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Phase 1b/2a Study Assessing the Safety and Efficacy of Felzartamab in Anti-Phospholipase A2 Receptor Autoantibody–Positive Primary Membranous Nephropathy

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Introduction: Primary membranous nephropathy (PMN) is most often caused by autoantibodies to phospholipase A2 receptor (PLA2R). M-PLACE (NCT04145440) is an open-label, phase 1b/2a study that assessed the safety and efficacy of the fully human anti-CD38 monoclonal antibody felzartamab in high-risk anti-PLA2R+ PMN.

Methods: Patients with newly diagnosed or relapsed PMN (cohort 1 [C1]; $n = 18$) or PMN refractory to immunosuppressive therapy (IST) (cohort 2 [C2]; $n = 13$) received 9 infusions of felzartamab 16 mg/kg in the 24-week treatment period, followed by a 28-week follow-up. The primary end point was the incidence and severity of treatment-emergent adverse events (TEAEs).

Results: A total of 31 patients were enrolled and received felzartamab. Twenty-seven patients (87.1%) had TEAEs, including infusion-related reactions (IRRs) (29.0%), hypogammaglobulinemia (25.8%), peripheral edema (19.4%), and nausea (16.1%). Five patients (16.1%) had serious TEAEs that all resolved. Immunologic response (anti-PLA2R titer reduction ≥50%) was achieved by 20 of 26 efficacy-evaluable patients (76.9%) (C1, 13/15 [86.7%]; C2, 7/11 [63.6%]). Anti-PLA2R titer reductions were rapid (week 1 response, 44.0%; response 7 months after last felzartamab dose [end of study, EOS], 53.8%). Partial proteinuria remission (urine protein-to-creatinine ratio [UPCR] reduction ≥50%, UPCR <3.0 g/g, and stable estimated glomerular filtration rate [eGFR]) was achieved by 9 of 26 patients (34.6%) (C1, 7/15 [46.7%]; C2, 2/11 [18.2%]) before or at EOS (median follow-up, 366 days). Serum albumin increased from baseline to EOS in 20 of 26 patients (76.9%) (C1, 12/15 [80.0%]; C2, 8/11 [72.7%]).

Conclusion: In this population with high-risk anti-PLA2R+ PMN, felzartamab was tolerated and resulted in rapid partial and complete immunologic responses and partial improvements in proteinuria and serum albumin in some patients.

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PMN is a rare autoimmune kidney disease and is the leading cause of nephrotic syndrome in adults.[1,2] Patients with PMN typically present with proteinuria, edema, hypoalbuminemia, hematuria, and hyperlipidemia.[1,3,4] The M-type PLA2R expressed by glomerular podocytes is the most common autoantigen

in PMN, with anti-PLA2R autoantibodies present in 70% to 80% of patients with active disease.[5-15] Anti-PLA2R autoantibodies bind to podocyte PLA2R and form immune complexes that activate complement, leading to glomerular C5b–9 deposition, podocyte injury, thickening of the glomerular basement membrane, and impaired glomerular function.[1]

The standard-of-care for PMN is off-label therapy with renin-angiotensin-aldosterone system inhibitors and IST with the anti-CD20 monoclonal antibody rituximab, cyclophosphamide, and/or calcineurin inhibitors.[16,17] However, treatment resistance and relapse are common, and the risk of toxicity may be high, particularly with conventional ISTs.[13,15,18-26] In addition, patients with high baseline anti-PLA2R titers are less likely to respond to rituximab and calcineurin inhibitors. Therefore, there is an unmet therapeutic need for PMN, especially for patients with relapsed or refractory disease and high anti-PLA2R titers.

Antibody-secreting plasma cells and plasmablasts express high levels of CD38 but lack or have downregulated CD20 expression.[27-32] Because $CD38^{+}CD20^{-}$ long-lived plasma cells produce autoantibodies to PLA2R and other antigens,[33] therapies targeting plasma cells and plasmablasts may reduce pathogenic anti-PLA2R autoantibodies and halt PMN progression. Felzartamab is an investigational, fully human IgG1 monoclonal anti-CD38 antibody that depletes plasmablasts and plasma cells through antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.[34-36] M-PLACE is a proof-of-concept phase 1b/2a study that assessed the safety and efficacy of felzartamab in patients with high-risk anti-PLA2R+ PMN.

METHODS

Study Design and Participants

M-PLACE (ClinicalTrials.gov, NCT04145440) is an open-label, multicenter, multinational, phase 1b/2a study that enrolled patients between February 20, 2020, and June 30, 2021, at 31 centers in Belgium, the United States, Italy, France, Poland, Australia, Spain, South Korea, and The Netherlands. There was a safety run-in for the first 3 patients. The study had a 6-week screening period, a 24-week treatment period, and a 28-week posttreatment follow-up.

Eligible patients (aged 18–80 years) had biopsy-confirmed, anti-PLA2R+ PMN requiring IST; screening UPCR of ≥3.0 g/g or proteinuria ≥3.5 g/d from a 24-hour collection; eGFR ≥50 ml/min per 1.73 m^2 as per the Chronic Kidney Disease-Epidemiology Collaboration formula,[37,38] or eGFR ≥30 and <50 ml/min per 1.73 m^2 with interstitial fibrosis and tubular atrophy score of <25% within 6 months before screening; and resting systolic blood pressure ≤150 mm Hg and diastolic blood pressure ≤100 mm Hg. The study enrolled 2 cohorts. Patients in C1 were stable on supportive care with angiotensin-converting enzyme inhibitors or angiotensin II blockers; were eligible for IST per the investigator; and had PMN with proteinuria that was either newly diagnosed with screening serum anti-PLA2R titer ≥50.0 RU/ml (the 2021 Kidney Disease: Improving Global Outcomes threshold for high-risk PMN[16]), or that was relapsed after complete immunologic response and/or clinical remission lasting ≥6 months with screening serum anti-PLA2R titer ≥50.0 RU/ml. Patients in C2 had PMN refractory (i.e., did not achieve immunologic complete response [ICR] and/or clinical remission) ≥6 months after starting a standard IST; had no therapeutic options due to efficacy or safety; and had screening serum anti-PLA2R antibody titers ≥20.0 RU/ml.

Patients were excluded for hemoglobin <80 g/l; platelets $<100 \times 10^9$/l; neutrophils $<1.5 \times 10^9$/l; leukocytes $<3.0 \times 10^9$/l; serum total immunoglobulin ≤4.0 g/l; B cells $<5 \times 10^6$/l; secondary membranous nephropathy; other concomitant renal disease; type 1 diabetes; uncontrolled type 2 diabetes ≤6 months before screening; prior anti-CD38 treatment; mycophenolate mofetil or high-dose corticosteroids ≤30 days before screening, alkylating agents ≤90 days before screening, or biologic treatment or IST ≤180 days before screening; or malignancy ≤5 years of screening (except adequately treated cervical or uterine carcinoma or non-melanoma skin cancer).

Study Oversight

M-PLACE was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study protocol was approved by the ethical review committees and institutional review boards at each site. Patients provided written, informed consent.

Treatment

Nine intravenous infusions of felzartamab 16 mg/kg in six 28-day cycles were planned. The first 4 infusions were administered weekly on day 1 of the first 4 weeks (cycle 1; days 1–22). The last 5 infusions were administered every 4 weeks on day 1 of subsequent cycles (cycles 2–6; days 29, 57, 85, 113, and 141). If no IRRs occurred during the first 90-minute infusion, infusions could be shortened to ≥30 minutes. Dexamethasone or glucocorticoid prophylaxis was required for the first 3 infusions. Antihistamine and an antipyretic were used per local guidelines or investigator discretion.

