# A randomized, controlled, multicenter, phase 2 clinical study evaluating the efficacy, safety, and tolerability of HLX79/ E-602 combined with a rituximab biosimilar in patients with active glomerulonephritis

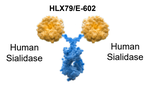
Xueqing Yu[1], Li Peng[2], Lizhi Cao[2], Paul G. Brunetta[2, 3], Yunna Zang[4], Cong Chen[4], Xujia Zeng[4], Lin Han[4]

*1. Guangdong Provincial People's Hospital, Guangzhou, China. 2. Palleon Pharmaceuticals Inc, Waltham, MA, United States.3. University of California San Francisco, San Francisco, CA, United States.4. Shanghai Henlius Biotech Inc, Shanghai, Shanghai, China.*

## HLX79/ E-602 Background

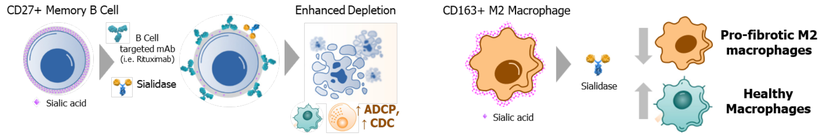
Multiple clinical studies have shown that the persistence or repopulation of CD27⁺ memory B cells following treatment with B cell–depleting agents is associated with suboptimal therapeutic outcomes in autoimmune diseases (1, 2). Furthermore, several studies have linked elevated levels of CD163⁺ M2 macrophages to inflammatory damage, functional impairment, and fibrosis in autoimmunity (3). Therapeutic approaches that target and reduce these two key pathogenic immune cell subsets may therefore have a meaningful impact on the treatment of autoimmune disorders.
Sialoglycans—cell-surface glycans that terminate with sialic acid—play a critical role in suppressing immune clearance and promoting cell survival. Elevated sialoglycan expression may contribute to the persistence of pathogenic CD27⁺ memory B cells and CD163⁺ macrophages in autoimmune disease.

HLX79/ E-602 is a human sialidase-Fc dimer that removes sialic acid from cell surfaces with high sialoglycan levels. **Desialylation** with HLX79/ E-602 enhances the antibody-mediated **reduction** of **CD27+ memory B cells** and the direct clearance of **CD163+ M2 macrophages.** HLX79/ E-602 thus offers a novel therapeutic strategy through enzymatic desialylation to enhance the clearance of these two critical pathogenic immune cell populations and restore immune balance in a wide range of patients with autoimmune diseases.




**Enhanced CD27+ Memory B Cell Depletion**
High sialoglycan levels on CD27+ memory B cell surfaces play a critical role in promoting their resistance to depleting antibody-mediated clearance (4,5).
Desialylation enhances mAb-targeted depletion of **CD27+ memory B cells**

**Reduced CD163+ M2 Macrophages**
High sialoglycans also enable the persistence of CD163+ M2 macrophages in disease tissues, which contributes to fibrosis and tissue damage.
Desialylation increases the clearance of **CD163+ M2 macrophages**




### HLX79/ E-602 enhanced ADCP and CDC function of anti-CD20 mAbs

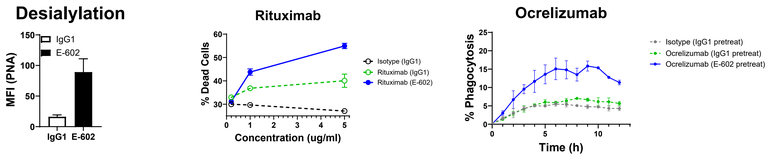



**Figure 1**. **left**) Desialylation of primary human B cells. **middle**) HLX79/ E-602 enhanced rituximab-mediated CDC of primary human B cells. **right**) Time course of phagocytosis using live cell imaging demonstrates HLX79/ E-602 mediates early and sustained increase in ocrelizumab-mediated ADCP of Raji cells.

