Poster #2293

CLN-978, a CD19xCD3 T Cell Engager, Leads to Rapid and Deep B Cell Depletion *In Vitro* and *In Vivo*, Supporting Clinical Development Across Multiple Autoimmune Diseases

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BACKGROUND

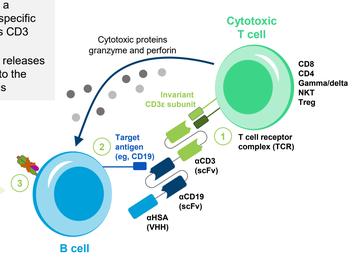
- B cell depleting therapies targeting CD19 have shown benefit in a range of autoimmune diseases, including systemic lupus erythematosus (SLE)[1], Sjögren's disease (SjD)[2], and rheumatoid arthritis (RA)[3]
- T cell engagers (TCEs) offer off-the-shelf convenience and predictable pharmacokinetic/pharmacodynamic (PK/PD) properties of monoclonal antibodies, as well as potential to achieve deep B cell depletion similar to chimeric antigen receptor (CAR) T cell therapy[4,5] (**Figure 1**)

Figure 1. TCEs: protein constructs engineered to redirect T cells to eliminate cells, such as B cells, expressing a specific cell surface target[6]

HOW T CELL ENGAGERS WORK

- Bispecific TCEs are designed to co-engage a cytotoxic T cell and a target cell by binding specific cell surface molecules on each cell, such as CD3 epsilon on T cells and CD19 on B cells
- The CD3 binding activates the T cell, which releases cytotoxic proteins granzyme and perforin into the CD19 positive cell, leading to target cell lysis

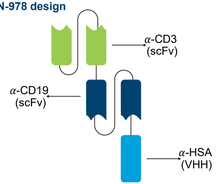
1. **Do not require a specific T cell receptor**
2. **Can make any T cell recognize a surface antigen at low target density**
3. **Do not require MHC class I and peptide antigen (No immune escape by loss of MHC)**



CLN-978: NOVEL CD19 x CD3 T CELL ENGAGER

- Comprised of tandemly arranged CD19- and CD3-binding single-chain fragment variable domains and a single-domain albumin binder for serum half-life extension (**Figure 2**)
- Picomolar affinity (very high) for CD19 and nanomolar affinity (moderate) for CD3
- Administered via subcutaneous (SC) injection
- In a Phase 1, first-in-human study (NCT05879744), patients with B cell non-Hodgkin lymphoma received a starting dose of 30 micrograms (µg) SC weekly, achieving a favorable safety profile in 3 of 3 patients and a complete metabolic response in 1 patient[7]

Figure 2. CLN-978 design



Objective

- Assess the PD and efficacy of CLN-978 in disease-relevant preclinical models

METHODS

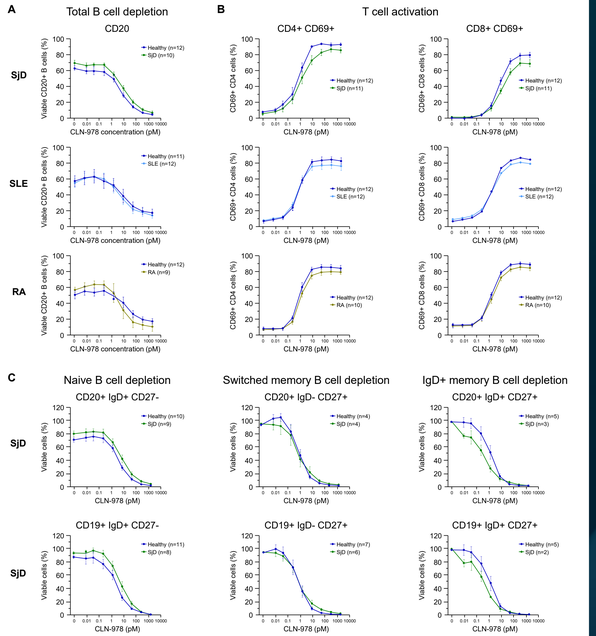
- *In vitro* studies: Peripheral blood mononuclear cells (PBMCs) from healthy donors or patients with SjD, SLE, or RA were cultured with varying concentrations of CLN-978 for 48 hours followed by flow cytometry analysis
- Non-human primates: CLN-978 was administered to cynomolgus monkeys as 4 weekly SC doses of 10–100 µg/kg
  - Peripheral blood and tissues (lymph nodes, spleen, and bone marrow) were assessed for B cell depletion by flow cytometry and quantitative immunohistochemistry (QIHC), respectively
- Mouse model of SLE: NOD scid gamma (NCG) mice engrafted with SLE-derived PBMCs were injected with PBS or CLN-978 (30 µg/kg) on days 7, 14, and 21, followed by blood and tissue analysis on day 28

KEY TAKEAWAYS

- **In this study, we demonstrate the PD activity and therapeutic potential of CLN-978 in disease-relevant preclinical models**
- **In PBMCs from healthy donors and patients with SjD, SLE, and RA, a similar dose-dependent B cell depletion was observed with CLN-978**
- **In a humanized mouse model of SLE, CLN-978 had strong PD activity in the periphery and eliminated deposition of pathogenic anti-DNA antibodies in the kidney**
- **In cynomolgus monkeys treated with CLN-978, robust B cell depletion was observed in peripheral blood and in lymph nodes, spleen, and bone marrow**
- **This deep B cell depletion in both peripheral blood and tissue, along with clinical data in patients with B cell non-Hodgkin lymphoma, supports broad development of CLN-978 across autoimmune diseases**
- **Phase 1b studies of CLN-978 are ongoing in patients with SjD, SLE, or RA**