Felzartamab was to be withheld for hemoglobin <60.0 g/l until resolution to ≥80 g/l; platelet count <75.0 × 10^9/l until resolution to ≥100 × 10^9/l; neutrophil count <1.0 × 10^9/l until resolution to ≥1.5 × 10^9/l; or any other grade ≥3 adverse event until resolution to grade ≤2. Infusions were stopped immediately for IRRs but could be restarted at a reduced rate depending on the IRR grade; if symptoms returned, infusion was discontinued for that visit, and treatment resumed at the next visit per investigator discretion. Felzartamab was to be permanently discontinued for grade 4 IRR; platelet transfusion; failure to resolve grade ≥3 treatment-related adverse event to grade <2 within 21 days; progressive disease (decrease of eGFR by >30% of baseline, or increase in 24-hour UPCR by >50% of baseline and <10% decline of anti-PLA2R titer vs. baseline); pregnancy; withdrawal of consent; use of prohibited IST; and at investigator discretion.

End Points and Assessments

The primary end point was the incidence and severity of TEAEs graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

The key secondary end point was the best immunologic response rate based on the reduction of anti-PLA2R antibody titer using a qualified enzyme-linked immunosorbent assay (EUROIMMUN). Anti-PLA2R titer was assessed at screening; on days 1, 8, 15, 22, 29, 57, 85, 113, 141, 169 (or end of treatment [EOT]), 267, and 366 (EOS). Immunologic response categories were immunologic partial response (IPR; reduction of anti-PLA2R titer by ≥50% from baseline) and ICR (anti-PLA2R titer <14.0 RU/ml). Best overall immunologic response was defined as IPR or ICR at any time before use of prohibited medication or disease progression.

Other secondary end points included felzartamab immunogenicity and pharmacokinetics. Serum samples were analyzed for antidrug antibodies using a validated enzyme-linked immunosorbent assay with solid phase extraction and acid dissociation (MorphoSys AG) at screening and on days 1, 57, 113, 141, 169 (or EOT), 267, and 366 (or EOS). Felzartamab concentrations were measured with a validated (serum) or qualified (urine) electrochemiluminescence-based ligand binding assay (MorphoSys AG) using blood and urine samples collected at screening and on days 1, 8, 15, 22 (serum only), 29, 57, 85, 113, 141, 169 (or EOT), 267, and 366 (or EOS). Urine felzartamab concentrations were normalized to urine creatinine concentrations.

Exploratory end points included change from baseline in immunoglobulin, hemoglobin, platelets, and immune cell populations; change from baseline in anti-PLA2R titer, serum albumin, and eGFR; time-to-first immunologic response; proteinuria remission; and change in health-related quality of life. For the assessment of proteinuria remission by UPCR, 24-hour urine samples were collected at screening and on days 1, 85, 169 (or EOT), 267, and 366 (or EOS). Proteinuria remission categories were proteinuria partial remission (Prot-PR; ≥50% reduction from baseline to any visit in 24-hour UPCR, proteinuria <3.0 g/g, and stable eGFR [≥80% of baseline]) and proteinuria complete remission (reduction of proteinuria to <0.5 g/g, serum albumin within the reference range [3.5–5.2 g/dl], and stable eGFR [≥80% of baseline]).

Health-related quality of life was assessed using Kidney Disease Quality of Life 36 Survey (KDQOL-36) on days 1, 169 (or EOT), and 366 (or EOS). Serum biochemistry and immunoglobulins were assessed at screening and on days 1, 8, 15, 22, 29, 57, 85, 113, 141, 169 (or EOT), 267, and 366 (or EOS). Hematology test was performed on days 1, 8, 15, 22, 29, 57, 85, 113, and 141.

Statistical Analysis

The sample size was determined without formal hypothesis testing. *P*-values were exploratory and were not adjusted for multiple comparisons. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute) or R software version 4.3.0 (R Foundation).

Safety analyses included patients who received ≥1 dose of felzartamab (full analysis set; $n = 31$). Analyses of anti-PLA2R titer, immunologic response, serum albumin, 24-hour UPCR, and proteinuria response were performed using the efficacy analysis set ($n = 26$; C1, $n = 15$; C2, $n = 11$): efficacy-evaluable patients who received ≥5 of 9 felzartamab doses without discontinuing the study for prohibited medication use. Sensitivity analyses of immunologic and proteinuria response were performed using the full analysis set population. Immunologic response was tabulated by baseline anti-PLA2R titer. Pharmacokinetics, immunogenicity, and exploratory variables were assessed for patients who received ≥1 dose of felzartamab and had ≥1 sample.

Time-to-event variables were estimated using Kaplan-Meier methods. Confidence intervals for response rates were calculated using the Clopper-Pearson exact method. Pearson correlations were used to assess the strength and direction of relationships between variables. Missing data for anti-PLA2R titer, immunologic response, serum albumin, 24-hour UPCR, and proteinuria response were imputed using last observation carried forward for EOS analyses.

RESULTS

Study Population

Sixty-five patients were screened, and 31 patients were enrolled (C1, $n = 18$; C2, $n = 13$). The mean (SD) age was 57.5 (11.8) years; 24 (77.4%) were men (Table 1; Supplementary Table S1). In C1, 15 patients (83.3%) had newly diagnosed PMN and 3 (16.7%) had relapsed PMN (prior Prot-PR, $n = 2$; prior IPR, $n = 1$). In C2, all 13 patients (100%) had PMN that was refractory to IST (no ICR and/or no Prot-PR). Prior ISTs included rituximab ($n = 12$), cyclophosphamide ($n = 7$), tacrolimus ($n = 6$), and alternating cyclophosphamide and glucocorticoids ($n = 3$).

Patients had high-risk disease per Kidney Disease: Improving Global Outcomes (Table 1).[16,17] Median (interquartile range) baseline PMN parameters in C1 were as follows: anti-PLA2R titer, 182.0 (116.0–264.0)

