550 (4.4500, 11.3690)
eGFR (mL/min/1.73m²)					
Mean (SD)	92.923 (33.0680)	74.583 (29.8954)	93.099 (16.2532)	91.904 (24.9403)	88.464 (25.8935)
Median (Q1, Q3)	101.500 (85.260, 111.000)	83.500 (42.300, 91.200)	94.760 (83.200, 102.460)	90.000 (85.390, 101.300)	92.600 (83.200, 102.460)
Albumin (g/L)					
Mean (SD)	26.72 (4.927)	24.82 (7.140)	28.76 (6.186)	31.59 (3.919)	28.14 (5.873)
Median (Q1, Q3)	27.10 (23.70, 31.20)	25.40 (22.00, 31.30)	30.10 (20.60, 33.10)	30.50 (27.50, 34.60)	29.65 (24.60, 31.90)
Creatinine (μmol/L)					
Mean (SD)	82.733 (35.1347)	109.280 (56.3243)	78.900 (13.0857)	75.129 (24.9279)	85.780 (35.3751)
Median (Q1, Q3)	67.400 (63.600, 86.000)	91.350 (77.000, 151.480)	74.000 (72.000, 83.300)	64.100 (60.000, 91.400)	75.500 (64.100, 91.400)
Risk stratification, n (%)					
High risk	4 (66.7)	5 (83.3)	4 (57.1)	3 (42.9)	16 (61.5)
Non-high risk	2 (33.3)	1 (16.7)	3 (42.9)	4 (57.1)	10 (38.5)

Overall TEAE summary: well-tolerated in all HLX79/E-602 treated subjects

Category	HLX79 Placebo (N=6)	10 mg/kg (N=6)	20 mg/kg (N=7)	30 mg/kg (N=7)	Total (N=26)
n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events
Any TEAEs	5 (83.3) 27	5 (83.3) 29	6 (85.7) 25	4 (57.1) 23	20 (76.9) 104
TEAEs related to any study drug	4 (66.7) 10	4 (66.7) 17	4 (57.1) 8	4 (57.1) 7	16 (61.5) 42
Related to HLX79/Placebo	3 (50.0) 9	4 (66.7) 16	4 (57.1) 8	3 (42.9) 4	14 (53.8) 37
Related to HLX01	4 (66.7) 10	4 (66.7) 15	4 (57.1) 8	4 (57.1) 6	16 (61.5) 39
CTCAE grade ≥3 TEAEs	2 (33.3) 9	0 0	0 0	1 (14.3) 1	3 (11.5) 10
CTCAE grade ≥3 TEAEs related to any study drug	1 (16.7) 1	0 0	0 0	1 (14.3) 1	2 (7.7) 2
Related to HLX79/Placebo	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Related to HLX01	1 (16.7) 1	0 0	0 0	1 (14.3) 1	2 (7.7) 2
TESAEs	2 (33.3) 2	0 0	0 0	0 0	2 (7.7) 2
TESAEs related to any study drug	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Related to HLX79/Placebo	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Related to HLX01	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
CTCAE grade ≥3 TESAEs	2 (33.3) 2	0 0	0 0	0 0	2 (7.7) 2
CTCAE grade ≥3 TESAEs related to any study drug	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Related to HLX79/Placebo	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Related to HLX01	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
AESIs	5 (83.3) 9	3 (50.0) 11	3 (42.9) 3	3 (42.9) 5	14 (53.8) 28
Infusion-related (ir) reactions	2 (33.3) 5	3 (50.0) 9	1 (14.3) 1	1 (14.3) 1	7 (26.9) 16
irAEs	1 (16.7) 1	0 0	0 0	1 (14.3) 1	2 (7.7) 2
Thromboembolism	0 0	0 0	0 0	0 0	0 0
Infection	2 (33.3) 3	2 (33.3) 2	2 (28.6) 2	3 (42.9) 4	9 (34.6) 11
AESIs related to any study drug	4 (66.7) 7	3 (50.0) 10	2 (28.6) 2	2 (28.6) 3	11 (42.3) 22
Related to HLX79/Placebo	2 (33.3) 5	2 (33.3) 8	1 (14.3) 1	1 (14.3) 1	6 (23.1) 15
Related to HLX01	3 (50.0) 6	3 (50.0) 8	2 (28.6) 2	2 (28.6) 2	10 (38.5) 18
Serious AESIs	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1

