Poster #0003

CLN-978, a CD19-directed T-cell engager (TCE), leads to rapid and deep B-cell depletion and has broad potential for development in autoimmune diseases

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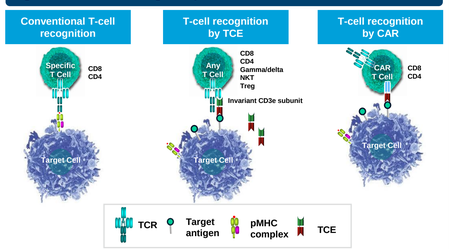
BACKGROUND

- Chimeric antigen receptor T-cell (CAR T) therapy targeting CD19 can induce profound B-cell depletion, potential immune reset and repopulation of naive B cells, and long-lasting clinical responses in patients with systemic lupus erythematosus (SLE)[1]
- However, the CAR-T modality is associated with significant safety risks and logistical challenges[2]
- T-cell engagers (TCEs) are protein therapeutics that redirect T cells to lyse antigen-expressing target cells (**Figure 1**)
- CD19-targeted TCEs have the potential to induce B-cell depletion with potentially better safety than CAR-T therapy and off-the-shelf convenience[2,3]

Figure 1: T-cell redirecting therapies

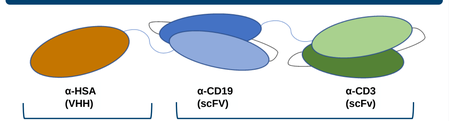


CAR, chimeric antigen receptor; NKT, natural killer T cell; pMHC, peptide major histocompatibility complex; TCE, T-cell engager; TCR, T-cell receptor complex; Treg, regulatory T cell

CLN-978: NOVEL CD19 x CD3 T-CELL ENGAGER

- CLN-978 is a TCE with binding domains for CD19, CD3, and serum albumin (for extended half-life) that can be administered subcutaneously (SC; **Figure 2**)[4]
- Here, we report preclinical and clinical data characterizing the activity of CLN-978

Figure 2: CLN-978 design[3]



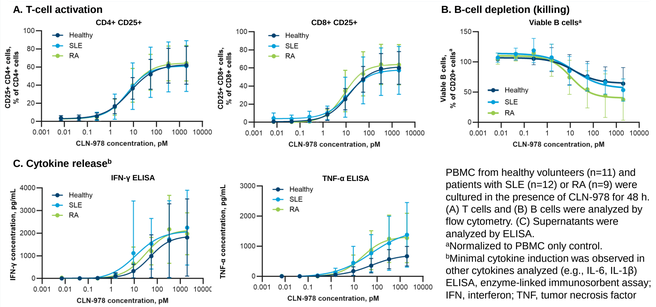
HSA, human serum albumin; scFv, single-chain variable fragment; VHH, variable domain of the heavy chain

PRECLINICAL DATA SHOW ROBUST B-CELL DEPLETION

In vitro, CLN-978 induced T-cell activation, B-cell killing, and cytokine production in human peripheral blood mononuclear cells (PBMCs)

- In vitro, CLN-978 induced relatively similar T-cell activation, B-cell killing, and cytokine production in PBMCs from healthy volunteers and patients with SLE or rheumatoid arthritis (RA) (**Figure 3**)
- These results are similar to those observed with CLN-978 in vitro models of NHL (Meetze et al, 2023), suggesting that the B-cell depletion and cytokine window observed in patients with NHL may translate to patients with SLE, RA, and other autoimmune diseases

Figure 3: CLN-978 showed activity in PBMCs from healthy donors and patients with SLE or RA

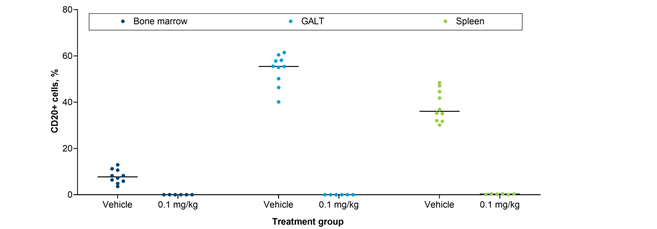


PBMC from healthy volunteers (n=11) and patients with SLE (n=12) or RA (n=9) were cultured in the presence of CLN-978 for 48 h. (A) T cells and (B) B cells were analyzed by flow cytometry. (C) Supernatants were analyzed by ELISA.
[a]Normalized to PBMC only control.
[b]Minimal cytokine induction was observed in other cytokines analyzed (e.g., IL-6, IL-1β)
ELISA, enzyme-linked immunosorbent assay; IFN, interferon; TNF, tumor necrosis factor

