Exposure-response relationship of the Bruton tyrosine kinase inhibitor, zanubrutinib (BGB-3111) in patients with hematologic malignancies

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Background:

Zanubrutinib (BGB-3111) is a highly selective, potent, irreversible inhibitor of Bruton tyrosine kinase (BTK), currently in phase 3 development for the treatment of hematologic malignancies, including mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia (WM). In a dose escalation study evaluating doses of 40, 80, 160, and 320 mg once daily and 160 mg twice daily, no dose limiting toxicities were observed and maximum tolerated dose (MTD) was not established. Objective responses have been observed in patients with various B-cell malignancies (including CLL, MCL, WM) at all tested dose levels. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes in patients treated at 160 mg twice daily (Tam et al. Blood 2016;128:642). To support dose selection, this exposure-response (E-R) analysis evaluated exposure-safety and exposure-efficacy (in MCL) relationships in patients with B-cell malignancies receiving zanubrutinib monotherapy.

Methods:

A population pharmacokinetic (PopPK) model was developed from 600 subjects enrolled in 9 clinical studies in patients with B-cell malignancies and healthy volunteers. Exposure data such as steady-state area under the plasma concentration time curve (AUC0-24,ss), maximum observed plasma concentration (Cmax) or steady state trough concentration (Cmin) derived from the PopPK analysis were used in the E-R analysis. Exposure-efficacy analyses were performed using exposure metrics and overall response rate (ORR) data from two studies in patients with relapsed/refractory (R/R) MCL (n=51), including Study 206, a pivotal Phase 2 study conducted in China and study AU-003, a global Phase 1, dose escalation/cohort expansion study. The efficacy endpoint evaluated was ORR, as assessed by an independent review committee (IRC) as well as by investigators, according to 2014 Lugano Classification. Exposure-safety analyses were conducted using data from 4 studies in patients with B-cell malignancies (n=372) receiving zanubrutinib as monotherapy at a total daily dose from 40 mg to 320 mg. The safety endpoints evaluated included Grade ≥ 3 adverse events (AE) and AEs of interests, including neutropenia, thrombocytopenia, anemia, infections/infestations, all events of secondary primary malignancies, all events of atrial fibrillation and flutter, major bleeding events, and any bleeding events.

Results:

PopPK analysis demonstrated that race, body weight, age, CrCL, sex, tumor type, and use of acid-reducing agents did not show a statistically significant impact on the PK of zanubrutinib. The PK profile of zanubrutinib was comparable between Asians and non-Asians, which allows for bridging of clinical efficacy and safety data across the pivotal studies conducted globally (AU-003) and in China (206). The analysis showed that the median AUC0-24,ss and Cmax values were 1736 ng·h/mL and 275 ng/mL in responders compared with 1326 ng·h/mL and 175 ng/mL in nonresponders, respectively. Although overall median exposure (AUC0-24,ss, Cmax) was higher in responders compared with nonresponders, no significant E-R relationship was identified for efficacy based on probability of observing ORR and

logistic regression model (Fig 1). The E-R relationships based on investigator assessments were consistent with those based on IRC assessments. For the exposure-safety analysis, the exposure ranges were similar in patients experiencing adverse events of interests relative to those who were not. There were no evident E-R relationships between PK exposure (AUC0-24,ss, Cmax, or Cmin) and the probability to have adverse events of interest (eg., Fig. 2).

Conclusion:

E-R analyses indicate that higher plasma exposures of zanubrutinib were not associated with higher probability to have adverse events across the dose range of 40 mg to 320 mg in patients with B-cell malignancies. This result supports the recommended dose of 160 mg twice daily in patients with MCL, based on high rates of objective response in patients with R/R MCL, generally favorable safety and tolerability profiles, and complete and sustained BTK occupancy in PBMCs and target tissues at this dose.

