Felzartamab Reduces Anti-PLA2R Autoantibodies by Selectively Depleting CD38+ Plasma Cells and Plasmablasts, the Main Pathogenic Cellular Drivers of Disease in Primary Membranous Nephropathy (PMN)

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Introduction

- Primary Membranous Nephropathy (PMN) is one of the most common causes of nephrotic syndrome and is characterized by severe proteinuria (> 3.5 g/d).[1]
- Renal dysfunction results from deposition of immune complexes, formed predominantly by anti-PLA2R autoantibodies in the subepithelial space between podocytes and the glomerular basement membrane.
- Higher anti-PLA2R levels are associated with higher risk for loss of renal function, relapse, and lower chance to develop disease remission spontaneously or with immunosuppressive treatments (ISTs), including anti-CD20 therapies.[2,3]
- Pathogenic anti-PLA2R autoantibodies are secreted by autoreactive $CD20^{-}/CD38^{high}$ plasma cells and plasmablasts.[4,5]
- CD38 expression is absent in naïve and memory B cells and highly expressed on terminally differentiated plasma cells, making it an attractive target for selectively depleting the cellular source of anti-PLA2R autoantibodies.[6,7]
- Felzartamab (felza), a fully human IgG1 monoclonal antibody, selectively binds to CD38 and depletes CD38+ plasma cells via antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) with minimal or absent complement-dependent cytotoxicity (CDC).

Figure 1. Proposed Felzartamab MOA in PMN

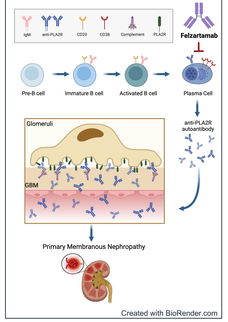
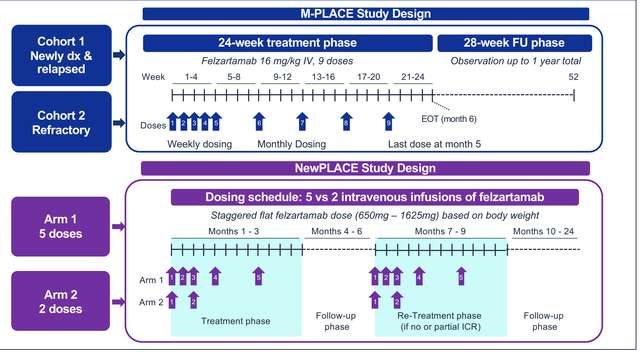


Figure 2. M-PLACE and NewPLACE study designs



- Felzartamab efficacy, safety, and pharmacokinetics/pharmacodynamics were evaluated in anti-PLA2R positive PMN patients in the M-PLACE (NCT04145440) and NewPLACE (NCT04733040) trials.
- Proteinuria partial remission was observed across patient groups in these studies, including those starting with high anti-PLA2R titers or refractory to prior immunosuppressive therapies.
- Clinical results of the M-PLACE study have been reported elsewhere[8-10], and primary completion of the NewPLACE study is estimated in January 2024.

Here, we present exploratory biomarker data from these two trials demonstrating that felzartamab lowers pathogenic anti-PLA2R autoantibody titers by specifically targeting key pathogenic drivers while preserving humoral immunity.