Studies in cynomolgus monkeys showed deep B-cell depletion in peripheral blood and tissue

- In cynomolgus monkeys treated with CLN-978, deep B-cell depletion was observed in peripheral blood and tissue (**Figure 4**), including bone marrow, spleen, and gut-associated lymphoid tissue (GALT)
- CLN-978 was well tolerated in monkeys following administration of multiple weekly subcutaneous (SC) doses

Figure 4: Deep B-cell depletion in cynomolgus monkey tissue after 4 weekly SC doses of CLN-978



CLINICAL DATA IN NON-HODGKIN LYMPHOMA SUPPORT POTENTIAL FOR DEEP B-CELL DEPLETION WITH BROAD THERAPEUTIC INDEX

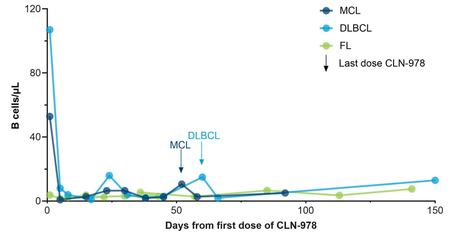
- In a phase 1, first-in-human study of CLN-978, 3 patients with B-cell non-Hodgkin lymphoma (B-NHL) received weekly SC injections of 30 µg CLN-978
  - 2 patients with bulky lymphoma experienced grade 1 cytokine release syndrome (CRS; fever) following only the first administration of CLN-978 (**Table 1**)
  - One serious adverse event (grade 1 influenza A infection) was observed
  - A complete metabolic response was observed using fludeoxyglucose-18 positron emission tomography (FDG-PET) in 1 patient who did not develop CRS (**Table 1**)
- Within 96 h after the first dose, peripheral B cells were depleted by 93% and 98% in the 2 patients with detectable B cells at baseline (**Figure 5**)

Table 1: Clinical responses and TEAEs in patients with B-NHL treated with CLN-978 (30 µg SC weekly)

Lymphoma diagnosis	No. of CLN-978 administrations	CRS	ICANS	Lymphopenia	Best clinical response[5]
Mantle cell	7	None	None	Grade 3	Complete response
Diffuse large B cell	9	Grade 1	None	Grade 4[a]	Progressive disease
Follicular	24	Grade 1	None	Grade 4[a]	Stable disease

[a]Transient lymphopenia occurred after the first dose only, consistent with the mechanism of action of CLN-619 (B-cell depletion + transient T-cell margination). Lymphocyte counts in patients with grade 4 lymphopenia returned to baseline by day 7.
TEAEs, treatment-emergent adverse events; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; SC, subcutaneous

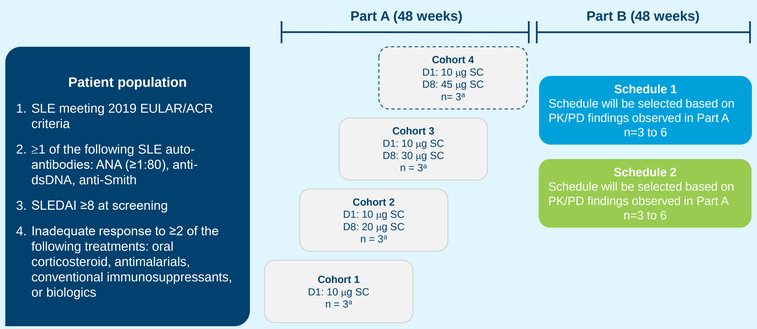
Figure 5: Peripheral B-cell depletion in patients with B-NHL treated with CLN-978 (30 µg SC weekly) shown by flow cytometry



Note: The patient with FL received the last dose of CLN-978 on day 161 post first dose.
MCL, Mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

PLANNED PHASE 1b STUDY IN PATIENTS WITH SLE (NCT06613360)

Figure 6: CLN-978-SLE-001 Study Schema (NCT06613360)



[a]Up to 3 additional patients may be added following cohort review by the Safety Review Committee.
ACR, American College of Rheumatology; ANA, antinuclear antibody; D1, day 1; D8, day 8; dsDNA, double-stranded DNA; EULAR, European Alliance of Associations for Rheumatology; SLEDAI SLE Disease Activity Index; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous

CONCLUSIONS

- **CLN-978 is a highly potent, SC-administered, CD19-directed TCE with off-the-shelf convenience and a potentially differentiated safety profile**
- **Both preclinical and clinical data for CLN-978 provide a strong rationale for broad clinical development in autoimmune diseases that benefit from B-cell depletion**
- **Phase 1b studies of CLN-978 are planned in patients with SLE and in patients with RA**

REFERENCES
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DISCLOSURES
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