Table 1. Demographics and baseline disease characteristics

Characteristics	Cohort 1 newly diagnosed / relapsed ($n = 18$)	Cohort 2 refractory ($n = 13$)	*P*-value[a]	All patients ($N = 31$)
Mean (SD) age, yr	59.2 (11.3)	55.0 (12.5)	0.373	57.5 (11.8)
Sex, *n* (%)			1.0	
Male	13 (72.2)	11 (84.6)		24 (77.4)
Female	5 (27.8)	2 (15.4)		7 (22.6)
Race, *n* (%)			0.145	
White	13 (72.2)	8 (61.5)		21 (67.7)
Asian	4 (22.2)	0		4 (12.9)
Black	0	1 (7.7)		1 (3.2)
Other[b]	1 (5.6)	4 (30.8)		5 (16.1)
Median (IQR) time since PMN diagnosis, mo	4.1 (2.1–9.3)	25.8 (15.4–38.0)	0.558	11.9 (3.0–32.8)
Baseline disease status, *n* (%)			0.001	
Newly diagnosed	15 (83.3)	0		15 (48.4)
Relapsed	3[c] (16.7)	0		3 (9.7)
Refractory	0	13 (100)		13 (41.9)
Prior proteinuria remission, *n* (%)			0.156	
No remission	16 (88.9)	8 (61.5)		24 (77.4)
Complete remission	0	1 (7.7)		1 (3.2)
Partial remission	2 (11.1)	4 (30.8)		6 (19.4)
Median (IQR) prior lines of IST, *n*	0 (0–4)	1 (1–5)	0.001	0 (0–5)
Prior lines of IST, *n* (%)				
0	16[d] (88.9)	0		16 (51.6)
1	0	7 (53.8)		7 (22.6)
2	1 (5.6)	2 (15.4)		3 (9.7)
≥3	1 (5.6)	4 (30.8)		5 (16.1)
Rituximab	1 (5.6)	11 (84.6)		12 (38.7)
Cyclophosphamide	1 (5.6)	6 (46.2)		7 (22.6)
Tacrolimus	2 (11.1)	4 (30.8)		6 (19.4)
Median (IQR) baseline anti-PLA2R antibody titer,[e] RU/ml			0.637	
Median (IQR)	182.0 (119.3–262.0)	122.0 (55.0–283.0)		161.0 (90.5–273.5)
Mean (SD)	207.9 (118.9)	301.5 (377.6)		247.1 (259.3)
Median (IQR) baseline proteinuria (24-h UPCR),[f] g/g			0.301	
Median (IQR)	5.9 (4.9–7.5)	6.2 (4.4–7.7)		6.1 (4.6–7.6)
Mean (SD)	6.2 (2.0)	6.7 (2.5)		6.4 (2.2)
Median (IQR) baseline eGFR, ml/min per 1.73 m^2			0.098	
Median (IQR)	64.5 (48.8–80.8)	60.0 (46.0–62.0)		61.0 (47.5–69.5)
Mean (SD)	64.8 (21.9)	53.7 (15.6)		60.2 (20.0)
Median (IQR) baseline serum albumin,[g] g/l			0.198	
Median (IQR)	24.5 (21.3–30.3)	28.0 (26.0–30.0)		26.0 (23.0–30.5)
Mean (SD)	25.9 (5.4)	28.0 (4.2)		26.8 (5.0)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; IST, immunosuppressive therapy; PLA2R, phospholipase A2 receptor; UPCR, urine protein-to-creatinine ratio.
[a]*P*-values are for descriptive purposes only and were generated using the nonparametric Wilcoxon rank-sum test for continuous covariates and the chi-square test for categorical covariates.
[b]Race is not reported for patients in France (cohort 2, $n = 3$). Other includes American Indian or Alaskan Native (cohort 1, $n = 1$) and Hispanic or Latino (cohort 2, $n = 1$).
[c]In cohort 1, 2 patients had prior proteinuria partial remission and 1 patient had prior immunologic response.
[d]One patient was recorded as being relapsed but not having received prior immunosuppressive therapy. However, this patient's medications before study entry were listed as furosemide, ramipril, atorvastatin, carvedilol, nifedipine, and rivaroxaban, which are not immunosuppressive therapies.
[e]Baseline anti-PLA2R antibody titer was the last value before starting treatment.
[f]Baseline UPCR value was defined as the mean of values at screening and before the first dose (day 1, cycle 1).
[g]Reference range: 3.5–5.2 g/dl.

RU/ml; proteinuria, 5.9 (4.9–7.5) g/g; eGFR, 64.5 (48.0–81.0) ml/min per 1.73 m^2; and serum albumin, 24.5 (21.0–31.0) g/l. Median (interquartile range) baseline PMN parameters in C2 were as follows: anti-PLA2R titer, 122.0 (55.0–283.0) RU/ml; proteinuria, 6.2 (4.4–7.7) g/g; eGFR, 60.0 (46.0–62.0) ml/min per 1.73 m^2; and serum albumin, 28.0 (26.0–30.0) g/l.

Exposure and Compliance

All 31 patients received felzartamab. Twenty-three patients (74.2%) reached the EOT period, and 8 (25.8%) discontinued felzartamab due to adverse events ($n = 5$), disease progression due to ≥30% decrease of eGFR from baseline ($n = 2$), and use of prohibited medication ($n = 1$; Supplementary Figure S1). Twenty-one patients (67.7%) (C1, $n = 13$; C2, $n = 8$) received all 9 infusions (Table 2). The overall compliance rate for planned infusions was 86.3%. The median (range) follow-up time was 364 (206–432) days.

Safety

TEAEs occurred in 27 of 31 patients (87.1%) (C1, $n = 15$ [83.3%]; C2, $n = 12$ [92.3%]; Table 3) and were predominantly mild or moderate in severity. The most common TEAEs (occurring in ≥10% of patients) were IRR (29.0%), hypogammaglobulinemia (25.8%), peripheral edema (19.4%), nausea (16.1%), and bronchitis (12.9%). Seven of 8 patients with TEAEs had hypogammaglobulinemia (≤4.0 g/l) at baseline. Eight patients (25.8%) had grade 3 or 4 TEAEs (C1, $n = 3$ [16.7%]; C2, $n = 5$ [38.5%]). There were no fatal TEAEs.

All 30 patients (100%) received prophylactic glucocorticoids, including 1 or more doses of dexamethasone 4 mg ($n = 1$), 8 mg ($n = 18$) or 16 mg ($n = 21$) and methylprednisolone 20 mg ($n = 1$), 40 mg ($n = 1$), 80 mg ($n = 5$), 100 mg ($n = 4$), or 500 mg ($n = 1$). IRRs (a prespecified TEAE of interest) occurred in 9 patients (29.0%) (C1, $n = 1$ [5.6%]; C2, $n = 8$ [61.5%]; Table 3). Following the first felzartamab infusion, a patient (C1) had a serious, treatment-related grade 3 IRR that resolved with medication and discontinuation of

Table 2. Felzartamab exposure and compliance

Exposure characteristics	Cohort 1 newly diagnosed / relapsed ($n = 18$)	Cohort 2 refractory ($n = 13$)	All patients ($N = 31$)
Felzartamab infusions per patient, *n* (%)			
1–2	1 (5.6)	0	1 (3.2)
3–4	0	1 (7.7)	1 (3.2)
5–6	3 (16.7)	3 (23.1)	6 (19.4)
7–8	1 (5.6)	1 (7.7)	2 (6.5)
9	13 (72.2)	8 (61.5)	21 (67.7)
Mean (SD) cumulative felzartamab dose, mg	10,315.2 (3650.2)	13,111.6 (5177.8)	11,487.9 (4499.1)
Mean (SD) duration of felzartamab exposure, mo	3.9 (1.4)	3.9 (1.3)	3.9 (1.4)
Mean (SD) compliance,[a] %	87.9 (25.5)	84.2 (23.7)	86.3 (24.4)

eGFR, estimated glomerular filtration rate; IST, immunosuppressive therapy; PLA2R, phospholipase A2 receptor; UPCR, urine protein-to-creatinine ratio.
[a]Compliance per patient, based on cumulative infusion volumes, was calculated as: (sum of actual infusion doses / sum of planned infusion doses) × 100.

