# PROSPECTOR: A Global, Prospective Study to Determine the Prevalence of the *KIT* D816V Mutation in Peripheral Blood From Patients With Evidence of Systemic Mast Cell Activation

Poster Number 161

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## Background

- Mast cell activation syndromes (MCAS) are a group of disorders characterized by systemic mast cell (MC) activation which can be caused by IgE-mediated and non-IgE-mediated triggers[1–3]
- Patients may experience debilitating symptoms associated with abnormal mast cell mediator release involving 2 or more organ systems (**Table 1**)[1,2,4]
- MCAS can be classified as clonal or non-clonal based on the presence or absence of the *KIT* D816V mutation and/or aberrant CD25 expression on MCs[2,5]
- Systemic mastocytosis (SM) is a rare clonal MC disease primarily driven by the *KIT* D816V mutation in approximately 95% of cases[6,7]
- Importantly, *KIT* D816V in bone marrow (BM) MCs can be detected in early stages of SM[5], however, the invasive nature of BM sampling required for diagnosis per World Health Organization (WHO)[8] criteria and limited molecular assay sensitivity can be barriers for diagnosis[7]
- The Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]) developed a scoring system, that is not dependent on BM biopsies, for predicting MC clonality in patients presenting with MCAS symptoms[9,10]
- Further, high sensitivity real-time qPCR assays, such as allele-specific oligonucleotides-PCR[6] or droplet digital PCR[11], are now available to detect the presence of *KIT* D816V more reliably in peripheral blood (PB)[12]
- Testing for increased *TPSAB1* gene copy number (GCN) as an indicator of hereditary alpha-tryptasemia (HaT), which causes elevated serum tryptase, may also aid in the diagnosis of SM[13]
- Despite these efforts, the prevalence of clonal mast cell disease with evidence of systemic MCA is still unknown and warrants further investigation

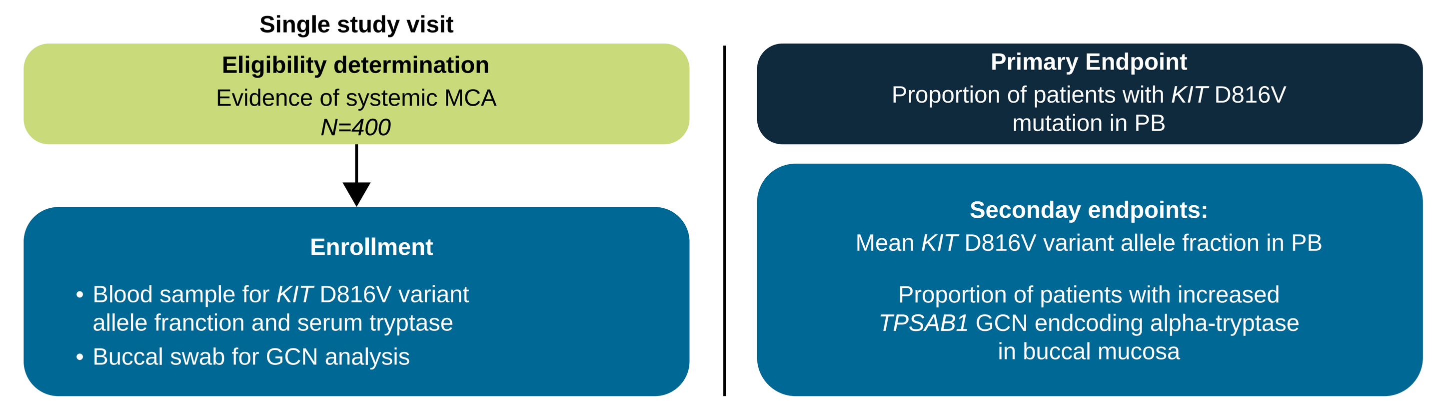
### Table 1. Summary of symptoms related to systemic mast cell activation

| Organ system | Symptoms |
|---|---|
| Skin | Pruritus, urticaria, angioedema, and flushing |
| Gastrointestinal | Nausea, vomiting, diarrhea, and abdominal cramping |
| Cardiovascular | Hypotensive syncope or near syncope, and tachycardia |
| Respiratory/naso-ocular | Wheezing, conjunctival injection, and nasal congestion |
| Neurological | Difficulty concentrating, fatigue, headaches |
| Musculoskeletal | Bone pain, muscle pain, osteopenia |

## Study design and objectives

- PROSPECTOR (NCT04811365) is a global, multi-center screening study determining the prevalence of *KIT* D816V mutation in PB in patients with evidence of systemic MCA (**Figure 1**)
- The key eligibility criteria and key study endpoints are shown in **Table 2** and **Table 3**, respectively

### Figure 1. PROSPECTOR study design


Single study visit
Eligibility determination
Evidence of systemic MCA
N=400
Enrollment
• Blood sample for KIT D816V variant allele franction and serum tryptase
• Buccal swab for GCN analysis
Primary Endpoint
Proportion of patients with KIT D816V mutation in PB
Seconday endpoints:
Mean KIT D816V variant allele fraction in PB
Proportion of patients with increased TPSAB1 GCN endcoding alpha-tryptase in buccal mucosa

GCN, gene copy number; MCA, mast cell activation; PB, peripheral blood; TPSAB1, tryptase Alpha/Beta 1.

