Phase 1 Study of Plamotamab, a Bispecific CD20xCD3 T-cell Engager, in Adult Patients With Rheumatoid Arthritis: Interim Results

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BACKGROUND

- B cells are important in rheumatoid arthritis (RA) pathogenesis through antigen presentation, pro-inflammatory cytokine secretion, and production of rheumatoid factor and anti-citrullinated protein antibodies.
- The efficacy of CD20-directed B-cell depletion with rituximab in the treatment of RA has validated B cells as a therapeutic target in RA. However, the extent of B-cell depletion in tissues, such as bone marrow and lymph nodes, is often incomplete, which may affect the overall therapeutic response and remains a limitation of conventional anti-CD20 monoclonal antibodies.
- Bispecific T-cell engagers may address these limitations in the treatment of RA by deeper B-cell depletion that could help "reset" the immune system for patients by dampening immune responses.

Figure 1: Plamotamab, a CD20 x CD3 bispecific T-cell engager

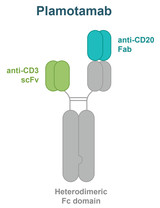
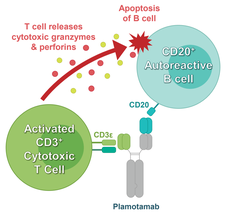


Figure 2: Plamotamab mechanism of action



- Plamotamab is a CD20xCD3 bispecific T-cell engager that redirects cytotoxic T cells toward CD20-expressing B cells, resulting in potentially deeper B-cell depletion in the tissues of interest compared to rituximab.
- In a completed phase 1 study in relapsed/refractory non-Hodgkin lymphoma (XmAb13676-01; NCT02924402), plamotamab demonstrated significant clinical activity in 154 heavily pretreated lymphoma patients, including those with prior CAR-T treatment, with an acceptable safety profile, including manageable cytokine release syndrome (CRS), and expected pharmacodynamic effects (Patel, 2022; Riedell, 2024).
- Given the established role of pathogenic B cells in RA and the potential for deeper and more rapid B-cell depletion through T-cell engagement, RA represents a compelling indication for investigation of CD20 T-cell engager therapy.

STUDY DESIGN

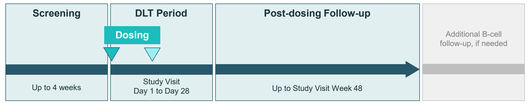
Objective

The objective of this Phase 1 study is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary clinical activity of plamotamab administered subcutaneously (SC) in participants with RA with continued disease activity despite prior treatment with conventional synthetic (csDMARD), targeted synthetic (tsDMARD), or biologic disease-modifying antirheumatic drugs (bDMARD).

Methods

- This ongoing global, multicenter, open-label phase 1 study includes dose-escalation/expansion cohorts in adults with active RA (NCT07230353).
- A stepwise dose regimen with one or more priming doses followed by ≥ 1 target dose is being assessed to optimize the safety profile (including mitigating the risk of CRS) and maintain cytotoxic activity against pathogenic B cells.
- Enrolled participants are required to be seropositive, age ≥ 18 years, and have had an inadequate or loss of response or intolerance to ≥ 1 csDMARD.
- The primary endpoint of the study is safety and tolerability of plamotamab.
- Exploratory endpoints include evidence of efficacy.

Figure 3: Study Schema



- Subcutaneous plamotamab with 48-hour hospitalization after each dose of plamotamab
- Dose Levels 1 to 3: single-dose administration cohorts
- Dose Level 4: two doses administered
- The highest dose administered in any subsequent cohort does not exceed the highest dose of the previous cohort by more than one-half logarithm

