**Introduction**

Systemic mastocytosis (SM) is a rare, clonal mast cell (MC) neoplasia driven by the KIT D816V mutation in >90% of cases. 1 The KIT D816V mutation leads to increased accumulation of neoplastic mast cells in bone marrow, skin, gastrointestinal tract, and other organs, which can result in debilitating symptoms that negatively impact quality of life (QoL). 2

Most patients with SM have non-advanced forms (non-AdvSM), including the World Health Organization (WHO) classified variant of indolent SM (ISM). 3

Approximately 5% of patients with ISM progress to advanced SM (AdvSM) associated with poor survival. 4 Therefore, novel therapeutic strategies are needed for ISM and AdvSM to delay or even prevent disease progression.

**Monoclonal mast cell activation syndrome (mMCAS)**

Is a rare, clonal MC disease which does not meet the WHO diagnostic criteria for SM but is defined by the presence of the KIT D816V mutation. 5

Most patients with SM have non-advanced forms (non-AdvSM), including the World Health Organization (WHO) classified variant of indolent SM (ISM). 6

**Study objectives and design**

**Part 1**

- **Study design**: Open-label, phase 1/2 study to determine the recommended dose (RD) of BLU-263 to be studied in part 2 and to evaluate the safety, tolerability, and efficacy of BLU-263 in patients with ISM or mMCAS who have not previously received any targeted KIT inhibitor therapy and in whom symptoms are not adequately controlled by best supportive care (BSC).

- **Objectives**: Measure the mean change in ISM-SAF TSS and ISM-SAF Individual Symptom Scores from baseline to Morgan-to-severe symptoms based on the ISM-SAF mean total symptom score (part 1).

- **Exclusion criteria**: Patients with history of a primary malignancy that has been diagnosis (neoplasms or organ damage C-findings attributable to SM).

**Part 2**

- **Study design**: Randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, and efficacy of BLU-263 vs placebo (PBO) in patients with ISM or mMCAS who have not previously received any targeted KIT inhibitor therapy and in whom symptoms are not adequately controlled by best supportive care (BSC).

- **Objectives**: Determine the RD of BLU-263 and to evaluate the safety, tolerability, and efficacy of BLU-263 in patients with ISM or mMCAS who have not previously received any targeted KIT inhibitor therapy and in whom symptoms are not adequately controlled by best supportive care (BSC).

- **Exclusion criteria**: Patients with history of a primary malignancy that has been diagnosis (neoplasms or organ damage C-findings attributable to SM).