Elenestinib, an Investigational, Next Generation KIT D816V Inhibitor, Reduces Mast Cell Burden, Improves Symptoms, and Has a Favorable Safety Profile in Patients with Indolent Systemic Mastocytosis: Analysis of the HARBOR Trial

Tsewang Tashi,[1] Olivier Hermine,[2] Mariana Castells,[3] Mar Guilarte,[4] Vito Sabato,[5] Marcus Maurer,[6,7] Jens Panse,[8] Ivan Alvarez-Twose,[9] Renata Cabral,[10,11] Robert Bird,[12] Stéphane Barete,[13] Laurence Bouillet,[14] Paul Van Daele,[15] David González-De-Olano,[16] Elizabeth A. Griffiths,[17] Joseph Jurcic,[18] Ingunn Dybedal,[19] Gandhi Laurent Damaj,[20] Philippe Schafhausen,[21] Chiara Elena,[22] Tse-Chieh Teh,[23] Pankit Vachhani,[24] Caroline Labe,[25] Saranya Venugopal,[25] Kevin He,[25] Javier Muñoz-González,[26] Ben Lampson,[25] Robyn Scherber,[25] Prithviraj Bose,[27] Clive Grattan,[28] Thanai Pongdee,[29] Tracy I. George,[30] and Cristina Bulai Livideanu[31]

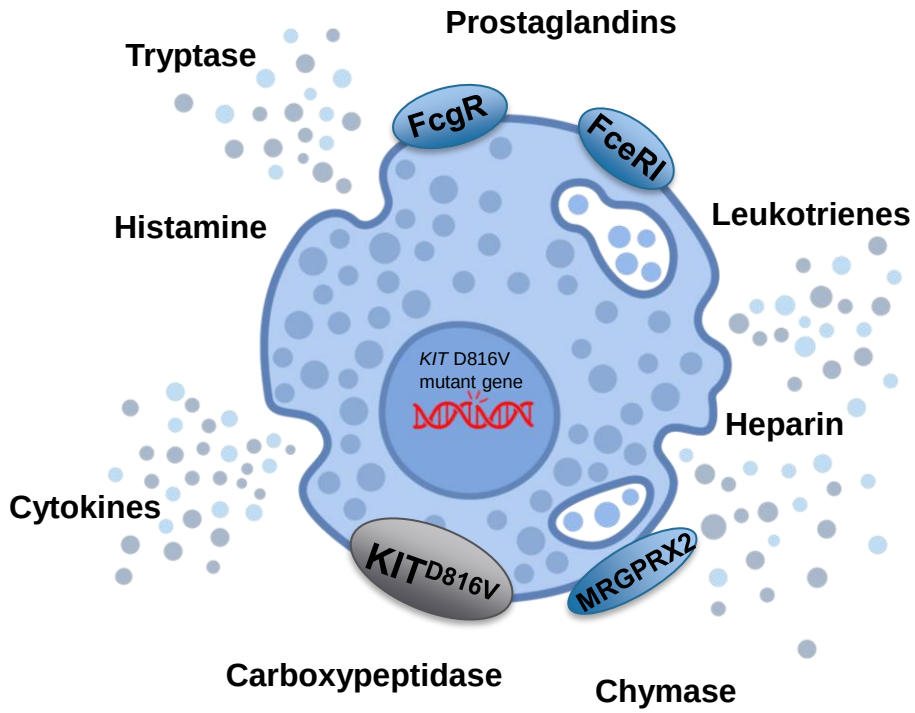
[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [2]Département d'Hématologie, CEREMAST, Hôpital Necker-Enfants Malades, APHP et Institut Imagine, Paris, France; [3]Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA; [4]Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Barcelona, Spain; [5]Department of Immunology, Allergology, and Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; [6]Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [7]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Hindenburgdamm, Berlin, Germany; [8]Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany; [9]Institute of Mastocytosis Studies of Castilla-La Mancha (CLMast), Virgen del Valle Hospital, Toledo, Spain; [10]Centro Hospitalar Universitário do Porto, Porto, Portugal; [11]ICBAS-School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal; [12]Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; [13]Unit of Dermatology Reference Centre for Mastocytosis (CEREMAST) AP-HP, Pitié-Salpêtrière Hospital, Sorbonne Université, Paris, France; [14]Internal Medicine Department, CHU Grenoble Alpes, Grenoble, France; [15]Erasmus Medical Center, Rotterdam, Netherlands; [16]University Hospital Ramón y Cajal, IRYCIS, Madrid, Spain; [17]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [18]Division of Hematology/Oncology, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; [19]Department of Hematology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [20]Hematology Institute, University Of Caen Normandie Hospital Center, Caen, France; [21]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [22]Department of Molecular Medicine & Department of Hematology and Oncology, University of Pavia, Pavia, Italy; [23]Alfred Hospital, Melbourne, Australia; [24]University of Alabama at Birmingham, Birmingham, AL; [25]Blueprint Medicines Corporation, Cambridge, MA; [26]Blueprint Medicines Corporation, Zug, Switzerland; [27]The University of Texas MD Anderson Cancer Center, Houston, TX; [28]St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom; [29]Division of Allergic Diseases, Mayo Clinic, Rochester, MN; [30]ARUP Laboratories, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT; [31]Département de Dermatologie Expert Centre of Mastocytosis (CEREMAST), CHU de Toulouse, Toulouse University Hospital - Larrey Hospital, Toulouse, France.