### HLX79/ E-602 durably desialylated immune cells *in vivo*, in cynomolgus monkeys and in humans

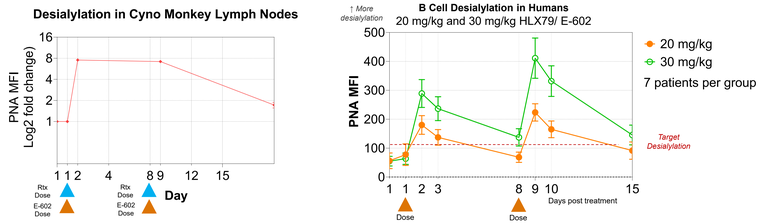



**Figure 2. left)** HLX79/ E-602 desialylation of CD3+ cells in lymph nodes of cynomolgus monkeys, as measured by PNA staining (since B cells have been depleted). N = 4 animals/group, all treatment was given i.v, rituximab dosed at 20 mg/kg, HLX79/ E-602 dosed at 90 mg/kg. **right**) Desialylation of B cells as measured by PNA, in peripheral blood of human subjects dosed with 20 mg/kg or 30 mg/kg of HLX79/ E-602 in the GLIMMER-01 study. MFI: Mean Fluorescence Intensity.

### HLX79/ E-602 enhanced Rituximab-mediated B cell depletion *in vivo and in vitro*

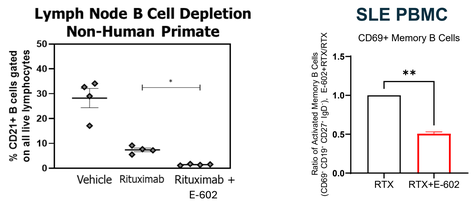



**Figure 3. left**) HLX79/ E-602 desialylation enhanced rituximab-mediated depletion of B cells in lymph nodes of cynomolgus monkeys in vivo. N = 4 animals/group, all treatment groups were given i.v. rituximab dosed at 20 mg/kg, HLX79/ E-602 dosed at 90 mg/kg. Lymph nodes were biopsied at 2 days post dosing. (* P < 0.05, ANOVA) **right**) HLX79/ E-602 enhanced the depletion of CD69+ memory B cells by rituximab in human SLE PBMCs.

| | CD27+Memory B Cell | CD163+ M2 Macrophage |
|---|---|---|
| **Role in Healthy Immunity** | **Immune Memory**<br>Long-lived cells that secrete antibodies to previously encountered antigens | **Wound Healing**<br>Play important role in wound healing and scar formation |
| **Dysfunction in Autoimmunity** | **Driver of Active Inflammatory Injury**:<br>Produce autoantibodies, present antigens to T cells, and secrete inflammatory cytokines | **Driver of Fibrosis**<br>CD163+ M2 macrophages cause excess collagen deposition, fibrosis, and loss of organ function in autoimmunity |
| **Validation as a Target** | B cell depletion is **clinically validated** strategy; memory B cell reconstitution is associated with relapse | Macrophage reduction is a **clinically validated** strategy in autoimmunity (CSF-1R inhibition in cGvHD) |
| **Role of Sialoglycans** | Memory B cells are naturally hypersialylated making them more resistant to antibody-mediated depletion | High sialoglycans allow dysfunctional CD163+ M2 macrophages to persist in inflamed tissue |
| **Impact of Desialylation** | **Desialylation improves mAb-mediated depletion of memory B Cells** | **Desialylation reduces pro-fibrotic M2 macrophages, reducing fibrosis** |
| | ***Improved Reconstitution Favoring Naïve over Memory B Cells***<br>***In combination with B Cell mAb***<br>Naïve B Cells, CD27+ Memory B Cells, Sialic acid | ***Enhanced Clearance of Pro-fibrotic CD163+ M2 Macrophages***<br>***Single Agent***<br>Healthy Macrophages, CD163+ M2 Macrophages, Sialic acid |

