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

Catherine Susaessa, Christian Gromayev, Samir Issaa, Renee Ward, Carolyn Petersen, Matt Creavety, Anita Mathew, Judith Sox, Brian Kelley, Zhangqiang Ding, Ishnael Youst, Mark Ross, Marla Steinberg, Han W. Turi

United Care, Saint-Cloud, France; Memorial Sloan Kettering Cancer Center, New York, NY, USA; Middlemore Hospital, Auckland, New Zealand; Gossamer Bio, Inc., San Diego, CA, USA; Mayo Clinic, Jacksonville, FL, USA

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 (NCT05242446).

Table 1. Objectives and Endpoints

<table>
<thead>
<tr>
<th>Phase 1 Dose Escalation</th>
<th>Phase 2 Dose Expansion</th>
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<tbody>
<tr>
<td>Primary: Determine safety, tolerability, PK, PD</td>
<td>Primary: Determine safety, tolerability, PK, PD</td>
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<tr>
<td>Secondary: Assess ORR according to IPCG criteria</td>
<td>Secondary: Assess ORR according to IPCG criteria</td>
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</tbody>
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Table 2. Selected Inclusion and Exclusion Criteria

Selected Inclusion Criteria | Selected Exclusion Criteria
---|---
- ≥ 18 years of age | - Active concurrent malignancy requiring active therapy
- Eastern Cooperative Oncology Group Performance Status ≤ 2 | - Bleeding diathesis (eg, von Willebrand’s disease) or hemophilia
- Historically/hyoetically confirmed PCNSL, PVRL, or CNS-only High-Grade B-cell lymphoma or CNS involvement with systemic High-Grade B-cell lymphoma | - Significant abnormalities on screening electrocardiogram and active and significant cardiovascular disease within 6 months of screening.
- R/R disease with at least one prior CNS-directed therapy | - History of active or chronic infection with hepatitis C or B virus
- Patients with parenchymal lesions must have measurable disease on imaging prior to first study dose | - History of infection with HIV
- Tolerated gadolinium-enhanced MRI scans, or contrast-enhanced computed tomography | - Uncontrolled infection
- Adequate bone marrow and organ function | - History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Active concurrent malignancy requiring active therapy | - 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.

REFERENCES


ACKNOWLEDGEMENT

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STUDY 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 trial experience with ibrutinib, a first-generation BTK inhibitor (BTKi), in relapsed/refractory 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 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 BTK inhibitor in development for hematologic malignancies with CNS involvement.

PRECLINICAL STUDIES

• Preclinical studies demonstrated that GB5121 exhibits several characteristics differing it from other BTKIs, including rapid equilibrium into brain, increased brain target occupancy, and better therapeutic outcomes in B cell malignancies with CNS involvement.

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

A. GB5121 AUC is not reported due to the lack of an appropriate probe. Zanubrutinib was also tested in Phase 1 for GB5121.

TRIAL STATUS (as of June 28, 2022)

• 3 investigator sites have been activated – Middlemore Hospital, Papatoetoe, Auckland, New Zealand
- Linear Clinical Research, Nendals, 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 05242446) in adult patients with R/R PCNSL/SCNSL or PVRL is currently enrolling.

Figure 2. STAR CNS Study Schema

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