Corresponding author: tsewang.tashi@utah.edu

Systemic mastocytosis (SM) is a clonal mast cell (MC) disease driven by the *KIT* D816V mutation[1,2]

- SM is a spectrum of diseases driven by aberrant MCs carrying a *KIT* D816V mutation in >95% of cases[1,2]
- Morbidity and mortality due to SM is mainly caused by the **accumulation of MCs** and **excessive release of numerous inflammatory mediators** from these MCs[3,4]
- Indolent systemic mastocytosis (ISM) is the most common subtype of SM and can progress to higher burden disease in up to 18% of cases[5]

ISM pathogenesis[3,4,6]

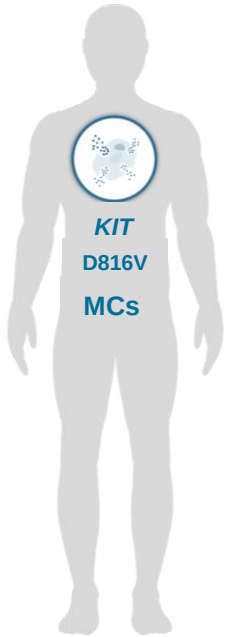


ISM, indolent systemic mastocytosis; MC, mast cell; SM, systemic mastocytosis.

1. Kristensen T et al. *J Mol Diagn.* 2011;13:180–188; 2. Cohen SS et al. *Br J Haematol.* 2014;166:521–528; 3. Pardanani A et al. *Am J Hematol.* 2023;98:1097–1116; 4. Theoharides TC et al. *N Engl J Med.* 2015;373:163–172; 5. Mukherjee S et al. Presented at ASH 2022. Poster #3053; 6. Metcalfe DD et al. Chapter 1. Overview of mast cells in human biology. In Akin C, ed. *Mastocytosis: A Comprehensive Guide*. Cham, Switzerland: Springer Nature; 2020.

Symptom improvement is the gold standard by which to measure success of ISM therapy

- Symptoms of ISM manifest in numerous organ systems and most commonly include cutaneous, gastrointestinal, and neurocognitive symptoms, which may be **debilitating**[1–4]



SKIN
Darier's sign, **urticaria pigmentosa**, extreme flushing, pruritus

CARDIOVASCULAR
Syncope, dizziness, palpitations, hypotensive anaphylaxis

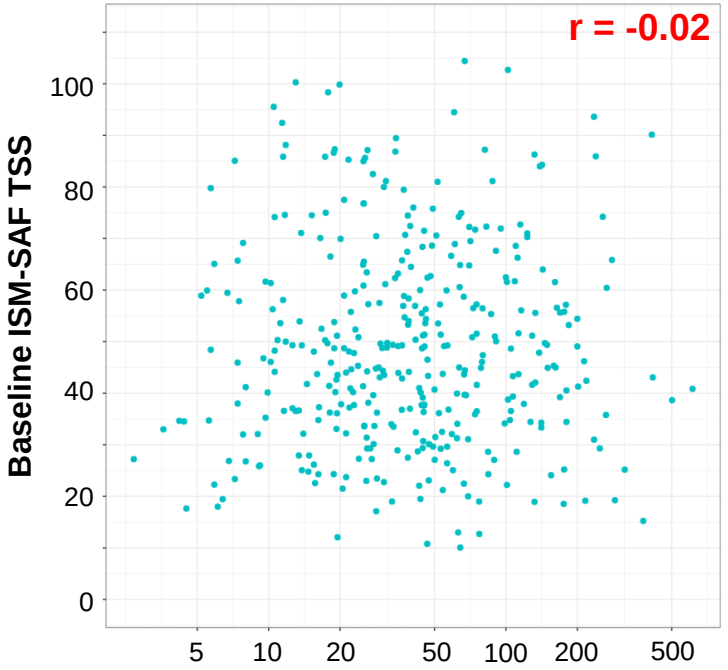
SYSTEMIC
Fatigue, malaise, weight loss

NEUROPSYCHIATRIC
Brain fog, depression, migraines, anxiety

MUSCULOSKELETAL
Bone/muscle pain, osteoporosis, osteopenia, bone fractures

GASTROINTESTINAL
Diarrhea, nausea/vomiting, abdominal pain

No correlation between tryptase and baseline symptoms (N=373)[a]