CTCAE ≥= Grade 3 summary

	HLX79 Placebo (N=6)	10 mg/kg (N=6)	20 mg/kg (N=7)	30 mg/kg (N=7)	Total (N=26)
n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events	n (%) Events
Subjects with at least one CTCAE Grade ≥= 3 TEAE	2 (33.3) 9	0 0	0 0	1 (14.3) 1	3 (11.5) 10
Blood creatinine increased	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Lymphocyte count decreased	0 0	0 0	0 0	1 (14.3) 1	1 (3.8) 1
Anemia	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Cardiac failure	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Generalized oedema	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Pneumonia	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Urinary tract infection	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Hypernatremia	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Hypokalemia	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1
Interstitial lung disease	1 (16.7) 1	0 0	0 0	0 0	1 (3.8) 1

Safety summary from prior Phase 1 study (NCT05259696)

HLX79/ E-602 was safe and well tolerated in a phase 1 safety study (NCT05259696) in patients with advanced solid cancers (n = 69 subjects). Dose escalation followed a standard 3+ 3 design, with no dose-limiting toxicity at any dose levels evaluated. Highest dose evaluated was 30mg/kg weekly, and average duration of treatment 7 weeks (range 1 to 44 weeks). Safety findings were consistent with the advanced cancer patient population, with most prevalent observation of infusion related reactions.

Study information and Contact

Study Sponsor: Shanghai Henlius Biotech. **Sponsor Contact:** Qi Jin, email: qi_jin@henlius.com.

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Lead investigator: Xueqing Yu at Guangdong Provincial People's Hospital, Guangzhou, China