Table 3. Summary of adverse events

Patients with an event	Cohort 1 newly diagnosed / relapsed ($n = 18$)	Cohort 2 refractory ($n = 13$)	All patients ($N = 31$)
Patients with any TEAE, *n* (%)	15 (83.3)	12 (92.3)	27 (87.1)
Patients with any grade 3 or 4 TEAE, *n* (%)	3 (16.7)	5 (38.5)	8 (25.8)
Patients with any serious TEAE, *n* (%)	2 (11.1)	3 (23.1)	5 (16.1)
Patients with any TEAE leading to treatment discontinuation, *n* (%)	3 (16.7)	2 (15.4)	5 (16.1)
Patients with a predefined TEAE of special interest,[a] *n* (%)	4 (22.2)	2 (15.4)	6 (19.4)
Allergic reaction	1 (5.6)	1 (7.7)	2 (6.5)
Grade ≥3 infection	1 (5.6)	0	1 (3.2)
Grade ≥3 infusion-related reaction	1 (5.6)	0	1 (3.2)
Grade ≥3 neutropenia (ANC $<1.0 \times 10^9$/l)	1 (5.6)	1 (7.7)	2 (6.5)
TEAEs occurring in ≥2 patients overall, *n* (%)			
Infusion-related reaction	1 (5.6)	8 (61.5)	9 (29.0)
Hypogammaglobulinemia	7 (38.9)	1 (7.7)	8 (25.8)
Peripheral edema	2 (11.1)	4 (30.8)	6 (19.4)
Nausea	4 (22.2)	1 (7.7)	5 (16.1)
Bronchitis	0	4 (30.8)	4 (12.9)
Arthralgia	3 (16.7)	0	3 (9.7)
Back pain	2 (11.1)	1 (7.7)	3 (9.7)
Chest pain	1 (5.6)	2 (15.4)	3 (9.7)
COVID-19	1 (5.6)	2 (15.4)	3 (9.7)
Dyspnea	1 (5.6)	2 (15.4)	3 (9.7)
Fatigue	2 (11.1)	1 (7.7)	3 (9.7)
Headache	3 (16.7)	0	3 (9.7)
Lipase increased	3 (16.7)	0	3 (9.7)
Neutropenia	2 (11.1)	1 (7.7)	3 (9.7)
Anemia	1 (5.6)	1 (7.7)	2 (6.5)
Cough	1 (5.6)	1 (7.7)	2 (6.5)
Diarrhea	2 (11.1)	0	2 (6.5)
Hyperkalemia	2 (11.1)	0	2 (6.5)
Insomnia	1 (5.6)	1 (7.7)	2 (6.5)
Lymphocyte percentage increased	2 (11.1)	0	2 (6.5)
Myalgia	2 (11.1)	0	2 (6.5)
Pyrexia	0	2 (15.4)	2 (6.5)
Rhabdomyolysis	0	2 (15.4)	2 (6.5)

ANC, absolute neutrophil count; TEAE, treatment-emergent adverse event.
[a]Allergic reactions occurred in 3 patients: grade 2 treatment-related allergic dermatitis (cohort 1) that resolved with medication; grade 2 treatment related drug hypersensitivity (cohort 1) that resolved with medication and temporary interruption of felzartamab; and grade 3 treatment-related type 1 hypersensitivity (cohort 2) that resolved with medication and discontinuation of felzartamab. Grade ≥3 neutropenia occurred in 2 patients: grade 3 treatment-related neutropenia (cohort 1) that resolved with medication and temporary interruption of felzartamab and grade 3 and 4 treatment related events of neutropenia (cohort 2) that both resolved with temporary interruption of felzartamab. A patient in cohort 1 had grade 4 COVID-19 infection not considered by the investigators to be related to felzartamab that resolved with medication and discontinuation of felzartamab.

felzartamab. Eight other patients had IRRs (grade 1, $n = 5$; grade 2, $n = 3$) that resolved. Other prespecified TEAEs of interest were treatment-emergent allergic reactions to felzartamab ($n = 3$), grade ≥3 neutropenia ($n = 2$), and grade ≥3 infection ($n = 1$).

Five patients (16.1%) had serious TEAEs (Table 3), all of which resolved. Three serious TEAEs were considered treatment-related (grade 3 IRR, grade 3 type 1 hypersensitivity, and grade 4 neutropenia). Five patients (16.2%) had TEAEs resulting in felzartamab discontinuation. In addition to treatment discontinuations due to grade 3 IRR and grade 3 type 1 hypersensitivity, patients discontinued treatment due to grade 3 treatment-related chest pain, grade 4 treatment-emergent COVID-19 infection, and grade 2 treatment-emergent nephrotic syndrome.

Serum IgG was monitored due to the mechanism of felzartamab. Reductions in serum IgG were modest, and median levels recovered to above baseline by EOS (C1, +27.9%; C2, +2.3%; Figure 1). Levels of hemoglobin, lymphocytes, monocytes, neutrophils, and platelets remained stable throughout the study (Supplementary Figure S2).

Immunogenicity

Treatment-induced or treatment-increased antidrug antibodies were not detected. Preexisting anti-felzartamab antibodies were detected at baseline in 2 of 28 patients with available samples and at EOT in 1 of the same patients. Preexisting antidrug antibodies had no apparent effect on felzartamab pharmacokinetics, safety, or efficacy.

Pharmacokinetics

Predose felzartamab serum concentration-versus-time profiles were consistent between C1 and C2 (Supplementary Figure S3a). Serum concentrations were greatest with weekly dosing (cycle 1, days 1–22; $n = 28$–31), with maximum mean trough concentrations reached on day 22 (C1, 214.5 μg/ml; C2, 295.3 μg/ml). The mean steady-state serum trough level at the end of every-4-weeks dosing (day 113) was 42.8 μg/ml (C1, 39.2 μg/ml; C2, 48.4 μg/ml).

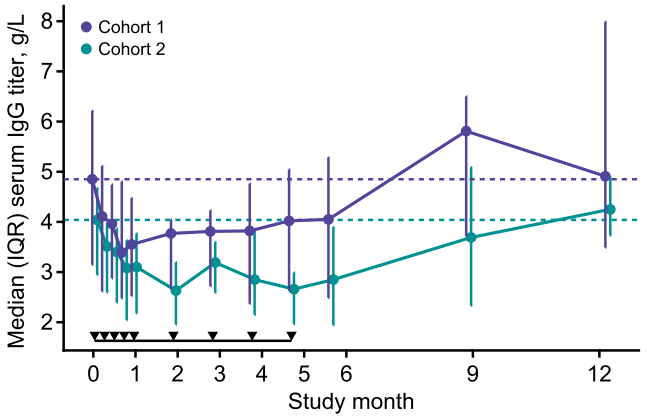

Figure 1. Median (± IQR) change from baseline to EOS in IgG. EOS, end of study; IQR, interquartile range. Dashed lines indicate the median baseline levels for each cohort (cohort 1, purple; cohort 2, teal). Arrows indicate felzartamab infusions.

Maximum mean predose felzartamab urine concentrations normalized to creatinine were reached on day 15 (C1 [$n = 17$], 0.43 g/mol; C2 [$n = 12$], 0.48 g/mol), remained elevated through day 29, and then declined (Supplementary Figure S3b). Predose serum felzartamab concentrations did not correlate with the felzartamab urine-to-creatinine ratio (Supplementary Figure S3c and S3d).

Immunologic Response

After 1 week of treatment with felzartamab (day 8), 22 of 25 patients (88.0%) in the EAS had reductions from baseline in anti-PLA2R titer (mean [SD] change, −40.0% [30.5%]), and the response rate was 44.0% (C1, $n = 7$ [46.7%]; C2, $n = 4$ [40.0%]), with 2 patients (8.0%) achieving ICR and 9 (36.0%) achieving IPR (Figure 2a; Supplementary Figures S4 and S5; Supplementary Table S2). Estimated median (95% confidence interval) time-to-first immunologic response ($n = 26$) was 0.49 (0.26–0.92) months (C1, 0.46 months [0.26–0.49]; C2, 0.49 months [0.26–not available]). At EOT (6 months), 20 of 26 patients (76.9%) had reductions from baseline in anti-PLA2R titer (mean [SD] change, −25.8% [109.0%]), and the response rate was 51.6% (C1, $n = 10$ [66.7%]; C2, $n = 5$ [45.5%]), with 6 patients (23.1%) achieving ICR and 9 (38.5%) achieving IPR (Figure 2b). At EOS (7 months after last felzartamab dose or last observation carried forward), 17 of 26 patients (65.4%) had reductions from baseline in anti-PLA2R titer (mean [SD] change, −17.3% [95.2%]), and the response rate was 53.8% (C1, $n = 9$ [60.0%]; C2, $n = 5$ [45.5%]), with 8 patients (30.8%) achieving ICR and 6 (23.1%) achieving IPR (Figure 2c). Of 15 patients in immunologic response at EOT, 12 (80.0%) were still responders at EOS (C1, $n = 8$; C2, $n = 4$), including 3 patients in C1 and 1 in C2 who improved from IPR to ICR (Figure 2d). In C1, patients with baseline anti-PLA2R titer 50 to 150 RU/ml, compared with >150 RU/ml, generally had higher rates of immunologic response at EOT (83.3% vs. 55.6%) and EOS (83.3% vs. 44.4%; Supplementary Table S3). In C2, there was no apparent difference in immunologic response by baseline anti-PLA2R titer.