### Table 2. Key eligibility criteria

**Inclusion criteria**

- Aged ≥18 years
- Evidence of systemic mast cell activation, based on meeting ≥1 of 3 criteria:
  - Involvement of ≥2 organ systems (cardiovascular involvement necessary) and serum basal tryptase ≥8 ng/mL
  - Severe anaphylaxis from hymenoptera sting
  - Severe anaphylaxis with cardiovascular involvement and event-related tryptase elevation fitting the formula 20% of baseline plus 2 ng/mL in ≥1 event

**Exclusion criteria**

- Patients with known diagnoses of mastocytosis, including:
  - Mastocytosis in the skin
  - Indolent systemic mastocytosis
  - Smoldering systemic mastocytosis
  - Systemic mastocytosis with associated hematologic neoplasm
  - Aggressive systemic mastocytosis
  - Mast cell leukemia
  - Mast cell sarcoma

### Table 3. Key study endpoints

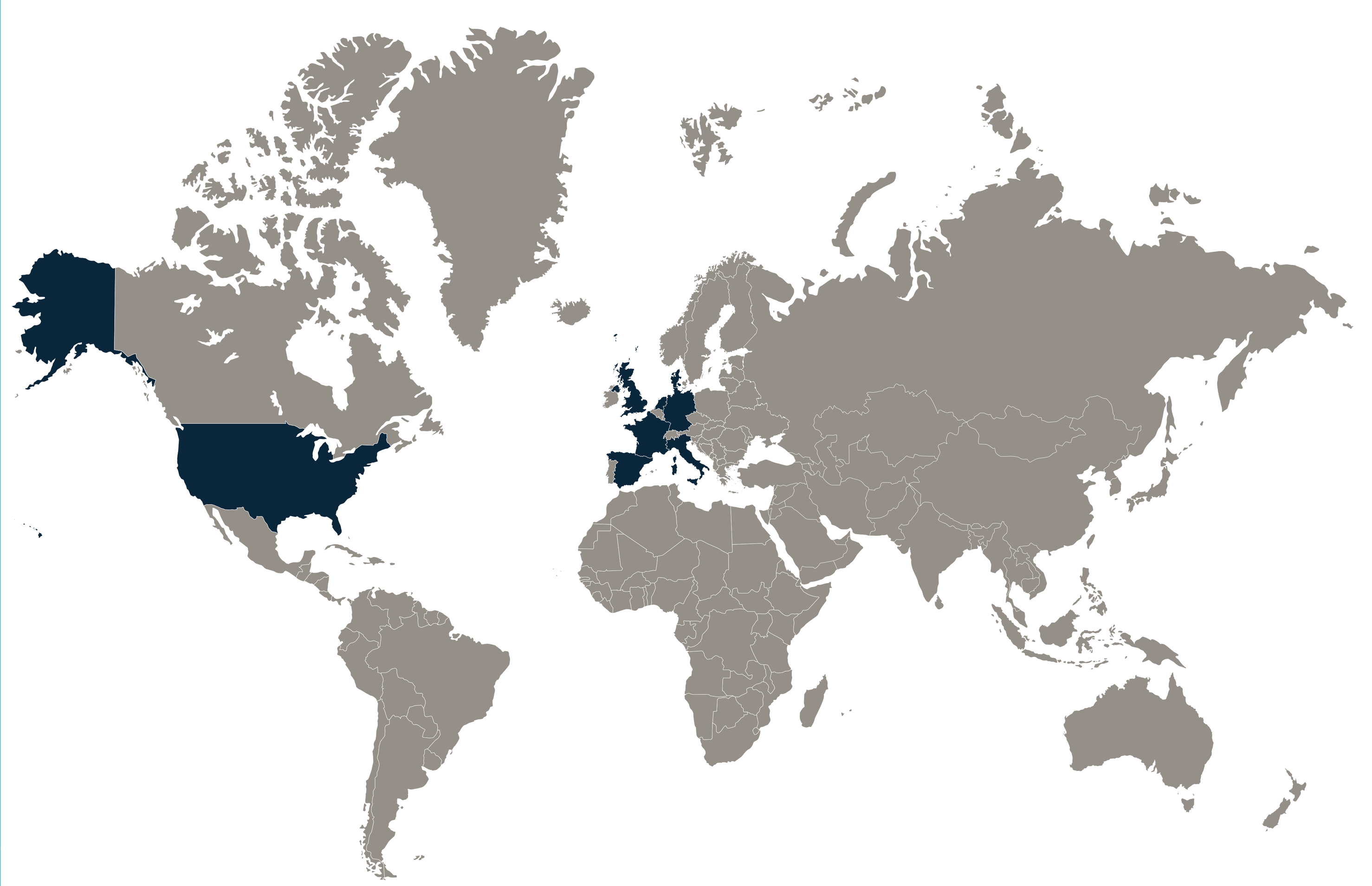
| Primary endpoint | Secondary endpoints |
|---|---|
| • The prevalence of *KIT* D816V mutation in PB by droplet digital PCR defined as the proportion of patients with evidence of systemic MCA and the *KIT* D816V mutation in PB | • *KIT* D816V variant allele fraction in PB<br>• The prevalence of HaT defined as the proportion of patients with an increased *TPSAB1* GCN encoding alpha-tryptase on a single allele in buccal mucosa<br>• The relationship between *KIT* D816V in PB and REMA score, other MCA clinical parameters or HaT diagnosis |