RESULTS

Baseline Demographics

Table 1: Baseline Demographics

	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Overall
N	1	1	3	4*	9
Age, mean (SD), years	68.0 (NA)	60.0 (NA)	65.7 (1.5)	58.5 (17.9)	62.1 (11.7)
Female, n (%)	1 (100)	0	3 (100)	4 (100)	8 (89)
Race, n (%) White	1 (100)	1 (100)	3 (100)	4 (100)	9 (100)
Ethnicity, n (%) Not Hispanic or Latino	1 (100)	1 (100)	3 (100)	4 (100)	9 (100)
Disease Duration, mean (SD), years	19.3 (NA)	19.4 (NA)	16.0 (15.0)	14.6 (10.7)	16.1 (10.1)
Baseline DAS28-ESR, mean (SD)	5.2 (NA)	5.1 (NA)	6.6 (0.2)	6.9 (0.7)	6.4 (0.9)
Baseline DAS28-ESR category, n (%) ≤ 3.2 > 3.2 and ≤ 5.1 > 5.1	 0 1 (100)	 0 0	 0 3 (100)	 0 4 (100)	 0 8 (89)
Baseline CDAI, mean (SD)	25.5 (NA)	25.0 (NA)	39.0 (7.7)	40.1 (7.5)	36.4 (8.7)
Baseline tender joint count (out of 28 joints), mean (SD)	10.0 (NA)	10.0 (NA)	18.3 (7.5)	16.0 (3.9)	15.4 (5.5)
Baseline swollen joint count (out of 28 joints), mean (SD)	7.0 (NA)	5.0 (NA)	8.7 (1.5)	8.0 (1.2)	7.8 (1.6)
Positive for RF, n (%)	1 (100)	0	2 (67)	2 (50)	5 (56)
Positive for ACPA, n (%)	1 (100)	1 (100)	3 (100)	4 (100)	9 (100)
Baseline concomitant RA therapy, n (%) **Any csDMARDs** **Methotrexate** Mean weekly MTX dose, mg (range) **Leflunomide** **Systemic corticosteroids** Mean CS dose, mg (range) **NSAIDs**	 1 (100) 1 (100) 10 (NA) 0 1 (100) 5 (NA) 1 (100)	 1 (100) 1 (100) 15 (NA) 0 0 0 1 (100)	 3 (100) 3 (100) 16.7 (15-20) 0 3 (100) 5 (5-5) 2 (67)	 4 (100) 3 (75) 13.3 (10-20) 1 (25) 2 (50) 5 (5-5) 1 (25)	 9 (100) 8 (89) 14.4 (10-20) 1 (11) 6 (67) 5 (5-5) 5 (56)

ACPA: anti-citrullinated protein antibody; CDAI: Clinical Disease Activity Index; CS: corticosteroid (prednisone equivalent); csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28-ESR: disease activity score with 28 joints and erythrocyte sedimentation rate; MTX: methotrexate; NA: not applicable; NSAIDs: nonsteroidal anti-inflammatory drugs; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation

* One participant in Dose Level 4 received only a single dose of plamotamab due to discontinuation after a serious TEAE

Safety

Table 2: Treatment-Emergent Adverse Events (TEAEs)

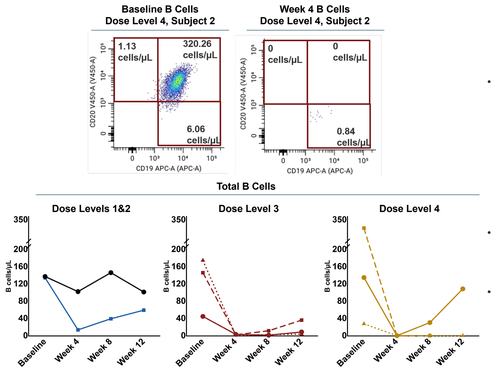
	Overall (N=9)
Number of participants with ≥ 1 TEAE	9 (100.0)
Number of participants with Grade ≥ 3 TEAE	4 (44.4)
Number of participants with serious TEAE	2 (22.2)
Number of participants with TEAE leading to discontinuation of study treatment	1 (11.1)
Any TEAE occurring in ≥ 3 participants: **Pyrexia** **Injection site erythema** **Neutrophil count decrease** **Neutrophil count increase**	 5 (55.6) 4 (44.4) 3 (33.3) 3 (33.3)

TEAE: treatment-emergent adverse event

- Seven Grade ≥ 3 adverse events were reported across 4 participants: neutrophil count decrease (2 events), lymphocyte count decrease, platelet count decrease, white blood cell count decrease, pyelonephritis, and sepsis.
- Two participants experienced serious TEAEs. One participant with a medical history of nephrolithiasis developed nephrolithiasis complicated by pyelonephritis with subsequent sepsis and hospitalization after receiving the first dose of plamotamab in Dose Level 4. This event was deemed unrelated to study drug. Another participant treated with 2 doses of plamotamab in Dose Level 4 experienced Grade 1 CRS and extended inpatient monitoring.
- No events of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) were observed.

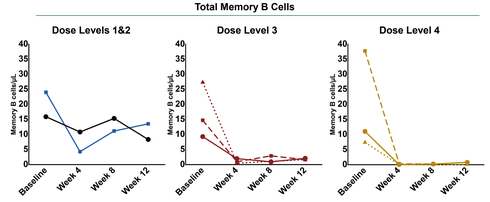
B Cells

Figure 4: Total B Cells (CD3⁻CD19⁺CD20⁺)



- Flow scatter plot analysis - plots from Dose Level 4 Subject 2, showing B cells present at baseline but were not detected at Week 4.
- Early signs of B-cell reconstitution emerged, in individual participants ranging from Dose Levels 2-4 at Week 12 and during Follow-up
- Memory B cells (CD27⁺IgD⁻) were rapidly depleted in the higher dose participants (Dose Level 4) with limited reconstitution through Week 12 and follow-up even when total B-cell counts began to recover.
- This suggests that early-reconstituting peripheral B cells are predominantly naive, with memory B-cell recovery presumably lagging behind.

