Trial in Progress: A Phase 1b/2 Study of GB5121, a Novel, Highly Selective, Potent, and CNS-Penetrant BTK Inhibitor for Relapsed/Refractory Primary/Secondary CNS Lymphoma and Primary Vitreoretinal Lymphoma (STAR CNS)

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BACKGROUND

- Bruton's tyrosine kinase (BTK) plays a critical role in malignant B cell receptor and Toll-like receptor signaling pathways, which are constitutively activated in most primary CNS lymphomas
- Clinical experience with ibrutinib, a first-generation BTK inhibitor (BTKi), in relapsed/refractory primary/secondary CNS lymphoma (R/R PCNSL, SCNSL) and primary vitreoretinal lymphoma (PVRL), is limited by small numbers of patients studied and toxicities related to off-target kinase inhibition[1]
- Next-generation BTKis that are more CNS penetrant and selective may achieve better therapeutic outcomes in B cell malignancies with CNS involvement
- GB5121 is an oral, brain-penetrant, potent, highly selective, irreversible small molecule BTKi in development for hematologic malignancies with CNS involvement

PRECLINICAL STUDIES

- Preclinical studies demonstrated that GB5121 exhibits several characteristics differentiating it from other BTKis, including rapid equilibrium into the brain, increased brain target occupancy, and fast inactivation rate (**Figure 1**)[2]
- Excellent brain exposure and selectivity combined with activity against DLBCL cell lines support the use of GB5121 as a novel molecule to treat human BTK-driven malignancies including CNS lymphoma

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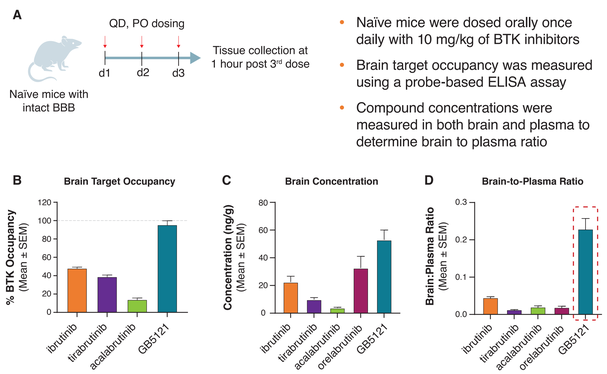
"GB5121 is a Novel, Highly Potent and Selective CNS-Penetrant BTK Inhibitor for CNS Malignancies"

Figure 1. GB5121 demonstrates superior brain target occupancy and exposure compared to other BTK inhibitors



- Naïve mice were dosed orally once daily with 10 mg/kg of BTK inhibitors
- Brain target occupancy was measured using a probe-based ELISA assay
- Compound concentrations were measured in both brain and plasma to determine brain to plasma ratio

A. Dosing schedule in naïve mice with intact BBB. **B.** BTK target occupancy in brain. **C.** Compound concentration in brain **D.** Brain to plasma ratio. GB5121 achieves higher CNS penetration with lower plasma exposures (dotted line).

NOTE: Brain target occupancy of orelabrutinib is not reported due to the lack of an appropriate probe. Zanubrutinib was also tested in this model, but data are not shown as levels of compound were below the limit of detection in the brain (5 ng/g). Data are average of 1-6 independent experiments. Each independent experiment included 3 mice per group. Graphs were generated in GraphPad Prism software.
Abbreviations: BBB, blood brain barrier; PO, by mouth; QD, daily

STUDY DESIGN

- STAR CNS is an open-label, multicenter, multinational dose escalation with expansion study of GB5121 in adult patients with R/R PCNSL or SCNSL or PVRL, with a Phase 2 open-label, single dose level study of GB5121 in adult patients with R/R PCNSL (**NCT05242146**)