The best immunologic response rate was 76.9% (95% confidence interval, 56.4%–91.0%) overall, 86.7% (59.5%–98.3%) in C1, and 63.6% (30.8%–89.1%) in C2 (Supplementary Table S4). A best result of ICR was achieved by 8 patients (30.8%) (C1, $n = 5$;

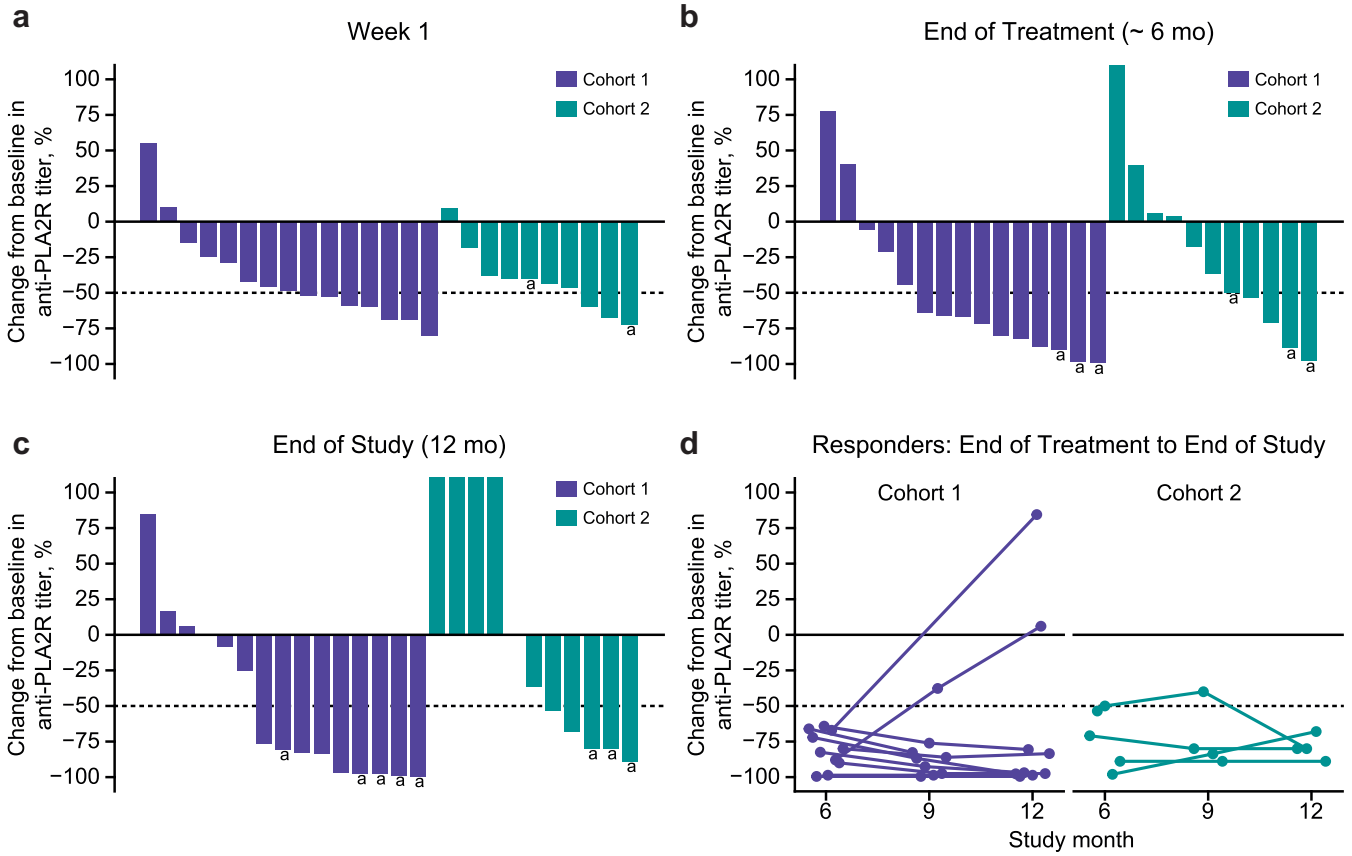

Figure 2. Change in anti-PLA2R titer. (a) Percentage change from baseline to week 1 in anti-PLA2R titer in cohorts 1 and 2. (b) Percentage change from baseline to EOT in anti-PLA2R titer in cohorts 1 and 2. (c) Percentage change from baseline to EOS in anti-PLA2R titer in cohorts 1 and 2. (d) Percentage change from baseline to EOT, month 9, and EOS in each patient who was a responder at EOT. Data in all panels are based on the EAS. For EOS evaluations, the median (range) day of last follow-up was 364 (141–393) days. EAS, efficacy analysis set; EOS, end of study; EOT, end of treatment; ICR, immunologic complete response; IPR, immunologic partial response; PLA2R, phospholipase A2 receptor; mo, months. Horizontal dotted lines indicate threshold for IPR (≥50% reduction from baseline in anti-PLA2R titer). [a]ICR at the specified time point.

C2, $n = 3$). A best result of IPR was achieved by 12 patients (46.2%) (C1, $n = 8$; C2, $n = 4$). Results were similar for the full analysis set (Supplementary Table S5).

Clinical Remission

Decreases in anti-PLA2R titer with felzartamab began before changes in proteinuria (24-hour UPCR) and serum albumin (Figure 3a and b, Supplementary Table S2). Estimated median (95% confidence interval) time to proteinuria remission was 12.2 (9.7–NA) months (C1, 12.2 months [9.4–NA]; C2, NA [2.8–NA]). At EOT using last observation carried forward, 14 of 26 patients (53.8%) (C1, $n = 9$; C2, $n = 5$) had decreases from baseline in 24-hour UPCR (mean [SD] change, −9.3% [50.5%]), with 4 (15.4%) achieving Prot-PR by EOT (C1, $n = 2$ [13.3%]; C2, $n = 2$ [18.2%]; Supplementary Figure S6; Supplementary Tables S6 and S7). At EOS using last observation carried forward, 17 of 26 patients (65.4%) (C1, $n = 11$; C2, $n = 6$) had decreases from baseline in 24-hour UPCR (mean [SD] change, −24.1% [45.3%]), with 9 (34.6%) achieving Prot-PR by EOS (C1, $n = 7$ [46.7%]; C2, $n = 2$ [18.2%]). All patients achieving Prot-PR remained in Prot-PR until EOS or last assessment. No patients achieved proteinuria complete remission.