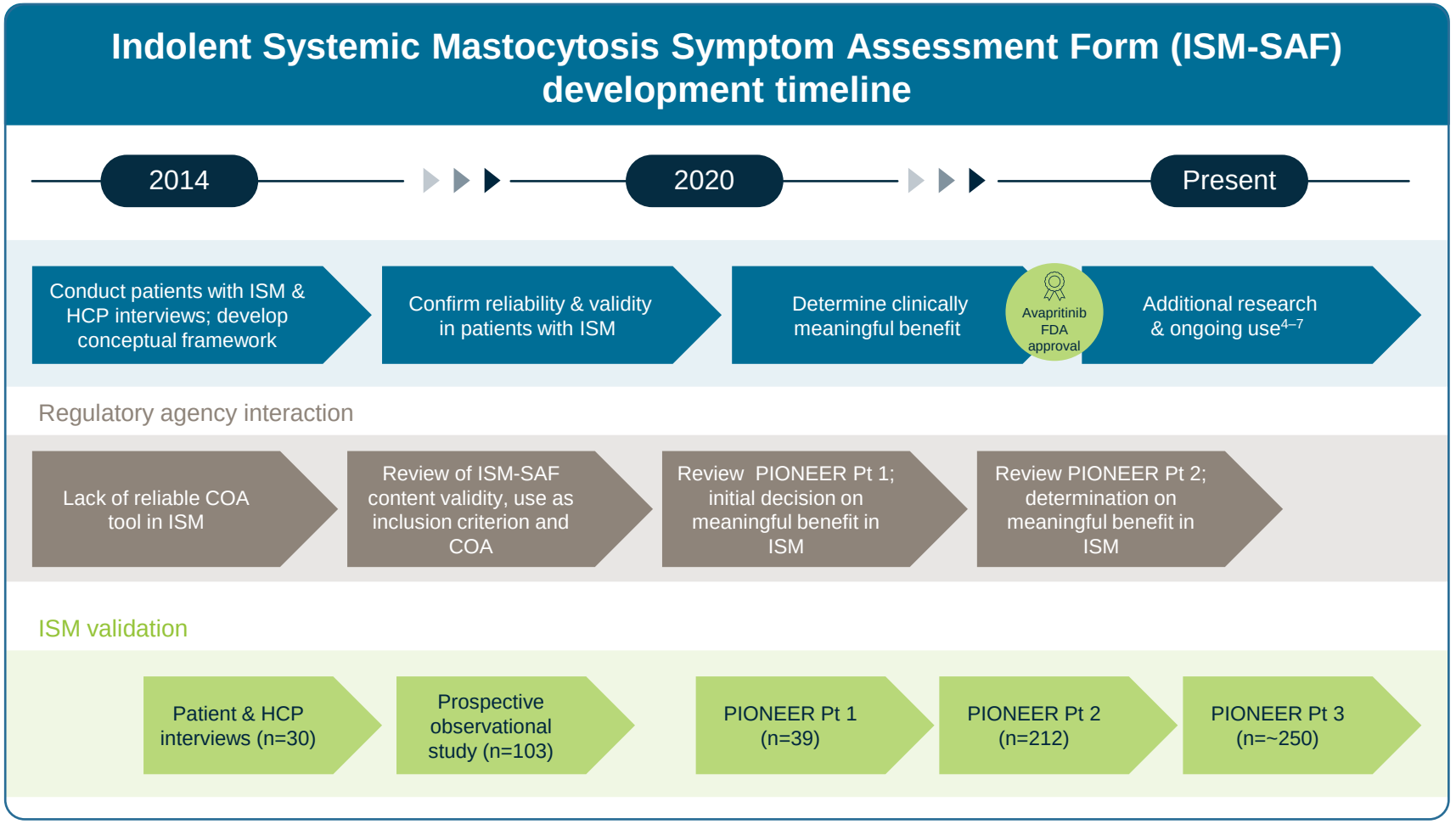
[a]based on patients with baseline assessments from PIONEER and HARBOR studies

- **Validated tools** are required to assess response to therapy and symptom improvement across a broad range of symptoms

1. Mesa RA et al. *Cancer.* 2022;128:3691–3699; 2. van Anrooij B. et al. *Allergy.* 2016;71:1585–1593; 3. Hartmann K et al. *J Allergy Clin Immunol.* 2016;137:35–45; 4. Hermine O et al. *PLoS One*.;3:e2266