Clinical Trials ID: NCT07038382

Phase 2A Results: Efficacy

Rapid clinical responses observed in high dose HLX79/E-602 group

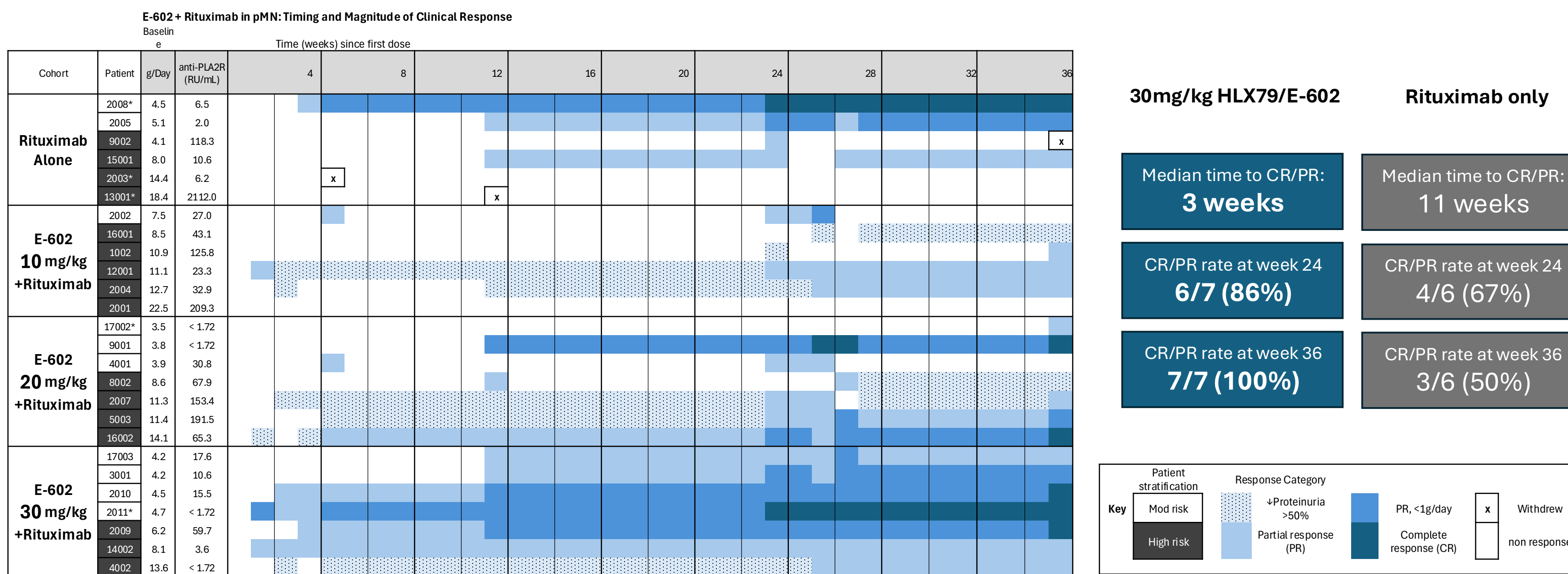
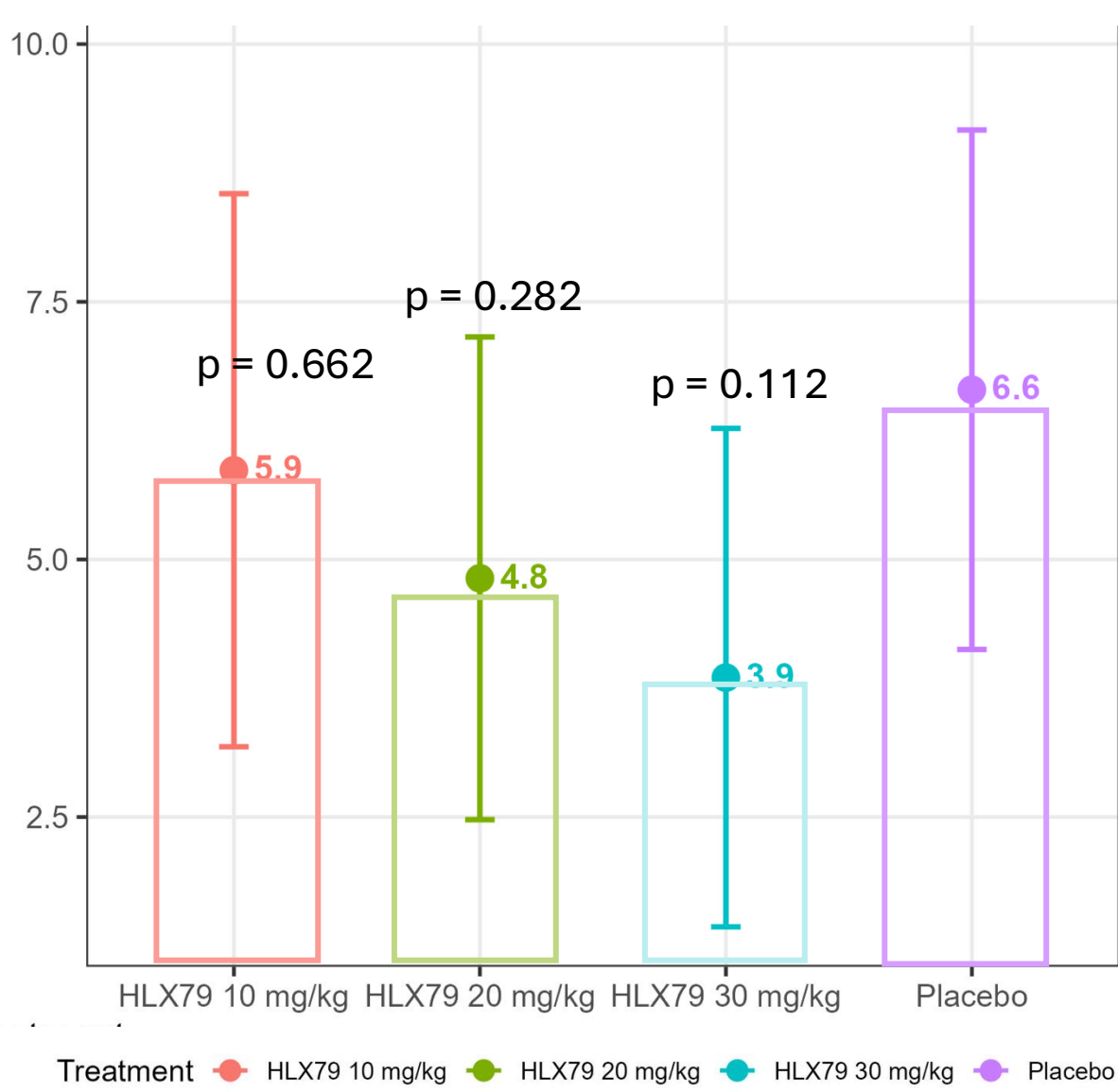