There was a positive correlation between change from baseline in anti-PLA2R titer at 3 months and change from baseline in 24-hour UPCR at EOS in C1 ($r = 0.70$, $P = 0.004$) but not C2 ($r = 0.15$, $P = 0.664$; Supplementary Figure S7). Of 9 patients achieving Prot-PR at EOS (C1, $n = 7$; C2, $n = 2$), 8 (88.9%; C1, $n = 6$; C2, $n = 2$) were immunologic responders at 3 months, and 9 (100%; C1, $n = 7$; C2, $n = 3$) were immunologic responders at EOT.

At baseline, 29 of 31 patients (93.5%) (C1, $n = 17$; C2, $n = 12$) had serum albumin below the normal range (35–52 g/l). At EOT, 18 of 26 patients (69.2%) (C1, $n = 11$; C2, $n = 7$) had increases from baseline in serum albumin (mean [SD] change, 12.8% [17.9%]), with 5 patients (16.1%) (C1, $n = 3$; C2, $n = 2$) within the normal range. At EOS, 20 of 26 patients (76.9%) (C1, $n = 12$; C2, $n = 8$) had increases in serum albumin (mean [SD] change, 21.0% [26.1%]; Figure 3c,

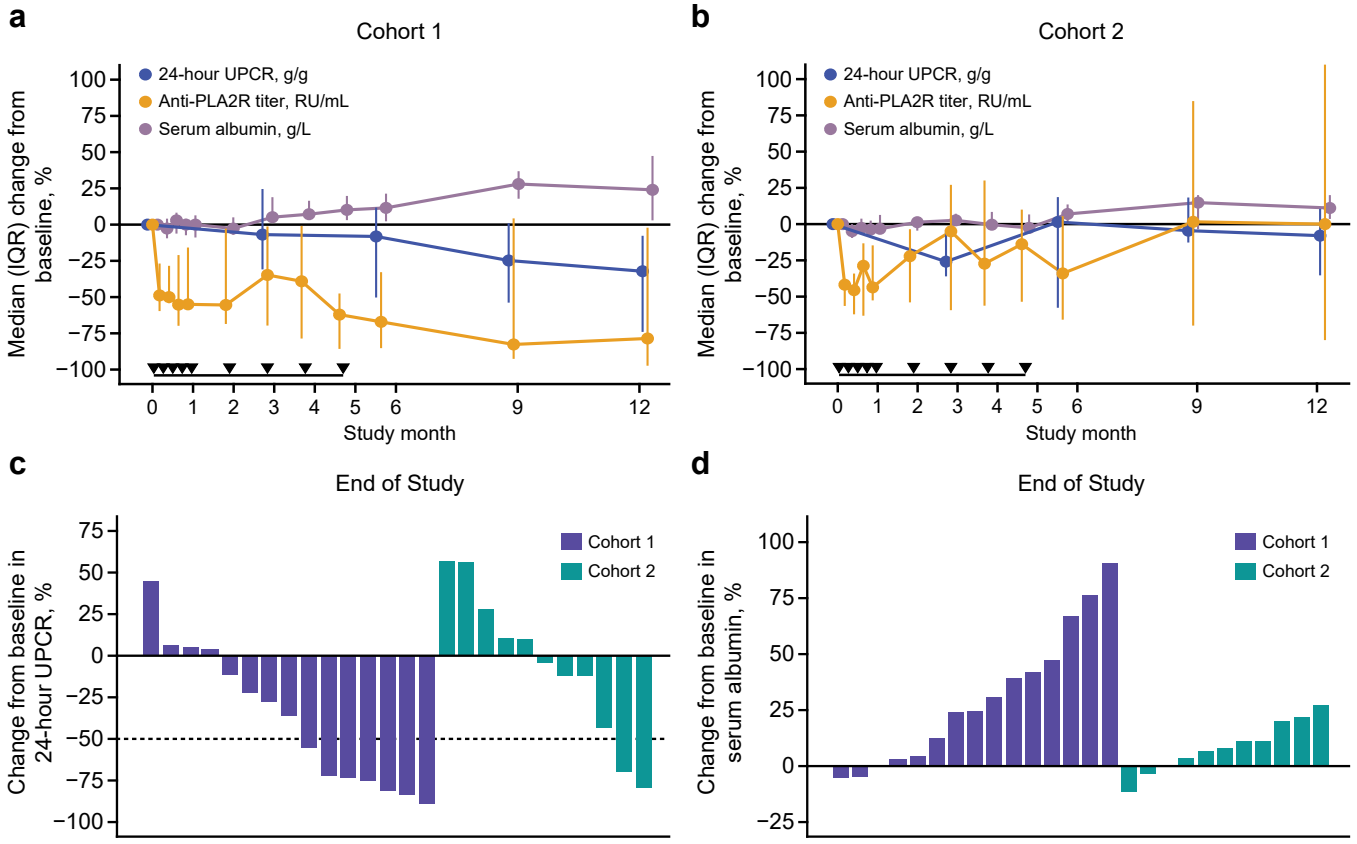

Figure 3. Change in albumin and 24-hour UPCR. (a and b) Comparison of median (± IQR) percentage change from baseline in 24-hour UPCR and serum albumin with median (± IQR) percentage change from baseline in anti-PLA2R titer in cohorts 1 and 2. (c) Percentage change from baseline to EOS in 24-hour UPCR in cohorts 1 and 2. The horizontal dotted line indicates threshold for proteinuria partial response (≥50% reduction from baseline in 24-hour UPCR). (d) Percentage change from baseline to EOS in serum albumin in cohorts 1 and 2. Data in all panels are based on the EAS. For EOS evaluations, the median (range) day of last visit was 364 (141–393) days for albumin and 363.5 (175–432) days for UPCR. Arrows indicate felzartamab infusions. EAS, efficacy analysis set; EOS, end of study; IQR, interquartile range; PLA2R, phospholipase A2 receptor; UPCR, urine protein-to-creatinine ratio.

Supplementary Figure S8; Supplementary Table S2), with 9 patients (34.6%) (C1, $n = 7$; C2, $n = 2$) within the normal range. Improvement from baseline to EOS in mean (SD) serum albumin was greater in C1 than in C2 (30.0% [30.2%] vs. 8.6% [11.5%]).

At baseline, 13 of 31 patients (41.9%) (C1, $n = 7$; C2, $n = 6$) had an eGFR <60 ml/min per 1.73 m^2. Mean eGFR generally remained stable throughout the study and increased from baseline to EOS among patients achieving Prot-PR ($n = 9$; mean [SD], 78.3 [20.2] vs. 66.9 [16.5] ml/min per 1.73 m^2) but decreased from baseline to EOS among patients who did not achieve Prot-PR ($n = 17$; mean [SD], 48.5 [23.9] vs. 55.4 [21.7] ml/min per 1.73 m^2; Supplementary Figures S9 and S10; Supplementary Table S2).

Health-related quality of life

Median baseline KDQOL-36 scores ($n = 30$) were lower in C2 than in C1 across all subscales; Figure 4). Treatment with felzartamab resulted in improvement across all KDQOL-36 subscales. In general, improvements in C1 continued from EOT to EOS, whereas improvements in C2 generally waned after EOT.