Patients and Methods

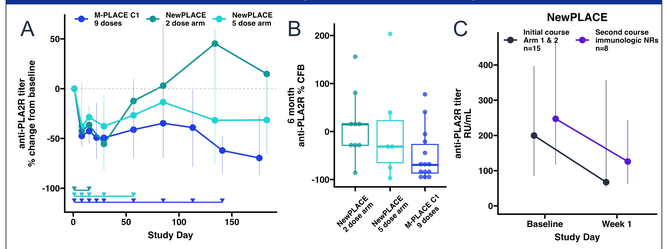
- Key inclusion/exclusion criteria for M-PLACE Cohort 1 and NewPLACE included: Active anti-PLA2R positive PMN in need of IST; UPCR ≥3.0 g/g or proteinuria ≥3.5 g/24h; eGFR ≥50 mL/min/1.73m^2; no remission despite proper treatment with ACE inhibitor and ARBs; serum anti-PLA2R ≥ 50 RU/mL.
- M-PLACE cohort 1 enrolled newly diagnosed (n=15) or relapsed patients (n=3).
- NewPLACE patients with prior IST within 180 days of baseline were excluded from the analysis.
- Serum and whole blood were collected at baseline and post-felzartamab treatment throughout the dosing and follow up periods in both M-PLACE and NewPLACE studies
- Serum was evaluated for anti-PLA2R (EUROIMMUN ELISA), polyclonal immunoglobulins IgA, IgG, and IgM (turbidimetry), and anti-Tetanus Toxoid (anti-TT) titers (ELISA).
- Whole blood was analyzed via flow cytometry for B cell subset immunophenotyping.
- Exploratory biomarker analyses were conducted on M-PLACE cohort 1 (newly diagnosed or relapsed) and NewPLACE Arm 1 (5 initial doses) and Arm 2 (2 initial doses) due to consistent patient population and biomarker methods utilized across the two studies.
- All M-PLACE cohort 1 and NewPLACE patients that received at least two doses and had baseline measurements were included in analysis.

Results

Table 1. Dose dependent decreases in anti-PLA2R levels were observed, with only modest decreases in total IgG and anti-Tetanus Toxoid

	Baseline Values			6 mo % Change from Baseline		
	Median	IQR	n	Median (% change)	IQR	n
Anti-PLA2R (RU/mL)						
2 dose arm NewPLACE	200	(83, 211)	9	+15	(-29, 16)	9
5 dose arm NewPLACE	291	(114, 478)	6	-31	(-65, 23)	6
9 dose M-PLACE C1	182	(119, 262)	18	-67	(-85, -33)	15
<150 RU/mL	115	(77, 123)	7	-76	(-88, -66)	6
≥150 RU/mL	256	(210, 291)	11	-66	(-83, -21)	9
Immunoglobulins (M-PLACE Cohort 1)						
Total IgG (g/L)	5.1	(4.6, 6.5)	12	-20.6	(-26.7, -13.0)	12
Anti-TT (IU/mL)	0.4	(0.1, 1.1)	18	-4.1	(-30.3, 25.5)	17

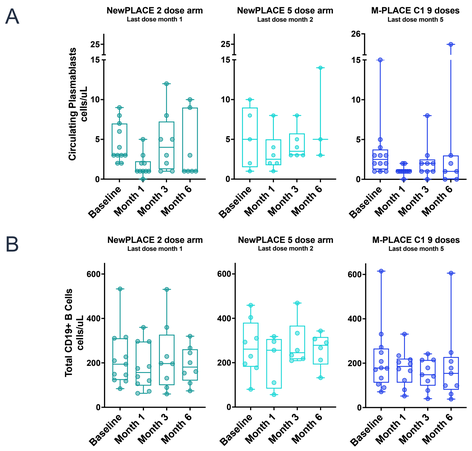
Figure 3. Greater durability of immunological response is observed with felzartamab 9 dose regimen vs 2 or 5 dose regimens



(A) Longitudinal changes (Median %CFB ± IQR) in anti-PLA2R titers across three dose regimens in PMN patients. M-PLACE C1 patients who completed 9 dose regimen (n=14) and NewPLACE patients who did not receive prohibited conmeds prior to 6 months (2 dose arm n = 9 , 5 dose arm n = 6) were included in analysis. (B) Boxplots show median %CFB ± IQR overlaid with individual data at month 6. (C) anti-PLA2R serum levels (median anti-PLA2R RU/mL + IQR) baseline (black) and 1 week after the first dose and prior to re-treatment dosing (purple) and 1 week after the first re-treatment dose.