Table 1. Objectives and Endpoints

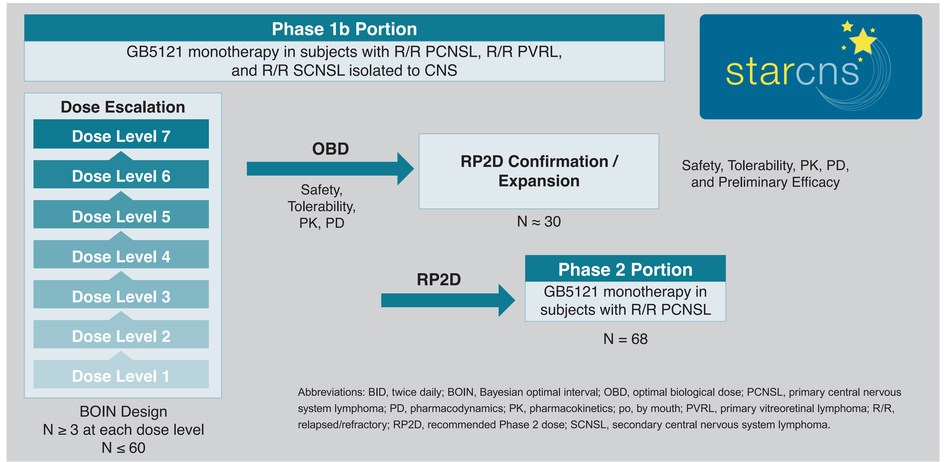
	Objectives	Endpoints
Phase 1 Dose Escalation	**Primary:** Evaluate safety and tolerability, determine OBD, MTD, RP2D **Exploratory Evaluations** • Plasma and CSF PK • PD biomarkers in blood and CSF, if available • Molecular tumor profiling measurements in blood, plasma, and CSF when available • DR and ER relationships	**Primary** • Incidence of AEs, DLTs, SAEs • OBD and/or MTD and RP2D **Exploratory Evaluations** • PK parameters in plasma and CSF compartments • PD biomarkers in blood and CSF • Molecular tumor profiling in blood, plasma, CSF • DR and ER relationships for selected efficacy and safety parameters
Phase 1 Dose Expansion	**Primary:** Determine safety, tolerability of RP2D **Secondary:** Assess ORR according to IPCG criteria	**Primary:** Incidence of AEs and SAEs **Secondary:** ORR according to IPCG criteria by investigator assesment
Phase 2	**Primary:** Assess response **Key Secondary:** Assess DOR	**Primary:** ORR according to IPCG criteria by BICR committee **Secondary:** DOR by BICR Committee

BICR; Blinded Independent Central Review; CSF, cerebrospinal fluid; DLT, dose-limiting toxicities; DOR, duration of response; DR, dose:response; ER, exposure:response; IPCG, International Primary CNS Lymphoma Collaborative Group; MTD, maximum tolerated dose; OBD, optimal biological dose; ORR, objective response rate; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended Phase 2 Dose; (S)AE, (serious) adverse event

Table 2. Selected Inclusion and Exclusion Criteria

Selected Inclusion Criteria	Selected Exclusion Criteria
• ≥ 18 years of age • Eastern Cooperative Oncology Group Performance Scale ≤ 2 • Histologically/cytologically confirmed PCNSL, PVRL, or CNS-only High-Grade B-cell lymphoma or CNS involvement with systemic High-Grade B-cell lymphoma • R/R disease with at least one prior CNS-directed therapy • Patients with parenchymal lesions must have measurable disease on imaging prior to first study dose • Tolerate gadolinium-enhanced MRI scans, or contrast-enhanced computed tomography • Adequate bone marrow and organ function	• Active concurrent malignancy requiring active therapy • Bleeding diathesis (eg, von Willebrand's disease) or hemophilia • Significant abnormalities on screening electrocardiogram and active and significant cardiovascular disease within 6 months of screening • History of active or chronic infection with hepatitis C or B virus • History of infection with HIV • Uncontrolled active infection • History of stroke or intracranial hemorrhage within 6 months prior to enrollment • Life-threatening illness, medical condition, or organ system dysfunction that, in the opinion of the Investigator, could compromise the subject's safety or put the study outcomes at undue risk • Prior allogeneic stem cell transplant

Figure 2. STAR CNS Study Schema



Abbreviations: BID, twice daily; BOIN, Bayesian optimal interval; OBD, optimal biological dose; PCNSL, primary central nervous system lymphoma; PD, pharmacodynamics; PK, pharmacokinetics; po, by mouth; PVRL, primary vitreoretinal lymphoma; R/R, relapsed/refractory; RP2D, recommended Phase 2 dose; SCNSL, secondary central nervous system lymphoma.

TRIAL STATUS (as of June 28, 2022)

- 3 investigator sites have been activated
  - Middlemore Hospital, Papatoetoe, Auckland, New Zealand
  - Linear Clinical Research, Nedlands, WA, Australia
  - Institut Curie Site Saint-Cloud, Ile-de-France, France
- Enrollment on this trial has commenced
- Additional sites will be recruited and initiated globally
- The Expansion and Phase 2 portion of the study will be initiated pending results from Dose Escalation

SUMMARY

- New treatment strategies for patients with R/R PCNSL and PVRL remain an unmet medical need
- GB5121 is an oral, potent, highly selective, irreversible, small molecule BTKi with superior brain target occupancy and exposure in preclinical testing when compared to other BTKis
- A Phase 1b/2 trial (STAR CNS; NCT 05242146) in adult patients with R/R PCNSL/SCNSL or PVRL is currently enrolling

REFERENCES

1. Nepal G., et al. *Neurol Int.* 2022;14:99-108; **2.** Yusuf I., et al. Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; *Cancer Res* 2022;82(12_Suppl):Abstract nr 3330.

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