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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**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 (NCT05242416).

**BACKGROUND**

-Brains of 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 a first-generation BTK inhibitor (BTK), 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.

- Next-generation BTKs that are more CNS penetrant and selective may achieve better pharmacodynamic outcomes in B cell malignancies with CNS involvement.

GB5121 is an oral, brain-penetrant, potent, highly selective, irreversible small molecule BTK in development for hematologic malignancies with CNS involvement.

**PRECLINICAL STUDIES**

- Preclinical studies demonstrated that GB5121 exhibited several characteristics differentiating it from other BTKIs, including rapid equilibrium into brain tissue, increased brain target occupancy, and fast inactivation rate (Figure 1).

- Excellent brain exposure and selectivity combined with activity against DBILC cell lines support the use of GB5121 as a novel molecule to treat human BTK-driven malignancies including CNS lymphoma.

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

**OBJECTIVES**

- 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.

**Phase 1 Dose Escalation**

- Primary: Evaluate safety and tolerability, determine OBD, MTD, RP2D.

**Phase 1 Exploratory Evaluations**

- Plasma and CSF PK.
- PD biomarkers in blood and CSF, if available.
- Molecular tumor profiling measurements in blood, plasma, and CSF, if available.
- DR and ER relationships.

**Phase 2 Dose Expansion**

- Primary: Determine safety, tolerability of RP2D: Secondary: Assess DR according to IPCG criteria.

Table 1: Objectives and Endpoints

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<th>Phase</th>
<th>Dose Escalation</th>
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<td>Primary</td>
<td>Safety and tolerability, determine OBD, MTD, RP2D</td>
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**Table 2: Selected Inclusion and Exclusion Criteria**

**Selected Inclusion Criteria**

- ≥ 18 years of age.
- Eastern Cooperative Oncology Group Performance Status ≤ 2.
- Histologically and cytologically confirmed PCNSL, PVRL, or CNS-only High-Grade B-cell lymphoma 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.
- Tolerable gadolinium-enhanced MRI scans, or contrast-enhanced computed tomography.
- Adequate bone marrow and organ function.

**Selected Exclusion Criteria**

- Active concurrent malignancy requiring active therapy.
- Bleeding diathesis (eg, von Willebrand's disease) or hemorrhage.
- Significant abnormalities on screening electrocardiogram and active and significant cardiovascular disease within 6 months.
- History of active or chronic infection with hepatitis C or B virus.
- History of infection with HIV.
- Uncontrolled 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 alelebrutinib treatment.

**TRIAL STATUS (as of June 28, 2022)**

- 3 investigator sites have been activated:
  - Middlemore Hospital, Papatoetoe, Auckland, New Zealand
  - Saint Cloud, France
  - 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 BTK with superior brain target occupancy and exposure in preclinical testing when compared to other BTKIs.

- A Phase 1b/2 trial (STAR CNS; NCT 05242416) in adult patients with R/R PCNSL/SCNSL or PVRL is currently enrolling.

**RESOURCES**