ISM-SAF: a validated clinical outcome assessment (COA) tool to determine meaningful symptom improvement in patients with ISM[1–3]

Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) development timeline



ISM-SAF

ISM symptom	Scoring
Abdominal pain	11 symptoms scored 0–10 daily on handheld device
Diarrhea	
Nausea	
Spots	
Itching	0 = no symptom 10 = **worst imaginable** symptom
Flushing	
Brain fog	
Headache	Analyzed as a 14-day moving average
Dizziness	
Bone pain	
Fatigue	

TSS (0–110)
Higher scores represent more severe symptoms

COA, clinical outcome assessment; HCP, healthcare professional; ISM-SAF, indolent systemic mastocytosis-Symptom Assessment Form (©2018); TSS, total symptom score.

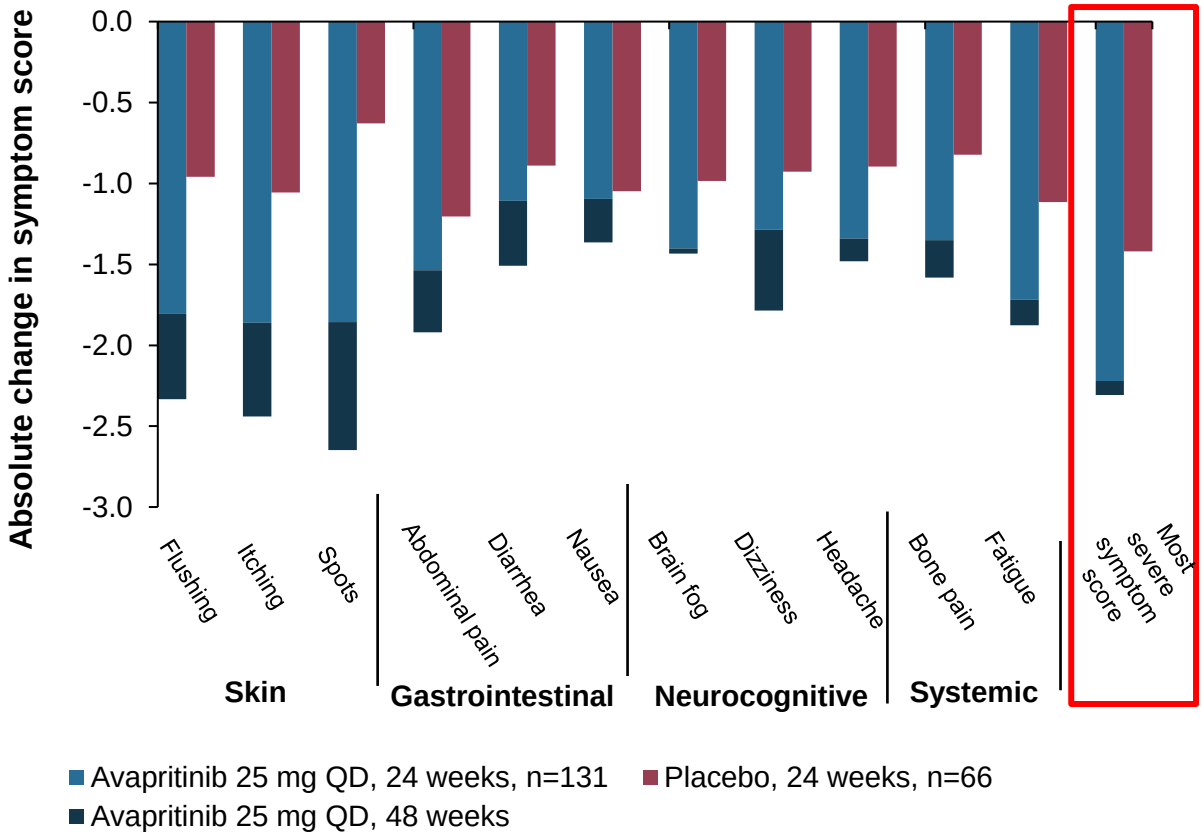
1. Shields A et al. *Orphanet J Rare Dis.* 2023;18:69; 2. Taylor F et al. *Orphanet J Rare Dis.* 2021;16:414; 3. Padilla B et al. *Orphanet J Rare Dis.* 2021;16:434; 4. Mesa R et al. *Cancer* 2022:128:3691; 5. Mesa et al. Presented at ISPOR EU 2023. Poster #PCR136; 6. Veitch et al. Presented at ASH 2023. Abstract #4579; 7. Gotlib J et al. *NEJM Evidence.* 2023;2

Targeting KIT D816V in Indolent Systemic Mastocytosis results in deepening symptom improvement

PIONEER[a], a randomized double-blind placebo-controlled trial of 251 patients with ISM, studied avapritinib, a KIT^{D816V}-specific inhibitor

- Avapritinib was well tolerated with a similar safety profile to placebo[1]
- Avapritinib improved symptoms and biomarkers of MC burden[1]
- Safety and efficacy resulted in the approval for patients with ISM, setting a new standard of care

Symptom improvement in the PIONEER Trial as measured by the ISM-SAF



[a]NCT03731260.