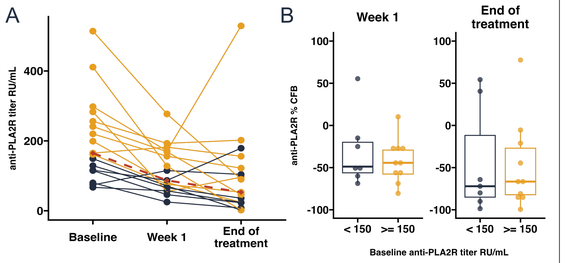
Results

Figure 4. Felzartamab treatment selectively depletes detectable circulating plasmablasts without impacting earlier B cell lineages



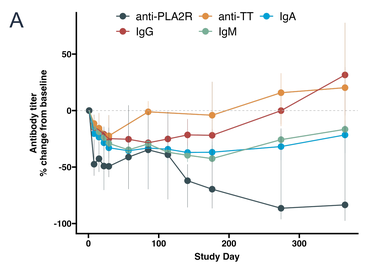
Absolute cell counts (cells/µl) of circulating plasmablasts ($CD19^{+}CD27^{br}CD38^{br}$) (A) and total B Cells ($CD3^{-}CD19^{+}$) (B) were assessed by flow cytometry at baseline (Day 1 predose) and months 1, 3, and 6 post-felza treatment. Boxplots show median ± IQR overlaid with all evaluable datapoints at each timepoint.

Figure 5. Baseline anti-PLA2R levels do not predict felzartamab immunological response in M-PLACE cohort 1 PMN patients



(A) Anti-PLA2R titer (RU/mL) at baseline, week 1 post-treatment, and at end of treatment (month 6) for patients that received at least 2 doses of felzartamab. Median titers shown in red (n=17). Patients with ≥150 RU/mL at baseline shown in gold (n=10) and patients with <150 RU/mL at baseline shown in dark gray (n=7). (B) Median reductions in pathogenic anti-PLA2R titers at week 1 and end of treatment in patients with <150 RU/mL and ≥150 RU/mL anti-PLA2R at baseline. Boxplots show median ± IQR overlaid with individual data.

Figure 6. Felzartamab reduces pathogenic anti-PLA2R autoantibodies to a greater extent than protective immunoglobulins in M-PLACE cohort 1



(A) Median %change from baseline ± IQR of evaluable circulating antibody titers in M-PLACE cohort 1 patients who received all 9 doses of felzartamab (n = 14). (B) EOT (6mo) Polyclonal IgG and (C) EOT (6mo) anti-TT %CFB versus EOT %CFB anti-PLA2R of individual patients. Median ± IQR is shown in red (n=17, n=16 respectively). Dashed line represents equivalent % change.

Summary

- In an exploratory biomarker analysis of felzartamab treated PMN subjects enrolled in the M-PLACE and NewPLACE studies, felzartamab selectively depleted CD38+ plasmablasts, reducing pathogenic anti-PLA2R to a greater extent than protective anti-TT titers and total IgG, in a durable and dose-dependent manner.
- Felzartamab rapidly (week 1) and durably (EOT, month 6) reduced anti-PLA2R levels, with comparable reduction in patients with baseline levels <150 and ≥150 RU/mL.
- Preservation of protective immunoglobulins including polyclonal IgG and anti-TT, is consistent with previous findings demonstrating effective COVID19 vaccine responses in M-PLACE[11]. Together these data suggest felzartamab preserves humoral immunity.
- A dose-dependent effect on anti-PLA2R titer reduction at 6mo was observed across both M-PLACE (9 infusions) and NewPLACE (5 or 2 initial infusions).
- Depletion of detectable CD38+ plasmablast cell counts was observed within 1 week of felza treatment, with durability of decrease maintained through treatment phase.
- Felzartamab treatment did not impact earlier B cell lineages.

Results suggest that treatment of PMN with felzartamab presents an efficient and selective treatment concept with preservation of vaccine response compared to conventional immunosuppressive therapies.

Acknowledgements and Disclosures

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About felzartamab: HI-Bio in-licensed felzartamab from MorphoSys in June 2022, and holds exclusive worldwide rights for felzartamab with the exception of Greater China. In 2017, MorphoSys entered into an exclusive regional licensing agreement with I-Mab Biopharma to develop and commercialize felzartamab in Greater China which encompasses Mainland China, Hong Kong, Macau and Taiwan. I-Mab is evaluating felzartamab in relapsed/refractory multiple myeloma. Felzartamab is an investigational drug that has not yet been approved by any regulatory authorities.

Conflicts of interest

DLF, MS, LK, JD, HNG, UDP: Employees of HI-Bio Inc., with stock or stock options; **RB, TK, SH:** Employees of Morphosys AG, with stock or stock options; **BHR:** consulting fees from HI-Bio.

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