DISCUSSION

M-PLACE was a proof-of-concept study that assessed the safety and efficacy of the anti-CD38 monoclonal antibody felzartamab in patients with high-risk anti-PLA2R+ PMN. Felzartamab was generally tolerated and resulted in rapid partial and complete immunologic responses. Some patients among those with newly diagnosed or relapsed PMN had partial improvements in proteinuria and serum albumin, as well as quality of life. These results are noteworthy considering the predominantly severe disease of the enrolled population. Compared with other studies of ISTs for PMN, baseline median anti-PLA2R titers in M-PLACE (C1, 182.0 RU/ml; C2, 122.0 RU/ml) were greater and baseline mean eGFR was lower.[13,15,25,26,39] Although some patients in C1 had baseline anti-PLA2R titers <150 RU/ml, which has recently been considered as an appropriate threshold for high-risk PMN, baseline titers of

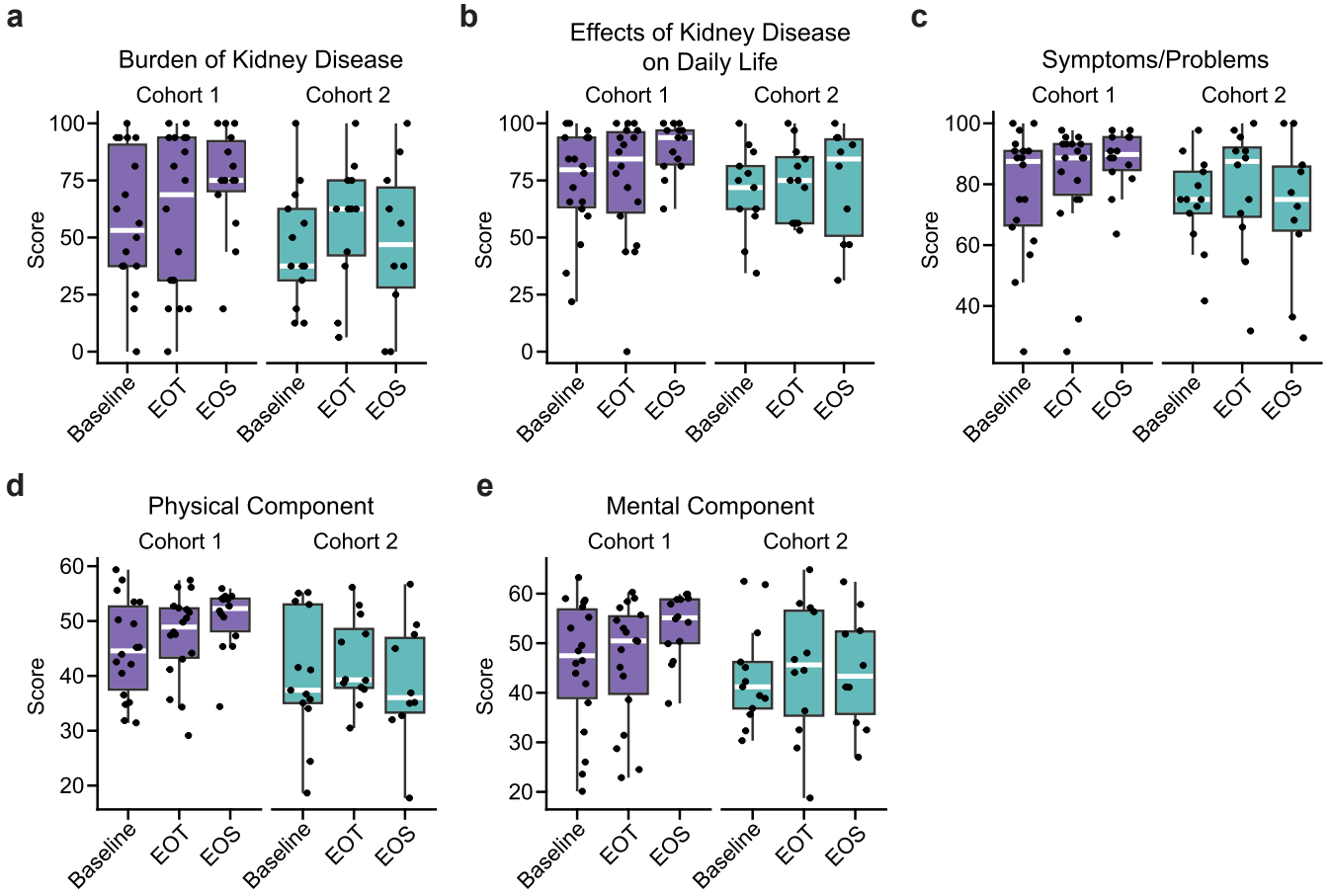

Figure 4. Change from baseline in health-related quality of life per KDQOL-36. (a) Change from baseline in burden of kidney disease score, (b) effects of kidney disease on daily life score, (c) symptoms/problems score, (d) physical component score, and (e) mental component score. Horizontal white lines represent the medians. Box ends represent the interquartile ranges. Vertical lines represent the ranges. Dots represent individual patients. EOS, end of study; EOT, end of treatment; KDQOL-36, Kidney Disease Quality of Life 36 Survey.

these patients exceeded 50 RU/ml—the 2021 Kidney Disease: Improving Global Outcomes threshold for high-risk PMN at the time M-PLACE was conducted.[16]

TEAEs were generally mild or moderate in severity. Consistent with the phase 1/2a first-in-human study of felzartamab in patients with multiple myeloma,[40] IRRs in M-PLACE were nearly all mild or moderate and occurred during the first infusion and resolved with medication and interruption or withdrawal of felzartamab. IRRs were common in studies assessing rituximab for PMN and idiopathic membranous nephropathy and anti-CD38 therapies for multiple myeloma.[15,41–43] Allergic reactions, grade ≥3 infection, and grade ≥3 neutropenia in M-PLACE were infrequent, and there was no evidence of prolonged or clinically meaningful decline in total IgG by felzartamab. Mean serum IgG quickly recovered to above baseline levels, and humoral immunity to SARS-Cov-2 vaccination was preserved after felzartamab infusions.[44] The only infection adverse event was grade 4 treatment-emergent SARS-Cov-2 that was not considered treatment-related. Peripheral edema, which is a common symptom of PMN and nephrotic syndrome,[1,3] was more frequent among patients in C2, who had greater baseline proteinuria and poorer outcomes than patients in C1.

Anti-PLA2R titer decreases began 1 week after the first infusion of felzartamab and remained decreased thereafter in some patients (predominantly in C1), with total (ICR + IPR) immunologic response rates of approximately 50% at EOT and EOS. Immunologic responses occurred regardless of baseline titer. However, patients in C1 with baseline anti-PLA2R titers of 50 to 150 RU/ml, compared with >150 RU/ml, had greater immunologic response rates after 6 months of treatment (83.3% vs. 55.6%) and at EOS (83.3% vs. 44.4%), potentially due to inadequate plasma cell depletion and the need for more intensive felzartamab dosing in patients with the highest anti-PLA2R titers. In clinical studies of rituximab for PMN, immunologic responses were more likely to occur in patients with lower baseline anti-PLA2R titers.[15,41]

Notably, compared with patients with refractory PMN (C2), patients with newly diagnosed or relapsed PMN (C1) had greater total rates of immunologic response (86.7% vs. 63.6%) and partial proteinuria remission before or at EOS (46.7% vs. 18.2%). The

difference in immunologic response between cohorts will require further investigation but may be due to the refractory nature of the disease among patients in C2. Patients with refractory PMN may require combined or sequential anti-CD38 and anti-CD20 IST. Indeed, a patient with multidrug-resistant PMN was reported to achieve partial clinical remission with rituximab following transient benefit with the anti-CD38 monoclonal antibody daratumumab.[45]

As expected,[6,13,15] proteinuria resolution in both cohorts was delayed by several months after felzartamab-induced resolution of immunologic disease. Nonetheless, neither cohort had a high rate of proteinuria remission. A longer duration of follow-up, particularly for C1, may have resulted in more complete proteinuria remission. Given the greater duration and refractory nature of the disease, patients in C2 may have developed nephrosclerosis and may never have achieved complete resolution of proteinuria; however, this requires biopsy confirmation.