Gotlib J et al. *NEJM Evidence.* 2023;2

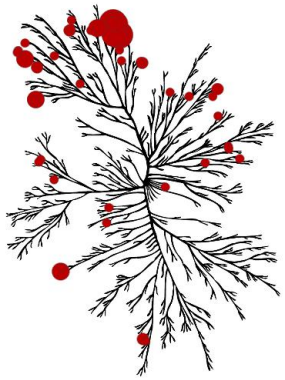
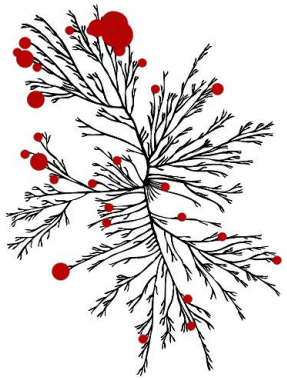
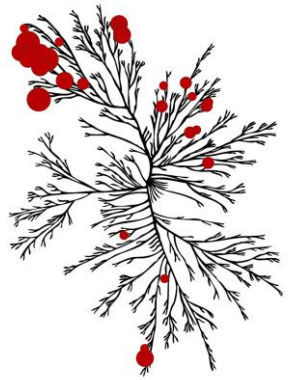
Elenestinib (BLU-263): A next-generation, potent, selective KIT D816V inhibitor

- **Elenestinib** is a novel, investigational, oral, next-generation tyrosine kinase inhibitor that is non-brain penetrant[1,2]
- **Potently** and **selectively** inhibits KIT D816V while **preferentially sparing** wild-type KIT

	KIT D816V phosphorylation IC_{50}	WT KIT proliferation IC_{50}	WT KIT phosphorylation IC_{50}
Elenestinib	**3.1 nM**	**95.9 nM**	**82.6 nM**
Avapritinib	**3.1 nM**	**85.8 nM**	**89.5 nM**
Bezuclastinib	**3.4 nM**	**26.4 nM**	**32.5 nM**

- **Well-characterized** product formulation allowing for **once-daily** (QD) dosing[1,2]

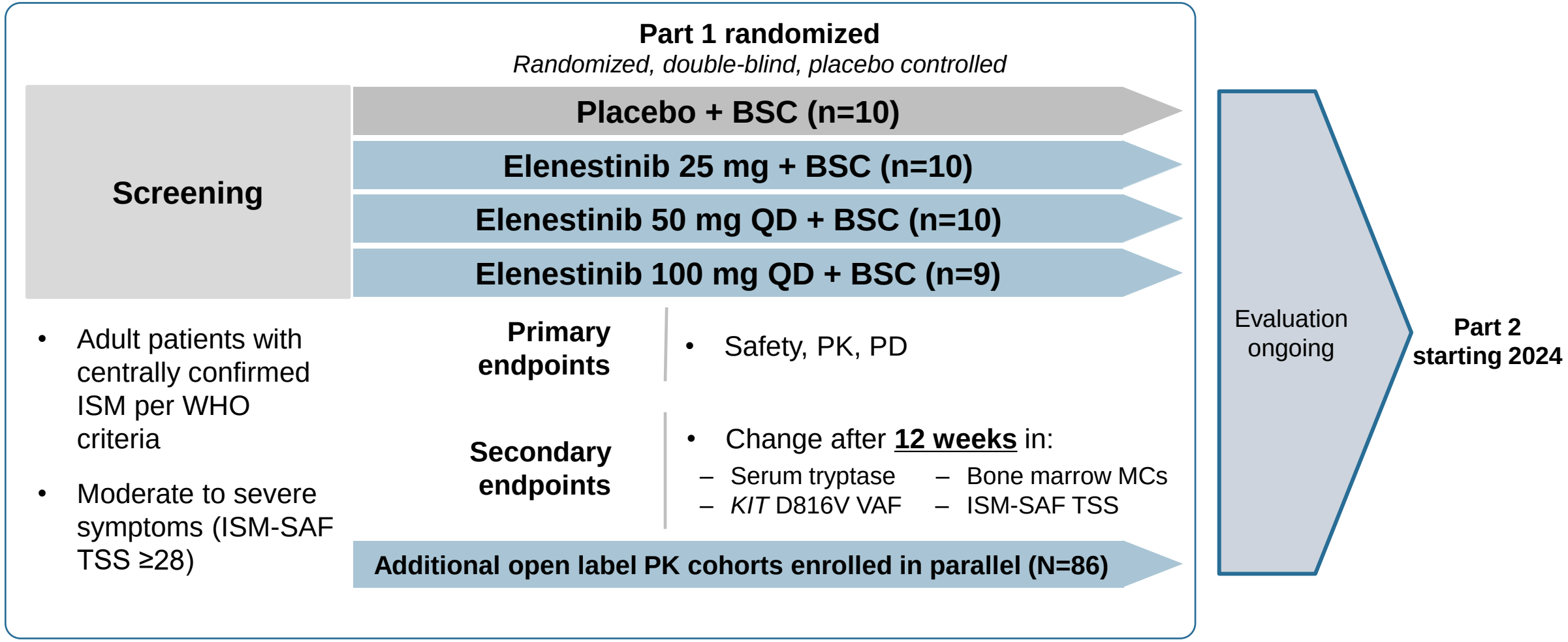
Selectivity profiles of KIT D816V inhibitors in clinical development or approved for systemic mastocytosis

