Poster INFO16-TH

A Phase 2/3, Multicenter, Randomized, Active-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of Zanubrutinib in Patients With Primary Membranous Nephropathy

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BACKGROUND

- Primary membranous nephropathy (pMN) is a podocyte-related disease that occurs most commonly in nondiabetic adults globally[1]
- Currently, there are no approved therapies for pMN, and there continues to be an unmet need for effective and safe options for patients with pMN[2]
- B cells play a pivotal role in the pathogenesis of pMN; B cell differentiation in the germinal center and extrafollicular pathways generates plasma cells that have direct or indirect pathogenic roles in several autoimmune diseases, including pMN[3]
- Bruton tyrosine kinase (BTK) is a pivotal component of the downstream signaling cascade of multiple immune immunoreceptors, including B cell receptors, Fc receptors, glycoprotein VI collagen receptors, chemokine receptors, and Toll-like receptors; inhibition of BTK may be a promising therapeutic target for pMN[4]
- Zanubrutinib (BGB-3111) is a highly selective, potent, irreversible, covalent BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase binding; it is approved in multiple regions for the treatment of various B cell malignancies[5]
- Notably, this is the first interventional study with BTK inhibition in pMN; it is designed to evaluate the efficacy of zanubrutinib versus tacrolimus, as well as the safety of zanubrutinib in patients with pMN

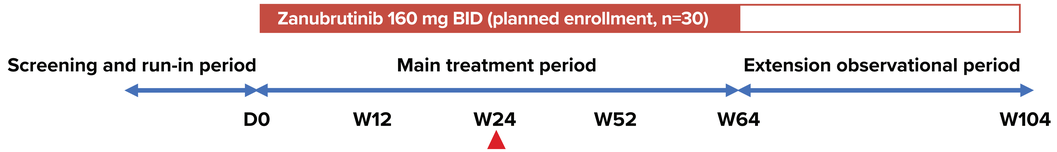
METHODS

- ALMOND (BGB-3111-309; NCT05707377) is a 2-part, phase 2/3, multicenter study investigating zanubrutinib in adult patients with pMN

Study Design: Part 1

- Part 1 is an open-label, single-arm preliminary evaluation of the efficacy and safety of zanubrutinib (**Figure 1**)
- Eligible patients will receive zanubrutinib (160 mg twice daily [BID]) for 64 weeks (planned enrollment, n=30)
- The primary endpoint is the reduction in urine protein:creatinine ratio (UPCR) from baseline at Week 24

Figure 1. Part 1 Study Design



Key inclusion criteria:

- Age 18 to 75 years
- Biopsy-confirmed pMN
- 24-hour UPCR >3.5
- Treatment with ACEI or ARB for ≥12 weeks before study drug initiation and with adequate BP control
- Anti-PLA2R antibody positive (>50 RU/mL)

Primary efficacy endpoint:

- Reduction in UPCR at Week 24 from baseline

Key secondary endpoints:

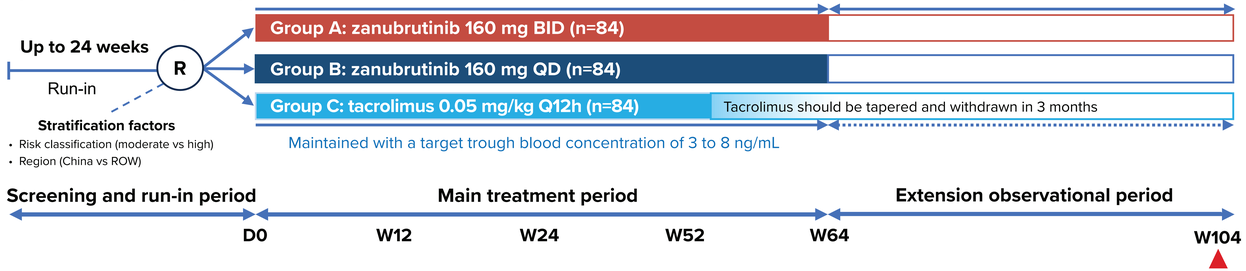
- Treatment failure rate by Week 24
- Immunological response rate at Week 24
- Complete remission rate at Weeks 24, 52, 76, and 104
- Overall remission rate at Weeks 24, 52, 76, and 104
- Relapse rate by Week 104
- Incidence and severity of TEAEs

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, twice daily; BP, blood pressure; D, day; PLA2R, phospholipase A2 receptor; pMN, primary membranous nephropathy; TEAE, treatment-emergent adverse event; UPCR, urine protein:creatinine ratio; W, week.

Study Design: Part 2

- Part 2 is a randomized, open-label, active-controlled evaluation of the efficacy of zanubrutinib versus tacrolimus and the safety of zanubrutinib in patients with pMN (**Figure 2**)
- Part 2 will begin enrollment once Part 1 enrollment has concluded
- Eligible patients will be randomized to receive zanubrutinib 160 mg BID (Group A), 160 mg once daily (Group B), or tacrolimus 0.05 mg/kg/day every 12 hours (Group C) for 64 weeks (planned enrollment, n=84 in each arm)
- The primary endpoint is the complete remission rate at Week 104

Figure 2. Part 2 Study Design



Key inclusion criteria:

- Age 18 to 75 years
- Biopsy-confirmed pMN
- 24-hour UPCR >3.5
- Treatment with ACEI or ARB for ≥24 weeks before randomization and with adequate BP control

Primary efficacy endpoint:

- Complete remission status at Week 104

Secondary efficacy endpoints:

- Overall remission rate at Week 104
- Complete remission rate at Weeks 24, 52, and 76
- Overall remission rate at Weeks 24, 52, and 76
- Treatment failure rate by Week 24, 52, 76, and 104
- Time to first complete remission
- Time to first overall remission
- Relapse rate by Week 104
- Time to first relapse
- HRQoL
- ≥30% eGFR reduction from baseline to Weeks 52 and 104
- Incidence and severity of TEAEs

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, twice daily; BP, blood pressure; D, day; eGFR, estimated glomerular filtration rate; HRQoL, health-related quality of life; pMN, primary membranous nephropathy; Q12h, every 12 hours; QD, once daily; R, randomization; ROW, rest of world; TEAE, treatment-emergent adverse event; UPCR, urine protein:creatinine ratio; W, week.

Statistical Assumptions

Part 1

- Approximately 30 patients will be enrolled
- With data from 30 patients, if the mean reduction in UPCR at Week 24 from baseline is <1.2 (assuming an SD of 2), the posterior probability that the mean reduction is ≥1.5 is less than 20%
- If this occurs, the study may be halted depending on the review of data from other efficacy and safety endpoints

Part 2

- The sample size is based on the following assumptions:
  1. Complete remission rate at Week 104: 5% for Group C[6] and 22% for Groups A or B
  2. Overall remission rate at Week 104: 25% for Group C[6] and 50% for Groups A or B
- With these assumptions, 1-sided α of 0.025, and randomization ratio of 1:1:1, a total of 252 randomized patients are needed to achieve approximately 90% power for the targeted treatment effect of the complete remission rate in assumption 1, and 82% power for the targeted treatment effect of the overall remission rate in assumption 2

Trial Status

- Study enrollment is ongoing

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DISCLOSURES

RL reports receiving compensation as a member of the study steering committee for BeiGene, Inc; **YC, SZ, JS,** and **ZY** report employment by BeiGene; **SB, CT, GL,** and **MZ** have nothing to disclose.

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