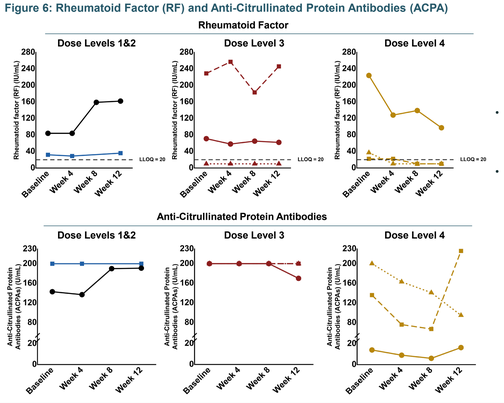
Figure 5: Memory B Cells (CD3⁻CD19⁺CD20⁺CD27⁺IgD⁻)



- Dose Level 1, Subject 1
- Dose Level 2, Subject 1
- Dose Level 3, Subject 1
- Dose Level 3, Subject 2
- Dose Level 3, Subject 3
- Dose Level 4, Subject 1
- Dose Level 4, Subject 2
- Dose Level 4, Subject 3

Disease-Related Biomarkers

Figure 6: Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA)



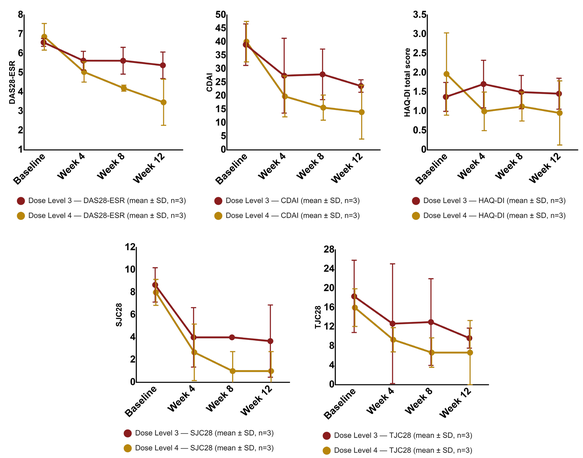
- At Dose Level 4, all participants experienced a decrease in RF levels, with 2 reaching levels below the lower limit of quantification (LLOQ)
- At Dose Level 4, all participants experienced a decrease in ACPA levels, but 2 experienced a rebound between Weeks 8 and 12

- Dose Level 1, Subject 1
- Dose Level 2, Subject 1
- Dose Level 3, Subject 1
- Dose Level 3, Subject 2
- Dose Level 3, Subject 3
- Dose Level 4, Subject 1
- Dose Level 4, Subject 2
- Dose Level 4, Subject 3

Efficacy

- Baseline mean DAS28-ESR and CDAI were indicative of moderate to high disease activity in all 4 cohorts (Table 1).
- Overall, clinical improvement at Week 12 was observed with Dose Levels 3 and 4.
- Dose Levels 3 and 4 showed moderate to good response at Week 12 in DAS28-ESR, with the highest response observed with Dose Level 4 (mean change from baseline -1.2 and -3.3, respectively).
- Dose Levels 3 and 4 showed clinically meaningful decreases in CDAI at Week 12, with more decrease observed with Dose Level 4 (mean change from baseline -15.3 and -25.0 [> 50%], respectively).
- Improvement in HAQ-DI > 0.22 was observed at Dose Level 4 at Week 12.
- Joint count improvements were also observed in all cohorts at Week 12, and swollen joint count showed complete resolution at Week 12 in 1 participant in Dose Level 3 and 2 participants in Dose Level 4.

Figure 7: Dose Level 4: Disease Activity: Disease Activity Score with 28 joints and erythrocyte sedimentation rate (DAS28-ESR), Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire Disability Index (HAQ-DI), Tender Joint Count 28 joints (TJC28), Swollen Joint Count 28 joints (SJC28)



CONCLUSIONS

- This is the first evaluation of plamotamab in RA to assess whether CD20-targeted T-cell engagement can achieve clinically meaningful immunomodulation with an acceptable safety profile.
- Single SC doses of plamotamab were well tolerated with an acceptable safety profile, while exhibiting deep B-cell depletion.
- Multiple SC doses of plamotamab were also well tolerated with a longer duration of deep B-cell depletion.
- One of the 9 participants who received plamotamab developed Grade 1 CRS; no ICANS was observed.
- Deeper and longer duration of B-cell depletion was associated with more effective decrease of disease activity.
- The multiple-dose phase of the study is ongoing.

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Disclosures: D.C. none; N.I., J.M., V.M., S.M., J.K. and M.O. are employees and shareholders of Xencor, Inc.; R.F. has received consulting fees from Xencor, Inc.

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Riedell PA, et al. Poster presented at: 66th ASH Annual Meeting and Exposition; December 9, 2024. Poster 4497.

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