Drug:	**Elenestinib**	**Avapritinib**	**Bezuclastinib**
Kinome tree[a]:			
Selectivity S-score: (fraction of kinome bound by drug, more selective = lower s-score)	**0.035**	**0.035**	**0.057**
	First in human 2020, investigational	First in human Oct 2015, **approved**	First in human Mar 2015, investigational

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.
IC_{50}, half-maximal inhibitory concentration; QD, once daily; WT, wild-type.

1. Dave N et al. Presented at AACR 2021. Poster #CT122; 2. Castells M et al. Presented at EHA 2022. Poster #1017

HARBOR Part 1[a]: Randomized, double-blind, placebo-controlled dose-finding part of elenestinib



[a]NCT04910685.
BSC, best supportive care; PD, pharmacodynamics; PK, pharmacokinetic; VAF, variant allele fraction; WHO, World Health Organization.

Baseline patient demographics and characteristics of Part 1 groups

- **A total of 39 patients** were randomized into the double-blinded, placebo-controlled dose-finding portion of HARBOR Part 1
- Baseline patient and disease characteristics were similar to those reported for the general ISM population

	Placebo (n=10)	Elenestinib All doses (n=29)
Patient demographic		
Age (years), median (range)	47.5 (25–65)	54.0 (24–74)
Female, n (%)	8 (80.0)	22 (75.9)
ISM symptom burden		
TSS score, mean (SD)	49.4 (13.8)	42.18 (18.04)
MC burden		
Median serum tryptase (central), ng/mL (range)	41.5 (5.2–129.0)	34.1 (6.8–612.0)
Median bone marrow biopsy MCs (central), % (range)	10.0 (1.0–25.0)	7.0 (2.0–60.0)
Median *KIT* D816V VAF in peripheral blood, % (range)[a]	0.1 (0.0–6.7)	0.11 (0.0–30.52)
Best supportive care use[b]		
Median (range) medications used	2.5 (1–6)	3.0 (0–6)

[a]By central assessment; [b]Categories included H1/H2 blockers, proton pump inhibitors, leukotriene receptor antagonists, cromolyn sodium, corticosteroids, omalizumab.
SD standard deviation.
Gotlib J et al. *NEJM Evidence.* 2023;2

Elenestinib was well-tolerated with most AEs reported as Grade 1–2

- Median treatment duration was 22 weeks and elenestinib was well tolerated at all dose levels
- There were no grade 4 or 5 AEs, no treatment-related SAEs, and no AEs that led to drug discontinuation
- At the time of data cut, all patients were still on treatment

Parameter	Placebo (n=10)		Elenestinib 25 mg QD (n=10)		Elenestinib 50 mg QD (n=10)		Elenestinib 100 mg QD (n=9)	
	ALL	RELATED	ALL	RELATED	ALL	RELATED	ALL	RELATED
Any grade AE	9 (90.0)	3 (30.0)	9 (90.0)	6 (60.0)	8 (80.0)	3 (30.0)	9 (100.0)	5 (55.6)
Grade 1–2 AEs, n (%)	9 (90.0)	3 (30.0)	9 (90.0)	6 (60.0)	5 (50.0)	3 (30.0)	7 (77.8)	4 (44.4)
Grade ≥3 AEs, n (%)	0	0	0	0	3 (30.0)[a]	0	2 (22.2)[a]	1 (11.1)[a]
SAEs, n (%)	0	0	0	0	1 (10.0)	0	2 (22.2)	0
AEs leading to discontinuation, n (%)	0	0	0	0	0	0	0	0