Figure 1: **Exposure-Response Between $AUC_{0\text{-}24,ss}$ and Efficacy (Overall Response Rate, IRC) in Studies AU-003 and 206 by Logistic Regression**

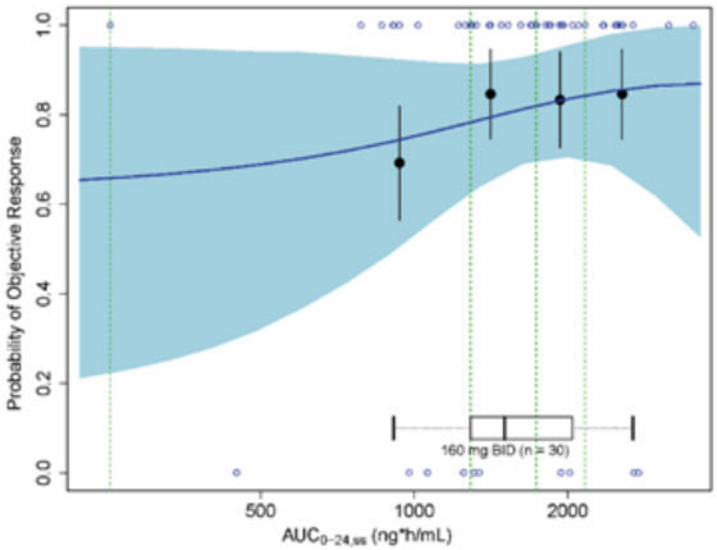
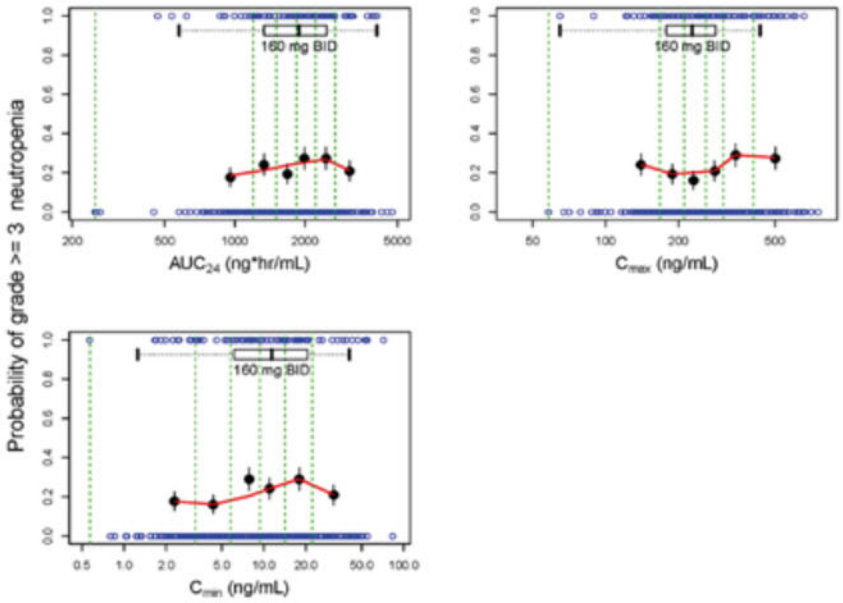


Figure 2: **Probability of Grade ≥ 3 Neutropenia vs Steady-State Exposures**



Abbreviations: AUC_{24}, steady-state area under the plasma concentration-time curve from time 0 to 24 hours; BID, twice a day; C_{max}, maximum observed plasma concentration; C_{min}, trough concentration.
The blue open circles reflect the observed events in zanubrutinib treated patients. The black solid circles are the observed probability of endpoints and the error bars are the standard errors (calculated as sqrt (P*(1-P)/N), where P is probability of endpoint and N is the number of patients in each quantile bin) for quantiles (at 100x(1/7)th percentiles, green vertical dotted lines) of exposures (plotted at the median value within each quantile). The red lines are smooth curves to show the relationship between 2 variables.

Disclosures