## Clinical Development

**Phase 1 Data**
HLX79/ E-602 was well tolerated in a phase 1 safety study (NCT05259696) in patients with advanced cancers, with no dose-limiting toxicity reported up to 30 mg/kg once weekly. A total of 69 patients were treated, and average length of treatment was 7 weeks (range 1 to 44 weeks).
- 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)**
Membranous nephropathy is a well characterized form of glomerulonephritis primarily driven by auto-antibodies to PLA2R. Despite SoC with B-cell depleting therapies, significant unmet need remains and leads to fibrotic kidney injury and loss of organ function.

## Phase 2 Study Objectives

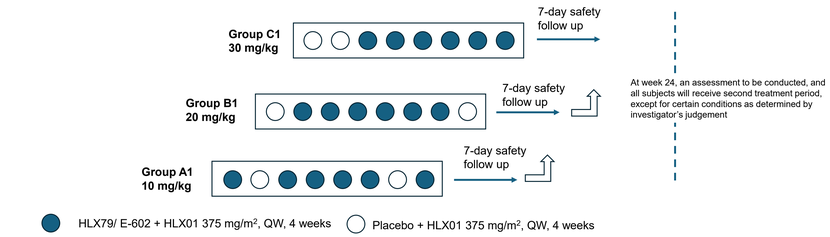
This study aims to evaluate the efficacy, safety, and tolerability of HLX79/ E-602 in combination with a biosimilar of RTX (HANLIKANG/ HLX01) in patients with active glomerulonephritis, starting with part 1) Membranous Nephropathy and potentially part 2) Lupus Nephritis
- Part A - Safety and Tolerability of HLX79/ E-602 + RTX biosimilar vs RTX biosimilar
- Part B - Efficacy measured as CR or PR at week 24

Biomarkers of interest: Peripheral blood B cell counts, subsets, and depletion kinetics. Serum immunoglobulins, urinary CD163, serum autoantibody levels (including anti-PLA2R, anti-dsDNA, etc.

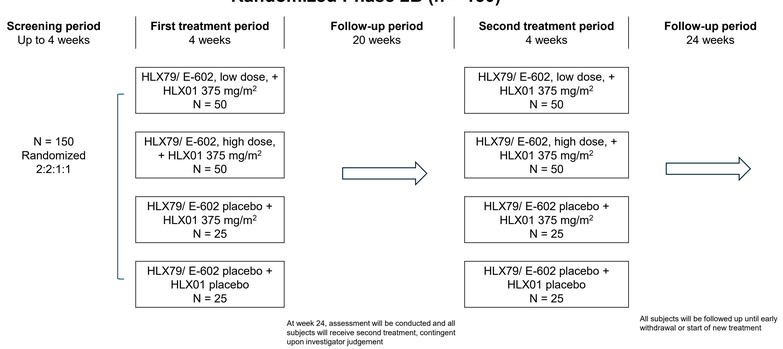
## Phase 2 Study Design

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

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




### Randomized Phase 2B (n = 150)




### 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
- Pregnant or lactating women
- 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)

## Study information and Contact

**Study Sponsor:** Shanghai Henlius Biotech. **Sponsor Contact:** Qi Jin, email: qi_jin@henlius.com.
**US Contact:** Maryann Timins email: mtimins@palleonpharma.com
**Lead investigator:** Xueqing Yu at Guangdong Provincial People's Hospital, Guangzhou, China
**Clinical Trials ID:** NCT07038382

**References**
1. Adlowitz et al, Plos One, 2015 Jun 5;10(6):e0128269
2. Grimsholm O. Clin Exp Immunol. 2023 Jul 21;213(2):164-172.
3. Mejia-Vilet et al. J Am Soc Nephrol. 2020 Jun;31(6):1335-1347.
4. Nakou et al. Arthritis Res Ther. 2009;11(4):R131.
5. Morel et al, Front Immunol, 2022 Aug 25;13:975963