GOLSEEK-4: a Phase 3, randomized study of golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, plus rituximab versus investigator's choice in patients with relapsed/refractory follicular lymphoma who have received ≥1 line of systemic therapy

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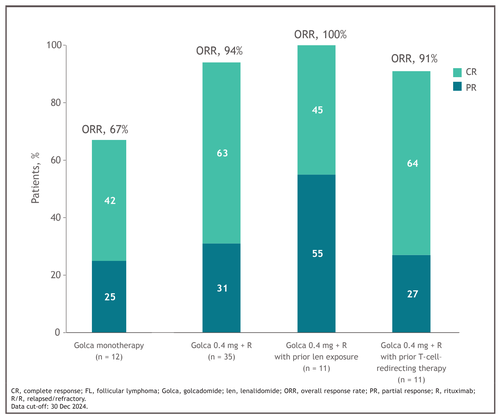
Background

- Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL), accounting for ≈20% of all NHL cases[1]
- While a long remission with frontline treatment can be expected in many patients with FL, the disease remains incurable, and subsequent relapses are associated with significantly shorter remissions[2]
- Commonly used treatment regimens for relapsed/refractory (R/R) FL include rituximab (R), lenalidomide (len), or non-cross-resistant chemoimmunotherapy such as R + cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) or R-bendamustine[3]
- More recently, T-cell-redirecting therapies such as chimeric antigen receptor T cells and bispecific antibodies in the third line or later have improved outcomes; however, they are associated with tolerability concerns and logistical challenges[4-7]
- An unmet need remains for highly efficacious, well tolerated, and more convenient chemotherapy-free regimens that improve outcomes in patients with R/R FL who have received 1 or more prior lines of systemic therapy
- Golcadomide is a potential, first-in-class, oral CELMoD agent for the treatment of lymphoma that induces rapid, deep, and sustained degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. Relative to other CELMoD agents, golcadomide was purposefully designed for lymphoma, with enhanced lymphoid organ distribution and activity in treatment-resistant cell lines[8-10] (**Key Figure A**)
- In the Phase 1/2 study CC-99282-NHL-001 (NCT03930953), the median number of prior treatments was 3 (range, 1–12); approximately one-third of the treated patients were exposed to prior T-cell-redirecting therapy, approximately one-third had prior lenalidomide (len) exposure, and approximately one-third were refractory to the last regimen received. Golcadomide alone or in combination with R showed promising efficacy and a tolerable safety profile in patients with heavily pretreated R/R FL (**Figure 1**)[11]
  - In efficacy-evaluable patients receiving golcadomide monotherapy (n = 12), the overall response rate (ORR) was 67% (complete response rate [CRR], 42%) (**Figure 1**)
  - In efficacy-evaluable patients receiving golcadomide 0.4 mg + R (n = 35), the ORR was 94% (CRR, 63%) (**Figure 1**)
  - Notably, the ORR and CRR in high-risk subsets, including patients with prior treatment with len and/or T-cell-redirecting therapy, were consistent with the results in the overall golcadomide 0.4 mg + R treatment group
  - The safety profile of golcadomide + R was manageable and predictable, and the most common treatment-emergent adverse event (TEAE) was neutropenia, an on-target effect resulting from golcadomide-mediated Ikaros degradation leading to reversible neutrophil maturation arrest
- Here, we present the study design of GOLSEEK-4 (NCT06911502), a multicenter, randomized, open-label, Phase 3 study comparing efficacy and safety of golcadomide + R vs investigator's choice (IC) in patients with R/R FL who have received ≥1 line of systemic therapy

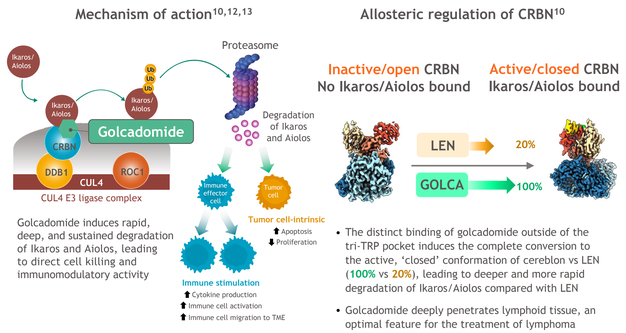
Figure 1. Phase 1/2 study (CC-99282-NHL-001): High response rates were observed with golcadomide 0.4 mg + R in heavily pre-treated R/R FL[11]



CR, complete response; FL, follicular lymphoma; Golca, golcadomide; len, lenalidomide; ORR, overall response rate; PR, partial response; R, rituximab; R/R, relapsed/refractory.
Data cut-off: 30 Dec 2024.