IN VITRO STUDIES WITH PBMCs FROM PATIENTS WITH SjD, SLE, OR RA

Figure 3. CLN-978 induced similar B cell depletion and T cell activation in PBMCs across patients with autoimmune disease and healthy donors

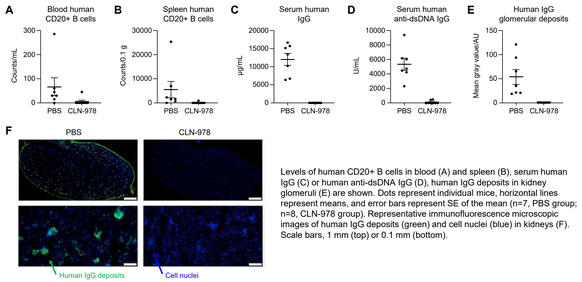


B cells and T cells were analyzed by flow cytometry and normalized to PBMC-only control. All analyzed cell populations have >500 events. Error bars denote standard error of the mean.

HUMANIZED MOUSE MODEL OF SLE

- In immunodeficient NCG mice engrafted with PBMCs from patients with SLE, CLN-978 treatment depleted human B cell populations in blood and spleen, reduced human immunoglobulin G (IgG) and anti–double-stranded (ds) DNA IgG serum levels, and abrogated human IgG deposition in kidney glomeruli compared with controls (**Figure 4**)

Figure 4. CLN-978 had strong PD activity in NCG mice engrafted with PBMC from patients with SLE

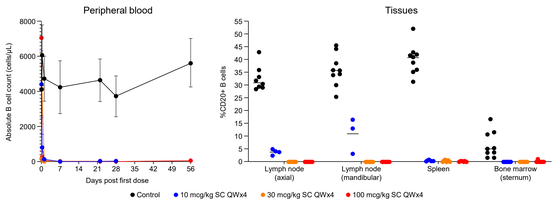


Levels of human CD20+ B cells in blood (A) and spleen (B), serum human IgG (C) or human anti-dsDNA IgG (D), human IgG deposits in kidney glomeruli (E) are shown. Dots represent individual mice, horizontal lines represent means, and error bars represent SE of the mean (n=7, PBS group; n=8, CLN-978 group). Representative immunofluorescence microscopic images of human IgG deposits (green) and cell nuclei (blue) in kidneys (F). Scale bars, 1 mm (top) or 0.1 mm (bottom).

NON-HUMAN PRIMATE STUDIES

- Cynomolgus monkeys treated with 4 weekly SC administrations of CLN-978 with doses ranging from 10 to 100 µg/kg showed the following:
  - B cell depletion in peripheral blood (**Figure 5A**)
  - Dose-related B cell depletion in lymph nodes, spleen, and bone marrow (**Figure 5B**)
  - Well tolerated at all dose levels during the treatment period

Figure 5. SC administration of CLN-978 induced B cell depletion in tissues of cynomolgus monkeys



ONGOING PHASE 1B CLINICAL STUDIES OF CLN-978

- Phase 1b studies of CLN-978 are currently being conducted in patients with SjD (**Figure 6**), SLE (**Figure 7**), or RA (**Figure 8**)

Figure 6. CLN-978-SJ-101 study schema (NCT07041099)

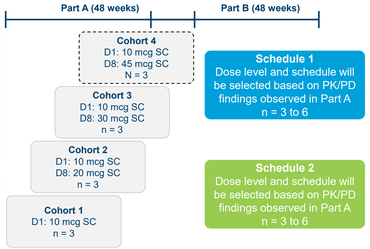


Figure 7. CLN-978-SLE-101 study schema (NCT06613360)

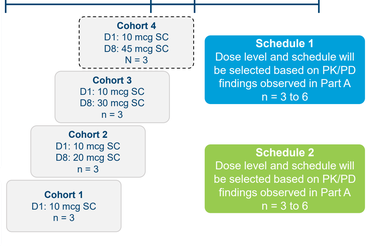
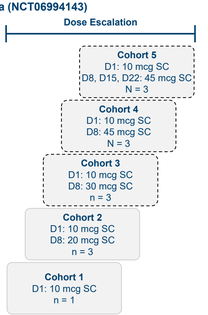


Figure 8. CLN-978-RA-101 study schema (NCT06994143)



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DISCLOSURES

EI, **KS**, **TS**, **JSM**, **JJ**, **YZ**, **SW**, and **AGS** are employees of Cullinan Therapeutics and hold stocks and stock options in the company.

ABBREVIATIONS

ACR, American College of Rheumatology; ANA, antinuclear antibody; AU, arbitrary unit; CAR, chimeric antigen receptor; csDMARD, conventional DMARD; D1, day 1; D8, day 8; ; D15, day 15; D22, day 22; DAS28-ESR, Disease Activity Score-28 with erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; dsDNA, double-stranded DNA; ESSDAI, EULAR Sjögren's syndrome disease activity index; EULAR, European Alliance of Associations for Rheumatology; HSA, human serum albumin; IgG, immunoglobulin G; MHC, major histocompatibility complex; NCG, NOD scid gamma; NKT, natural killer T cell; PBMC, peripheral blood mononuclear cell; PBS, phosphate-buffered saline; PD, pharmacodynamic; PK, pharmacokinetic; pMHC, peptide major histocompatibility complex; QIHC, quantitative immunohistochemistry; RA, rheumatoid arthritis; SC, subcutaneous; scFv, single-chain variable fragment; SE, standard error; SjD, Sjögren's disease; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; SoC, standard of care; TCE, T cell engager; TCR, T cell receptor complex; Treg, regulatory T cell; tsDMARD, targeted synthetic DMARD; µg, microgram; VHH, variable domain of the heavy chain.

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