[a]Including one event each of anaphylaxis, hypertension, esophageal candidiasis at 50 mg (all unrelated); one event each of leu kopenia (related); and renal failure (unrelated) at 100 mg.
Data cut off date October 17, 2022.
AE, adverse event; SAE, serious adverse event

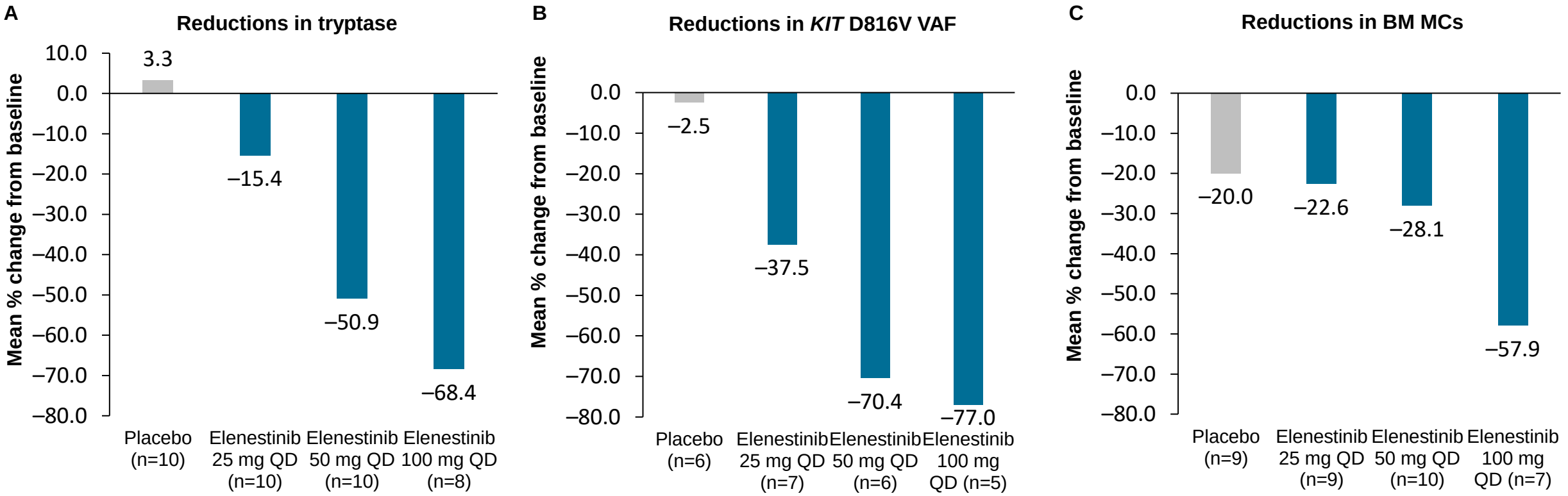
Adverse Events (AEs) occurring in >1 patient at any cohort

Adverse event[a]	Placebo (n=10)		Elenestinib 25 mg QD (n=10)		Elenestinib 50 mg QD (n=10)		Elenestinib 100 mg QD (n=9)	
	Any-cause	Treatment-related	Any-cause	Treatment-related	Any-cause	Treatment-related	Any-cause	Treatment-related[b]
Headache	2	0	2	2	3	1	2	0
Arthralgia	1	0	3	1	2	0	1	0
COVID-19	2	0	0	0	3	0	2	0
Diarrhea	2	1	0	0	1	0	4	1
AST increased	0	0	1	1	1	1	2	1
Edema peripheral	0	0	1	0	0	0	3	1
Back pain	0	0	0	0	0	0	3	0
Nausea	2	1	1	1	1	1	1	0
Pruritus	1	0	2	0	0	0	1	0
Urinary tract infection	1	0	2	0	0	0	1	0
Abdominal pain	2	0	0	0	2	0	0	0
Cystitis	0	0	0	0	0	0	2	0
Eyelid edema	0	0	0	0	0	0	2	1
Fatigue	0	0	0	0	0	0	2	0
Leukopenia	0	0	0	0	0	0	2	2
Rash maculo-papular	0	0	2	0	0	0	0	0

n refers to number of patients. [a]AEs are presented from highest to lowest incidence in reference to any-grade TEAEs in all treated patients (N=39). [b]The only related grade 3 AE was leukopenia (at a 100-mg dose). AST, aspartate aminotransferase.