Golcadomide, a potential, first-in-class, oral CELMoD™ agent for follicular lymphoma – design of the Phase 3, global, randomized, open-label GOLSEEK-4 study

Key Figure A. Golcadomide is a potential, first-in-class, oral CELMoD agent for lymphoma[8,10]

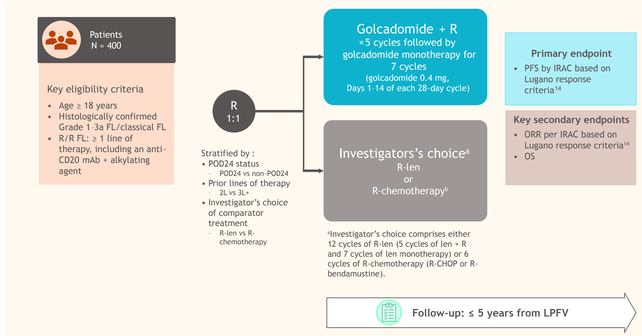


Golcadomide induces rapid, deep, and sustained degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity

- The distinct binding of golcadomide outside of the tri-TRP pocket induces the complete conversion to the active, 'closed' conformation of cereblon vs LEN (**100%** vs **20%**), leading to deeper and more rapid degradation of Ikaros/Aiolos compared with LEN
- Golcadomide deeply penetrates lymphoid tissue, an optimal feature for the treatment of lymphoma

CRBN, cereblon; CUL4, cullin-4A; DDB1, DNA damage-binding protein 1; Golca, golcadomide; LEN, lenalidomide; NHL, Non-Hodgkin lymphoma; ROC1, regulator of cullins 1; TME, tumor microenvironment; TRP, tryptophan; ub, ubiquitin.

Key Figure B. Overview of the multicenter, open-label, Phase 3 GOLSEEK-4 study (NCT06911502)



[b]For patients receiving R-chemotherapy, maintenance therapy with an anti-CD20 antibody is not allowed.
2L, second line; 3L+, third line and beyond; CD, cluster of differentiation; FL, follicular lymphoma; IRAC, Independent Radiology Adjudication Committee; len, lenalidomide; LPFV, last patient first visit; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R/R, relapsed/refractory.

Study design

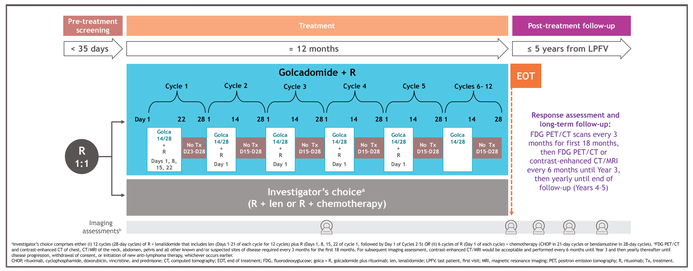
- A summary of the GOLSEEK-4 study design is presented in **Key Figure B**, and the patient journey and treatment schedule is summarized in **Figure 2**
- See **Table 1** for key eligibility criteria
- The primary objective is to assess the efficacy of golcadomide + R vs investigator's choice of R-len or R-chemotherapy in patients with R/R FL
- **Table 2** lists primary, key secondary, and other secondary endpoints, including exploratory objectives

Table 1. Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Participant must be ≥ 18 years of age	• Evidence or history of composite DLBCL and FL, transformed NHL, or any other indolent lymphoma
• Participant has histologically confirmed FL (Grade 1, 2, or 3a)	• Follicular large-cell disease as per 5th WHO sub-classification (or Grade 3b FL per 4th WHO classification) or duodenal-type FL
• Participant must have PET-positive disease with ≥ 1 PET-positive lesion and measurable disease by CT as defined by Lugano classification[14]	• Presence or history of CNS involvement by lymphoma
• Participants must require anti-lymphoma treatment per investigator assessment based on modified GELF criteria	• Participants who are refractory to both chemotherapies as well as lenalidomide, defined as: – SD/PD as best response to CHOP and bendamustine-based immunochemotherapy or a response to CHOP and bendamustine-based immunochemotherapy that lasted less than 6 months AND – SD/PD as best response to lenalidomide-based regimen or a response to lenalidomide-based regimen that lasted less than 6 months
• Participant has received ≥ 1 line(s) of systemic therapy with 1 line consisting of a combination, including an anti-CD20 monoclonal antibody (e.g. rituximab, obinutuzumab) and alkylating agent (e.g. cyclophosphamide, bendamustine)	Note: Participants previously refractory to lenalidomide and/or exposed to lenalidomide are eligible but will not be randomized in the R-lenalidomide arm; participants who are refractory to R-chemotherapy (both CHOP and bendamustine) are eligible but will not be randomized to R-chemotherapy arm

CD, cluster of differentiation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone); CNS, central nervous system; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; NHL, non-Hodgkin lymphoma; PD, progressive disease; PET, positron emission tomography; SD, stable disease; WHO, World Health Organization.