Felzartamab serum concentrations were similar between cohorts and were consistent with those expected for a monoclonal antibody. Urinary concentrations, which were measured given the proteinuric nature of PMN, were higher in C2 than in C1, potentially reflecting the comparatively worse proteinuria observed in C2. Nonetheless, urinary felzartamab excretion was low (0–1.2 g/mol), and there was no apparent relationship between felzartamab urine-to-creatinine ratio and felzartamab serum concentrations.

Improvements in KDQOL-36 mental, physical, burden of kidney disease, symptoms or problems, and effects on daily life subscales were observed through EOS in C1 and at EOT in C2. The improvements in median KDQOL-36 scores generally exceeded 3 to 5 points, which is considered the threshold for clinically meaningful improvement in health-related quality of life in the dialysis setting.[46]

The strengths of the M-PLACE design include enrollment of patients with high-risk PMN that was often relapsed and/or refractory to prior IST and the routine evaluation of anti-PLA2R titers, which enabled evaluation of the relationship between improvement in anti-PLA2R titer and improvement in proteinuria. In addition, due to the timing of the study, strength of the response to SARS-CoV-2 vaccination during felzartamab treatment was investigated.[44] Limitations of the study include the short duration of follow-up, particularly considering that complete remission of PMN often requires longer than 1 year of treatment, and the lack of retreatment, which may be needed among high-risk populations. Furthermore, the Kidney Disease: Improving Global Outcomes anti-PLA2R titer threshold (50 RU/ml) at the time this study was conducted is lower than the threshold of 150 RU/ml that some now consider more appropriate for classifying high-risk PMN. The NewPLACE study (ClinicalTrials.gov, NCT04733040) evaluated alternative felzartamab dosing regimens and felzartamab retreatment in patients with anti-PLA2R+ PMN.

In summary, in this study of patients with moderate to high-risk anti-PLA2R+ PMN, felzartamab had a tolerable safety profile and did not result in a clinically meaningful decline in total IgG. Regardless of baseline anti-PLA2R titer, felzartamab rapidly induced partial and complete immunologic responses. Some patients, particularly among those with newly diagnosed or relapsed PMN, exhibited partial decreases in proteinuria and improvements in serum albumin and quality of life. The tolerable safety profile and evidence of efficacy with felzartamab, along with the ability of patients to mount a humoral response to vaccination,[44] warrant further investigation of felzartamab in a sequential or combination therapy in PMN. Future studies may assess the efficacy of felzartamab in patients in broader PMN patient populations.

DISCLOSURE

BHR has been a paid consultant for Human Immunology Biosciences, Inc. and his institution (The Ohio State University Wexner Medical Center) has received support for this clinical study and manuscript from Human Immunology Biosciences, Inc. PMR has been a paid consultant for Human Immunology Biosciences, Inc. in the past 36 months; has received consulting fees from Human Immunology Biosciences, Inc., Alexion, and PureSpring; and has received payment for academic lectures in the US, EU, and Asian universities. JFMW has received author royalties from UpToDate; has received consulting fees from Novartis, Travere, Sobi, and Human Immunology Biosciences, Inc; has received honoraria from Otsuka; and has participated on an advisory board for CONVINCE the study. SGA has received grants and consulting fees from Human Immunology Biosciences, Inc.; has participated in an advisory board for Human Immunology Biosciences, Inc.; and has received support for this manuscript from Human Immunology Biosciences, Inc. IA has received salary support (paid to The Ohio State University Wexner Medical Center) for her contract with George Clinical as a National Leader on Spartacus; has received consulting fees from Aurinia, Sanofi, and Travere; has received honoraria from Travere; has participated in an advisory board for MorphoSys Ag; and is a member of the SCM24 Program Committee. SHH has received consulting fees from George Clinical for the role of National Leader in the Otsuka-sponsored clinical trial. JSD is an employee of

and owns stock in Human Immunology Biosciences, Inc., and is employed by Monograph Capital. HNG is an employee of and owns stock in Human Immunology Biosciences, Inc.; was an employee of and owned stock in Arcus Biosciences; and has received consulting fees from Arcus Biosciences. UDP is an employee of and owns stock in Human Immunology Biosciences, Inc., and has served as the chair of the Kidney Health Initiative. PTM is an employee of and owns stock in Human Immunology Biosciences, Inc. JJ-L was an employee of and owned stock in MorphoSys AG when this study was conducted. NF is an employee of and owns stock in MorphoSys AG. RB is an employee of and owns stock in MorphoSys AG and has patents related to felzartamab. SH is an employee of and owns stock in MorphoSys AG; owns stock in Human Immunology Biosciences, Inc.; is a coinventor of several patent applications for the felzartamab program; and has received patent-based royalties for the felzartamab program. BS has received honoraria for lectures from AstraZeneca, Vifor Pharma, and Janssen Cilag and has participated on an advisory board for MorphoSys AG and Boehringer. PZ declared no competing interests

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DATA AVAILABILITY STATEMENT

Data supporting this study are not publicly available due to the ongoing nature of the clinical development program. Data may be made available upon reasonable request 18 months after the final clinical study report has been completed and, as appropriate, once the regulatory review of the indication or drug has completed, whichever is later.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation and critical review of the manuscript and approved the final version for submission. BHR and PMR contributed to the study design, data analysis, and data interpretation. JFMW contributed to the study design and data interpretation. SGA, PZ, SHH, JSD, HNG, UDP, JJ-L, and NF contributed to the data interpretation. IA contributed to the recruitment into the study. PTM contributed to statistical analysis and data interpretation. RB contributed to the study conceptualization, data analysis, data interpretation, project administration, study supervision, and result visualization. SH contributed to the study conceptualization, data curation, formal analysis, methodology, project administration, study supervision, and result visualization. BS contributed to the data analysis and data interpretation.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Patient disposition during the study.

Figure S2. On-study changes in hematologic parameters.

Figure S3. Summary of felzartamab serum and urine pharmacokinetics.

Figure S4. Median (interquartile range) change from baseline in serum anti-PLA2R titer by visit and cohort.

Figure S5. Change from baseline in serum anti-PLA2R titer in individual patients in the efficacy analysis set.

Figure S6. Change from baseline in 24-hour urine protein-to-creatinine ratio in individual patients in the efficacy analysis set.

Figure S7. Correlation between change from baseline to 3 months in serum anti-PLA2R titer and change from baseline to end-of-study in 24-hour urine protein-to-creatinine ratio in the efficacy analysis set.

Figure S8. Change from baseline in serum albumin in individual patients in the efficacy analysis set.

Figure S9. Summary of estimated glomerular filtration rate in the efficacy analysis set.

Figure S10. Change from baseline in estimated glomerular filtration rate in individual patients in the efficacy analysis set.

Table S1. Demographics and baseline disease characteristics for the efficacy analysis set.

Table S2. Change from baseline in anti-PLA2R titer, urine protein-to-creatinine ratio, albumin, and estimated glomerular filtration rate in the efficacy analysis set.

Table S3. Summary of immunologic response stratified by baseline anti-PLA2R titer in the efficacy analysis set.

Table S4. Summary of best immunologic response in the efficacy analysis set.

Table S5. Summary of best immunologic response in the full analysis set.

Table S6. Summary of proteinuria remission in the efficacy analysis set.

Table S7. Summary of overall proteinuria remission in the full analysis set.

STROBE Statement.

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