# Abstract: PB2019

# Title: PHASE 1B CLINICAL STUDY OF IRAK 1/4 INHIBITION FOR LOW-RISK MYELODYSPLASTIC SYNDROMES REFRACTORY/RESISTANT TO PRIOR THERAPIES: A TRIAL IN PROGRESS

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**Background:**

Chronic stimulation of both interleukin-1 receptor (IL-1R) and toll-like receptors (TLRs) in myeloid progenitors is thought to cause a bone marrow proinflammatory environment responsible for persistent cytopenia in patients with low-risk (LR)-MDS. IRAK1 and IRAK4 are serine/threonine kinases that are critical for the downstream signaling of IL-1R and most TLRs resulting in the production of proinflammatory cytokines and NLRP3 inflammasome-driven pyroptosis leading to bone marrow inflammation and cell death. Thus, IRAK1/4 inhibition is a potential target for the treatment of LR-MDS by decreasing inflammation and cell death within the bone marrow allowing the restoration of hematopoiesis.

R289 is a prodrug that is converted to the active drug R835 in the gastrointestinal (GI) tract. R835 is a potent and selective inhibitor of IRAK1 and IRAK4 kinases and inhibits TLR and IL-1R-dependent proinflammatory cytokine production in multiple cell types. *In vivo*, R835 blocks TLR4 and IL-1R-dependent systemic cytokine release in mice.

The safety and pharmacokinetic properties of R289/R835 were evaluated in a phase 1 healthy volunteer study (Study C-906289-001). R289 was well tolerated with no serious or severe adverse events (AEs) reported. Most AEs were mild and transient; the most common AEs (mild/moderate) were headache and GI disturbance. Overall, the trial supported the advancement of R289 into further studies.

**Aims:**

An open-label Phase 1b study to determine the tolerability and preliminary efficacy of R289 for patients with LR-MDS refractory to prior therapies is currently enrolling patients.

**Methods:**

The current study (NCT05308264) includes a dose escalation phase (up to 12 patients) and a dose expansion phase (up to 10 patients). Inclusion criteria for both phases will include patients ≥18 years with a definitive diagnosis of LR-MDS. Exclusion criteria will include prior treatment for MDS that concluded <4 weeks prior to study treatment. **Dose Escalation Phase:** Dose escalation will utilize a 3+3 design to determine the maximum tolerated dose (MTD). R289 tablets can be taken orally with or without food. Dose limiting toxicity (DLT) will be assessed at each dose level. The DLT evaluation period will be 28 days. After completion of the DLT evaluation period, patients who do not experience DLTs may remain on treatment at their respective dose level if they continue to demonstrate clinical benefit without toxicity. **Dose Expansion Phase:** Up to 10 additional patients with LR-MDS will be enrolled; the primary endpoint of the study will be the safety and tolerability of R289. The secondary endpoints will include an assessment of preliminary efficacy and the characterization of the pharmacokinetics of R289. R289 will be administered to all patients at a dose not to exceed the MTD determined in the Dose Escalation Phase. The trial is currently recruiting at 8 US sites.