DAYBreak CLL-201: A Study of Bexobrutideg (NX-5948), a Bruton's Tyrosine Kinase (BTK) Degrader, in Patients with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Previously Treated with a Covalent BTK Inhibitor, a Non-covalent BTK Inhibitor and a BCL2 Inhibitor

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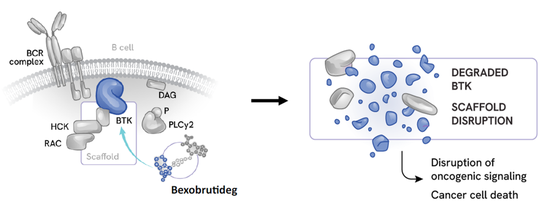
For information about this clinical trial please scan the QR code

Background

- BTK plays a central role in the BCR signaling pathway and is involved in the pathogenesis of several B-cell malignancies.[1,2]
- Although BTK inhibition has proven to be a successful treatment modality in CLL, the emergence of BTKi resistance mutations and identification of kinase-independent signaling via the scaffolding function of BTK underscore the need for alternative approaches to target the totality of BTK protein functions.[1,2]
- BCL2i therapy is another effective targeted approach for the treatment of CLL or SLL; however, similar to BTKi therapy, resistance to BCL2i(s) develops after prolonged exposure.[3,4] Patients who have developed resistance to BTKi therapy often switch to BCL2i therapy, or vice versa.
- Patients who have relapsed or refractory disease after treatment with both targeted therapies have poor outcomes and present a high unmet need.
- 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**).

Figure 1. Bexobrutideg mechanism of action



Bexobrutideg:

- Is active against not only wild-type BTK but also treatment-emergent resistance mutations.[5,6]
- Addresses both BTK scaffolding and kinase functions, unlike current BTKis[7]
- Acts catalytically driving degradation at low free-drug plasma concentrations
- Crosses the blood–brain barrier and demonstrates clinical activity in the CNS[8]
- Demonstrates robust clinical activity in difficult-to-treat B-cell malignancies[9–11]
- Has the potential to address significant unmet needs beyond CLL and NHL in autoimmune and inflammatory disorders

Abbreviations

BCL2i, BCL2 inhibitor; **BCR,** B-cell receptor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CAR**, chimeric antigen receptor; **cBTKi**, covalent BTKi; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **EORTC QLQ-C30**, European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire C30; **EQ-5D-5L**, European Quality of Life 5-Dimensions 5-Levels Health Questionnaire; **HCT**, hematopoietic cell transplant; **IRC**, independent review committee; **iwCLL**, International workshop on chronic lymphocytic leukemia; **ncBTKi**, non-covalent BTKi; **NHL**, non-Hodgkin's lymphoma; **ORR,** objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **PR-L**, partial response with lymphocytosis; **QD,** once daily; **PRO,** patient-reported outcome; **R/R**, relapsed/refractory; **SAE**, serious adverse event; **SLL**, small lymphocytic leukemia; **TEAE**, treatment emergent adverse events; **TTR**, time to response.

Methods

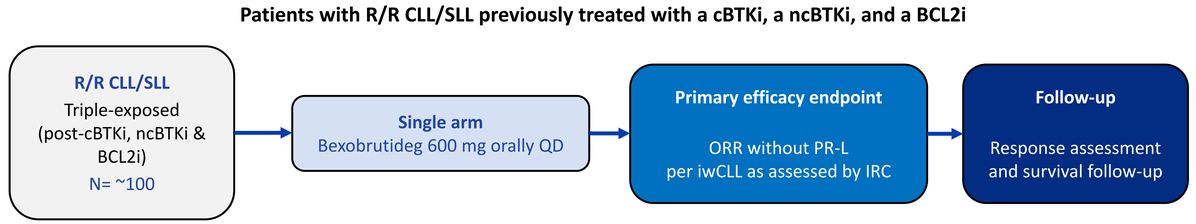
- NX-5948-201 (NCT07221500) is a single-arm, Phase 2, open-label, multicenter study designed to evaluate bexobrutideg in adults with R/R CLL/SLL previously treated with a cBTKi, a ncBTKi, and a BCL2i (**Figure 2**).
- The study consists of an initial screening phase, a treatment phase, and a follow-up phase.
- Bexobrutideg at 600 mg is 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
• Age ≥18 years
• Confirmed diagnosis of CLL/SLL per iwCLL (Hallek 2018)[12]
• ECOG performance status 0–2
• Prior exposure to a cBTKi, a ncBTKi and a BCL2i in either separate lines or in combination
• Patients with SLL must have measurable disease by computed tomography per iwCLL[12] (≥1 lymph node with longest diameter >1.5 cm)
• Adequate organ and bone marrow function

Key exclusion criteria
• Known or suspected prolymphocytic leukemia or Richter's transformation
• Palliative limited-field radiotherapy within 7 days of the first dose of study drug or broad field radiotherapy within 28 days of first dose of study drug
• Previous BTK degrader treatment
• Previous CAR T-cell therapy or allogeneic or autologous HCT within the past 90 days prior to enrollment
• Active second malignancy (unless in remission with a life expectancy >2 years)
• Current or history of CNS lymphoma or leukemia

Figure 2. NX-5948-201 study design



Study objectives and endpoints

	Objectives	Endpoints
Primary	• Evaluate the efficacy of bexobrutideg in adults with R/R CLL/SLL previously exposed to a cBTKi, a ncBTKi, and a BCL2i in accordance with iwCLL guidelines[12]	• ORR (without PR-L) as assessed by IRC
Secondary	• Further evaluate the efficacy of bexobrutideg in adults with R/R CLL/SLL previously exposed to a cBTKi, a ncBTKi, and a BCL2i in accordance with the 2018 iwCLL guidelines[12]	*Key secondary endpoint* • ORR with PR-L as assessed by IRC *Other secondary endpoints* • ORR (with and without PR-L) as assessed by investigator • DOR as assessed by IRC and by investigator • PFS as assessed by IRC and by investigator • Complete response rate as assessed by IRC and by investigator • TTR as assessed by IRC and by investigator • OS
	• Evaluate the safety and tolerability of bexobrutideg	• Including, but not limited to, incidence and severity of TEAEs, SAEs, and TEAEs leading to study drug discontinuation • Changes from baseline in laboratory parameters and vital signs
	• Evaluate the effect of bexobrutideg on quality of life	• PROs measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires
	• Characterize the PK of bexobrutideg	• Summary measures of PK trough concentrations

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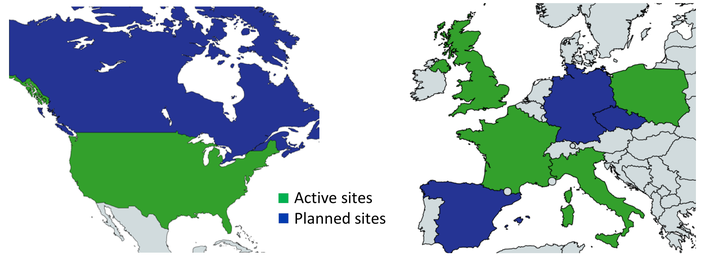
Study Sites



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