Figure 1. Overview of clinical responses in all subjects enrolled (n = 26) in phase 2A study. Baseline proteinuria (g/day) and anti-PLA2R IgG titers listed per subject. Subject 2008, 2011 assessed CR at week 24 and 36, without intervening visits. *All subjects re-dosed at 6 months, except: 2008, 17002, 2011, 2003, 13001. Values below the limit of detection of PLA2R assay are listed as < 1.72 RU/mL. Data cutoff date: Oct 9, 2026.

Trend towards decreased proteinuria quantified by Time Weighted Area Under the Curve (TWAUC) post-hoc analysis of 24h urine protein

Baseline-adjusted TWAUC of proteinuria by treatment



Proteinuria Burden - A time-integrated measure of disease burden

- Severity and duration of proteinuria together predict long-term renal function loss
- TWAUC is calculated as area under the curve of a patient's sequential proteinuria measurements divided by exposure time
- Proteinuria burden integrates the two prospective endpoints in this trial: response (achieving proteinuria below thresholds) and speed-to-response
- Regulatory precedent in IgAN (Reich et al, JASN, 2007)

Figure 2. Time weight AUC of 24h proteinuria, adjusted for baseline proteinuria per subject, against entire 26 subject dataset. Adjusted least-square means and two-sided 95% confidence intervals; values are LS means. P-value indicate comparison against placebo (Rtx only) group, one-way ANOVA.

Anti-PLA2R antibody levels by treatment group

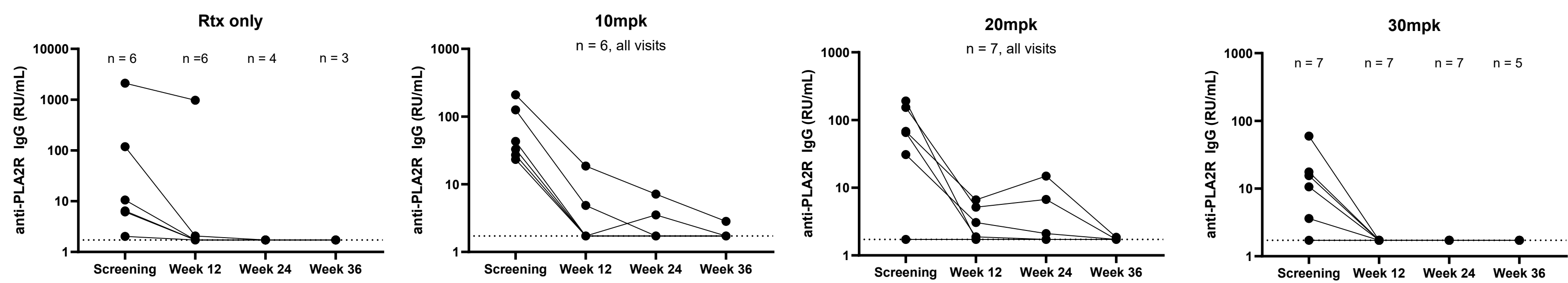


Figure 3. anti-PLA2R autoantibody levels by treatment group and visit. Dashed line indicates limit of detection of assay, (< 1.72 RU/mL)

Conclusion

HLX79/ E-602 at 30 mg/kg + RTX produced the fastest, most complete responses: over half of patients achieved CR/PR within 5 weeks, and 100% by 36 weeks. RTX-only patients gradually responded through week 24, suggesting HLX79 accelerates, broadens, and deepens response vs RTX alone, lowering proteinuria burden and potentially short and long-term risks. These findings support advancement of this novel, first-in-class molecule.