Figure 2. Patient journey in GOLSEEK-4



[a]Investigator's choice comprises either (i) 12 cycles (28-day cycles) of R + lenalidomide that includes len (Days 1-21 of each cycle for 12 cycles) plus R (Days 1, 8, 15, 22 of cycle 1, followed by Day 1 of Cycles 2-5; OR (ii) 6 cycles of R (Day 1 of each cycle) + chemotherapy (CHOP in 21-day cycles or bendamustine in 28-day cycles). [b]FDG PET/CT and contrast-enhanced CT of chest, CT/MRI of the neck, abdomen, pelvis and all other known and/or suspected sites of disease required every 3 months for the first 18 months. For subsequent imaging assessment, contrast-enhanced CT/MRI would be acceptable and performed every 6 months until Year 3 and then yearly thereafter until disease progression, withdrawal of consent, or initiation of new anti-lymphoma therapy, whichever occurs earlier.
CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; CT, computed tomography; EOT, end of treatment; FDG, fluorodeoxyglucose; golca + R, golcadomide plus rituximab; len, lenalidomide; LPFV, last patient, first visit; MRI, magnetic resonance imaging; PET, positron emission tomography; R, rituximab; Tx, treatment.

Table 2. Primary, Secondary, and Exploratory Endpoints

Primary
- PFS by IRAC by Lugano response criteria[14]

Key secondary
- ORR by IRAC by Lugano response criteria[14]
- OS

Other secondary
- PFS by investigator
- ORR by investigator
- CMRR by investigator
- DOR
- EFS
- MRD by ctDNA
- PFS2
- TTNT
- HRQoL
  - Change from baseline in domains of the EORTC QLQ-C30 and the EORTC QLQ-NHL-LG20

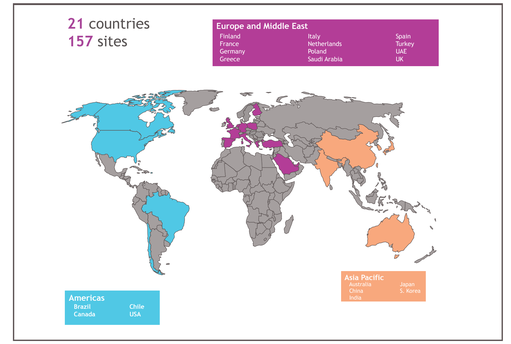
Exploratory endpoints
- Safety
- PK
- Biomarkers
- Healthcare resource utilization

CMRR, complete metabolic response rate; ctDNA, circulating tumor DNA; DOR, duration of response; ET's, event-free survival; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer-Quality of Life Core 30 Questionnaire; EORTC QLQ-NHL-LG20, European Organisation for Research and Treatment of Cancer-Non-Hodgkin Lymphoma-Low Grade-20 items; HRQoL, health-related quality of life; IRAC, Independent Response Adjudication Committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to a second progression event; PK, pharmacokinetics; TTNT, time to next anti-lymphoma treatment.

Global enrollment

- The study is being conducted at 157 sites in 21 countries worldwide (**Figure 3**)
- The first patient's first visit was 28 July 2025, and enrollment is ongoing
- Estimated primary analysis completion date: 24 April 2028
- Estimated study completion date: 31 July 2030

Figure 3. Participating countries



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Nowakowski et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, plus R-CHOP in patients (Pts) with previously untreated aggressive B-cell lymphoma (a-BCL): 24-month efficacy results
Sunday, December 7th, 2025. Presentation time: 9:45 AM - 10:00 AM
Room: OCCC - Tangerine Ballroom F3-4

Oral Presentation: 479
Hoffmann et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, ± rituximab (R) in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Phase 1/2 study extended follow-up results
Sunday, December 7th, 2025. Presentation time: 10:30 AM - 10:45 AM
Room: OCCC - Tangerine Ballroom F3-4

Oral Presentation: 1006
Chavez et al.
Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, ± rituximab (R) in patients with relapsed/refractory follicular lymphoma (R/R FL): Phase 1/2 study extended follow-up results
Monday, December 8th, 2025. Presentation Time: 5:15 PM - 5:30 PM
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Oral Presentation: 66
Andreadis et al.
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Saturday, December 6, 2025. Presentation time: 10:45 AM - 11:00 AM
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Poster presentation: 3704
Vassilakopoulos et al.
GOLSEEK-1: A Phase 3, double-blind, randomized study of golcadomide (GOLCA), a potential, first-in-class, oral CELMoD™ agent, + R-CHOP vs placebo + R-CHOP in patients with previously untreated, high-risk, large B-cell lymphoma
Sunday, December 7th, 2025. Session time: 6:00 PM - 8:00 PM
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Poster presentation at the American Society of Hematology (ASH) Annual Meeting and Exposition; December 6-9, 2025; Orlando, Florida.

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