HaT, hereditary alpha-tryptasemia; REMA, Red Española de Mastocitosis.

## Enrollment and status

- Enrollment in PROSPECTOR is ongoing with 24 planned centers participating in the United States, the United Kingdom, and Europe (**Figure 2**)
- As of August 15, 2022, there were 105 patients enrolled and evaluated for *KIT* D816V mutation (**Table 4**) in PB using droplet digital PCR
  - 3/105 patients (2.9%) had detectable *KIT* D816V mutation
  - 15/105 patients (14.3%) had tryptase levels ≥20 ng/ml and 23.8% (25/105) of patients had increased *TPSAB1* GCN

### Figure 2. Countries with active enrollment sites



### Table 4. Preliminary baseline demographics

| Characteristic | N=105 | | |
|---|---|---|---|
| Age, mean (range) | 55.7 (19–86) | | |
| Gender, n (%) | | | |
| Female | 59 (56.2) | | |
| Male | 46 (43.8) | | |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 2 (1.9) | | |
| Not Hispanic or Latino | 64 (61.0) | | |
| Not reported | 36 (34.3) | | |
| Unknown | 3 (2.9) | | |
| *KIT* D816V positive, n (%) | 3 (2.9)[a] | | |
| Increased *TPSAB1* GCN, n (%) | 25 (23.8) | | |
| Serum tryptase (ng/mL), n (%) | All patients | *KIT* D816V positive | Increased *TPSAB1* GCN |
| 0–<8 | 42 (40.0) | 1 (1.0) | 0 (0) |
| 8–<20 | 44 (41.9) | 2 (1.9) | 16 (15.2) |
| ≥20 | 15 (14.3) | 0 (0) | 8 (7.6) |
| Unknown | 4 (3.8) | 0 (0) | 1 (1.0) |
| REMA score, mean (range) | -1.3 (-4–7) | | |
| Inclusion criteria, n (%) | | | |
| Involvement of ≥2 organ systems (cardiovascular involvement necessary) and serum basal tryptase ≥8 ng/mL | 45 (42.9) | | |
| Severe anaphylaxis from hymenoptera sting | 44 (41.9) | | |
| Severe anaphylaxis with cardiovascular involvement and event-related tryptase elevation fitting the formula 20% of baseline plus 2 ng/mL in ≥1 event | 16 (15.2) | | |

[a]The number of *KIT* D816V positive patients was initially reported to be 7 (6.7%) but subsequently was amended to 3 (2.9%).

## Summary

- PROSPECTOR is a multicenter prospective screening study that aims to determine the prevalence of clonal mast cell disease in patients with evidence of systemic mast cell activation and the study is currently ongoing
- The frequency of patients positive for *KIT* D816V in this population suggests patients with MCA symptoms may have higher risk of clonal mast cell disease such as SM, which has a general prevalence of 1:10,000[14]
- Despite the high sensitivity of droplet digital PCR, the detection of low *KIT* D816V mutant allele frequency levels (<0.02%) in PB can be problematic; notably, some patients had increased serum tryptase without HaT, but were negative for *KIT* D816V
- Enrichment strategies and/or higher sensitive assays may be required to more accurately detect the *KIT* D816V mutation in patients with clonal mast cell disorders
- For more information, visit

**https://clinicaltrials.gov/ct2/show/NCT04811365**

- To learn more about our clinical trials, visit blueprintclinicaltrials.com or contact us in the USA at medinfo@blueprintmedicines.com or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at medinfoeurope@blueprintmedicines.com or +31 85 064 4001

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