DAYBreak CLL-306: A Phase 3 Randomized Open-Label Trial of the Novel Bruton's Tyrosine Kinase (BTK) Degrader Bexobrutideg (NX-5948) Versus Pirtobrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

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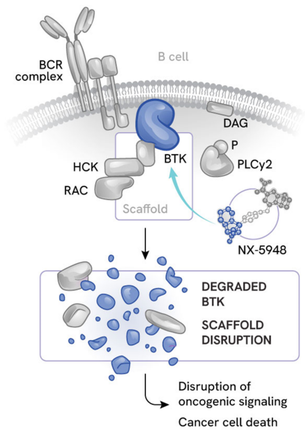
For information about this clinical trial please scan the QR code

Background

- BTK plays a central role in the B-cell receptor signaling pathway and is involved in the pathogenesis of several B-cell malignancies.[1,2]
- Covalent (c) and non-covalent (nc) BTK inhibitors (BTKi), including the ncBTKi pirtobrutinib, are effective in CLL/SLL, but the emergence of BTKi resistance mutations and kinase-independent signaling via the scaffolding function of BTK highlight the need for alternative approaches to target BTK protein functions.[1,2]
- Bexobrutideg (NX-5948) is a novel, highly selective, orally administered small molecule degrader that induces the removal of wild-type and mutant forms of BTK through ubiquitination by the cereblon E3 ligase complex and subsequent proteasomal degradation (**Figure 1**).
- In a Phase 1 trial in patients with relapsed/refractory B-cell malignancies, including CLL/SLL (NX-5948-301; NCT05131022), bexobrutideg was well tolerated and demonstrated rapid and durable responses, and a recommended Phase 2 dose of 600 mg once daily (QD) was identified.[3]

Figure 1. Bexobrutideg mechanism of action



✓Active against not only wild-type BTK but also treatment emergent BTK-inhibitor resistance mutations[4,5]

✓Addresses both BTK scaffolding and kinase functions, unlike current BTK inhibitors[6]

✓Acts catalytically, driving degradation at low free-drug plasma concentrations

✓Crosses the blood–brain barrier and demonstrates clinical activity in the CNS[7]

✓Demonstrates robust clinical activity in difficult-to-treat B-cell malignancies[8–10]

Methods

- NX-5948-306 (NCT07516093) is a Phase 3, randomized, open-label, multicenter Study of bexobrutideg versus pirtobrutinib in relapsed/refractory CLL/SLL (**Figure 2**).
- The study consists of an initial screening phase, a treatment phase, and a follow-up phase.
- Eligible patients are randomized in a 1:1 ratio to receive either bexobrutideg (Arm A) or pirtobrutinib (Arm B). Patients will be stratified based on presence of del (17p) and/or TP53 mutation (yes or no), prior BCL2i therapy (yes or no), and number of prior lines of therapy (<4 or ≥4). Crossover will not be permitted.
- Bexobrutideg at 600 mg or pirtobrutinib 200 mg are administered orally once daily in continuous 28-day cycles until treatment is discontinued due to disease progression, unacceptable toxicity, other reasons for treatment discontinuation, or upon study termination by the study sponsor.

Table 1. Key eligibility criteria

Key inclusion criteria
• ≥18 years of age
• Confirmed diagnosis of CLL/SLL per iwCLL (Hallek 2018)[11]
• ECOG PS 0–2
• ≥1 prior CLL/SLL therapy including a cBTKi, with documented progression on or after cBTKi
• Patients with SLL must have measurable disease by CT per iwCLL
• Adequate organ and bone marrow function

Key exclusion criteria
• Known or suspected prolymphocytic leukemia or Richter's transformation
• Investigational agent or anticancer therapy within 5 half-lives or 14 days (whichever is shorter) prior to planned start of study treatment
• Ongoing systemic corticosteroids ≥10 mg/day prednisone or equivalent
• Previous treatment with a BTK degrader or non-covalent BTKi
• Previous autologous or allogeneic stem cell transplant or CAR-T cell therapy within the past 90 days prior to enrollment
• Active second malignancy (unless in remission with life expectancy >2 years)
• Current or history of CNS lymphoma or leukemia

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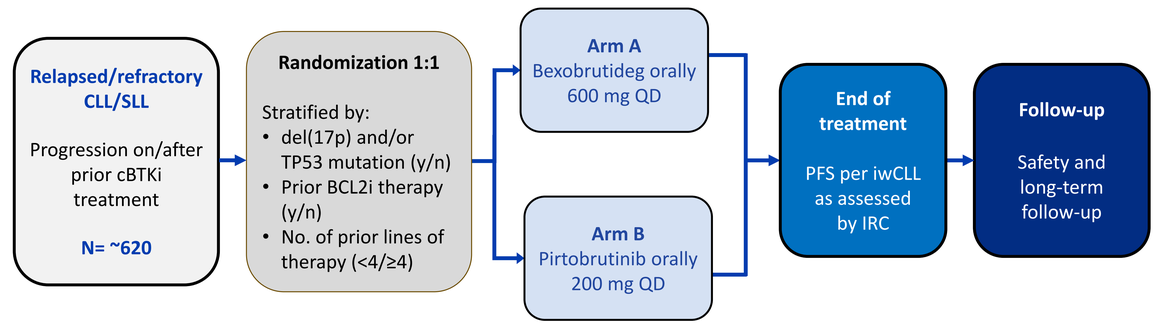
- Bexobrutideg (NX-5948) studies are sponsored by Nurix Therapeutics, Inc.

Figure 2. NX-5948-306 trial design



Study objectives and endpoints

Primary endpoint	Key secondary endpoint	Other secondary endpoints
Efficacy: PFS as assessed by IRC per iwCLL (Hallek 2018)	**Efficacy:** Overall Survival	**Additional efficacy:** PFS as assessed by investigator per iwCLL criteria; ORR (with and without PR-L) as assessed by IRC and investigator; DOR (with and without PR-L) as assessed by IRC and investigator; time to next anti-CLL/SLL treatment as assessed by IRC and investigator **Patient reported outcomes:** EORTC QLQ-C30, EORTC QLQ-CLL17 and EQ-5D-5L **Safety:** Including, but not limited to, incidence and severity of TEAEs, SAEs, and TEAEs leading to study treatment discontinuation; changes from baseline in laboratory parameters and vital signs **Pharmacokinetics:** Plasma concentrations of NX-5948

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Abbreviations

BCL2, B-cell lymphoma-2; **BCL2i,** BCL2 inhibitor; **BTKi**, Bruton tyrosine kinase inhibitor; **cBTKi,** covalent BTK inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **CT**, computed tomography; **DOR,** duration of response; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Core Questionnaire C30; **EORTC QLQ-CLL17**, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire CLL module; **EQ-5D-5L**, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire; **EoT**, end of treatment; **IRC**, Independent Review Committee; **iwCLL,** International Workshop on CLL; **ncBTKi,** non-covalent BTK inhibitor; **ORR**, objective response rate; **OS**, overall survival; **PR-L**, partial response with lymphocytosis; **PFS**, progression-free survival; **QD**, once daily; **SAE,** serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment emergent adverse event

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