After 12 weeks of elenestinib, all biomarkers of disease burden improved

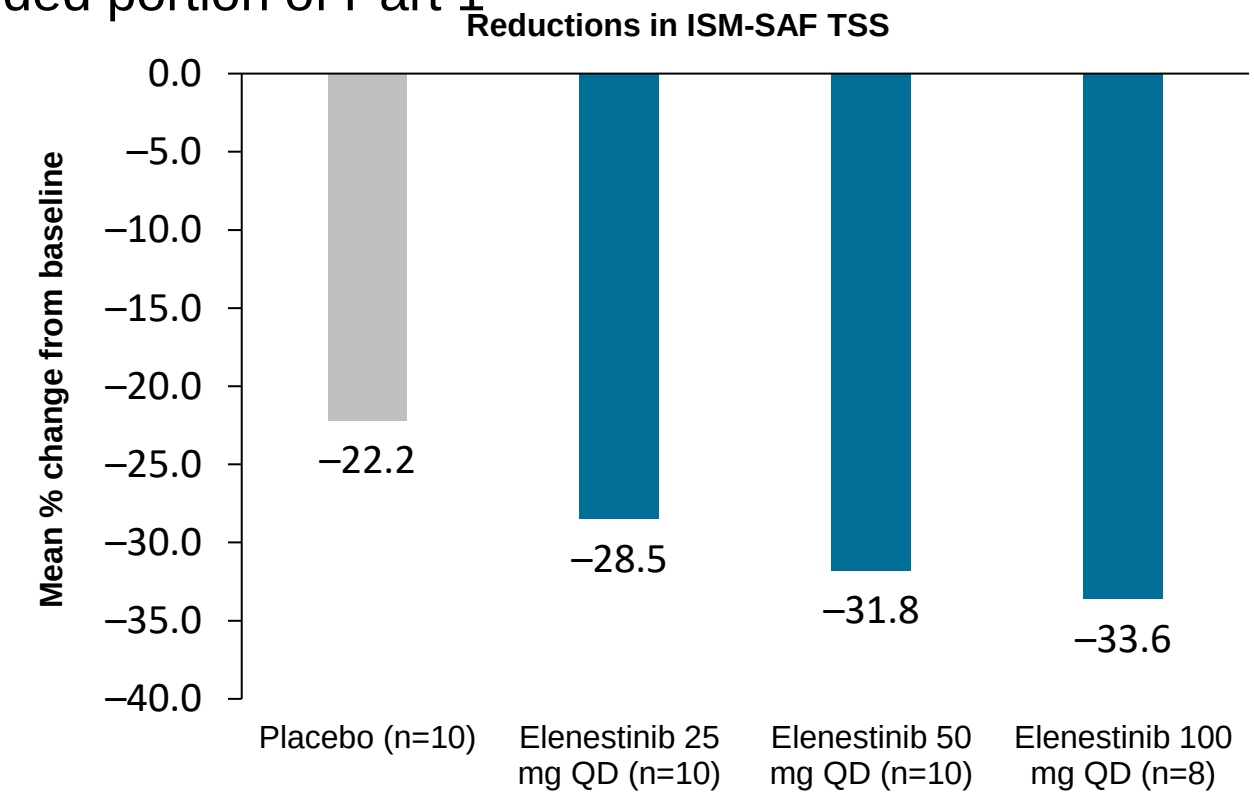
- Patients receiving elenestinib at doses of 25 mg, 50 mg, and 100 mg QD demonstrated dose-dependent mean percent reductions from baseline in **serum tryptase levels (A), *KIT* D816V VAF (B)**, and **bone marrow MCs (C)** *versus* placebo



BM, bone marrow.

After 12 weeks of elenestinib, symptom improvement was observed for all dose cohorts

- All elenestinib dose cohorts demonstrated clinically meaningful changes in symptoms without clear dose dependence
- Percentage change of symptom reduction in TSS was greater for patients on elenestinib *versus* placebo in the blinded portion of Part 1



Conclusions

- Indolent systemic mastocytosis is a *KIT* D816V-driven disease that can cause debilitating symptoms across a range of organ systems while also carrying the risk of progression to more advanced disease

- In this planned readout of HARBOR, Part 1 – a blinded, randomized cohort of patients with ISM and moderate-to-severe symptom burden, elenestinib across all dose levels:
  - Was well tolerated with no drug discontinuations due to AEs
  - Improved disease-related symptoms as assessed by the validated ISM-SAF
  - Reduced multiple biomarkers of MC burden

- Robust clinical activity and favorable tolerability were observed across a range of doses, demonstrating a promising benefit-risk profile
  - Part 2 of the study is expected to initiate in 2024
  - Dosing flexibility will be critical to allow for appropriate dosing across a broad spectrum of SM

Acknowledgments

- Patients and their families
- HARBOR investigators and research staff
- Colleagues at Blueprint Medicines Corporation

- Medical writing support was provided by Mathilde Sanson, PhD, and Travis Taylor, BA, of Paragon, Knutsford, UK. Funded by Blueprint Medicines Corporation.
- The sponsor reviewed and provided feedback on the poster. However, the authors had full editorial control and provided final approval of all content