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

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BACKGROUND

- Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of non-Hodgkin lymphoma that is restricted to the CNS
- Inhibitors of Bruton’s tyrosine kinase (BTK) are approved treatments for several B cell malignancies, but are characterized by modest selectivity and/or low CNS exposure
- GB5121 is an orally available, selective, irreversible small molecule BTK inhibitor chosen for development based on its potency, selectivity and high CNS exposure
- These features differentiate GB5121 from other BTK inhibitors and support its use in clinical trials for CNS malignancies

OBJECTIVE

- Profile GB5121 for selectivity and CNS exposure to ibritinib

METHODS

- Selectivity of GB5121 and ibritinib was profiled in kineome scans against 349 kinases at 1µM under conditions using 1mM ATP concentration; EGFR activity was further evaluated in a cell-based assay
- Irreversible and covalent nature of GB5121 was evaluated using enzymatic assays and no washout control compounds
- In vitro potency and inactivation kinetics of GB5121 were evaluated using biochemical and cell-based assays
- Comparative BTK target occupancy of GB5121 and ibritinib was assessed in perfused mice with an intact blood brain barrier (BBB) using a probe-based ELISA
- Pharmacokinetic profiles of GB5121 were obtained in multiple species using intravenous and oral dosing

RESULTS

Figure 2. GB5121 is a highly selective BTK inhibitor

- GB5121 demonstrates >50% inhibition of only two kinases besides BTK (TEC and TTK)
- Compared to ibritinib, GB5121 lacks activity against EGFR, ERBB2 (HER2) and ERBB4 (HER4)

Figure 3. GB5121 does not inhibit phosphorylation of EGFR in A431 cell line

Data are representative of 10 independent studies. Dose response curves were generated from duplicate values at each concentration of test article using a noninert, 4-parameter, variable slope curve-fitting function using GraphPad Prism software

Figure 4. GB5121 shows potent activity in vitro in diffuse large B cell lymphoma (DLBCL) cell lines regardless of phenotype and mutational profile

PELLEF GB5121 cell line

Table 4. GB5121 brain to plasma ratios after single or multiple daily oral (PO) dosing in multiple species

<table>
<thead>
<tr>
<th>Species</th>
<th>Strain</th>
<th>PO Dose (mg/kg)</th>
<th>Day</th>
<th>Brain/Plasma Ratio (Mean ± SD)</th>
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<tbody>
<tr>
<td>Mouse</td>
<td>C57BL/6</td>
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Figure 6. GB5121 demonstrates a 1:1 brain to plasma ratio in non-human primates (n=3) after an IV dose

Table 5. GB5121 brain to plasma ratios after single or multiple daily oral (PO) dosing in multiple species

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Figure 7. GB5121 shows superior CNS exposure with lower plasma exposures compared to ibritinib in naive mice with intact BBB

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SUMMARY AND CONCLUSIONS

- GB5121 is an orally available irreversible BTK inhibitor that is currently being investigated in a phase 1b/2 trial in patients with relapsed/refractory primary or secondary CNS lymphoma and primary vitreoretinal lymphoma (NCT05242146)
- Preclinical studies demonstrated GB5121 to exhibit several characteristics differentiating it from approved BTK inhibitors and those currently under clinical investigation, including:
  - rapid equilibrium into the brain
  - superior BTK inactivation rate and brain target occupancy
  - high selectivity over other kinases
- 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

REFERENCES


ACKNOWLEDGEMENTS

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