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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

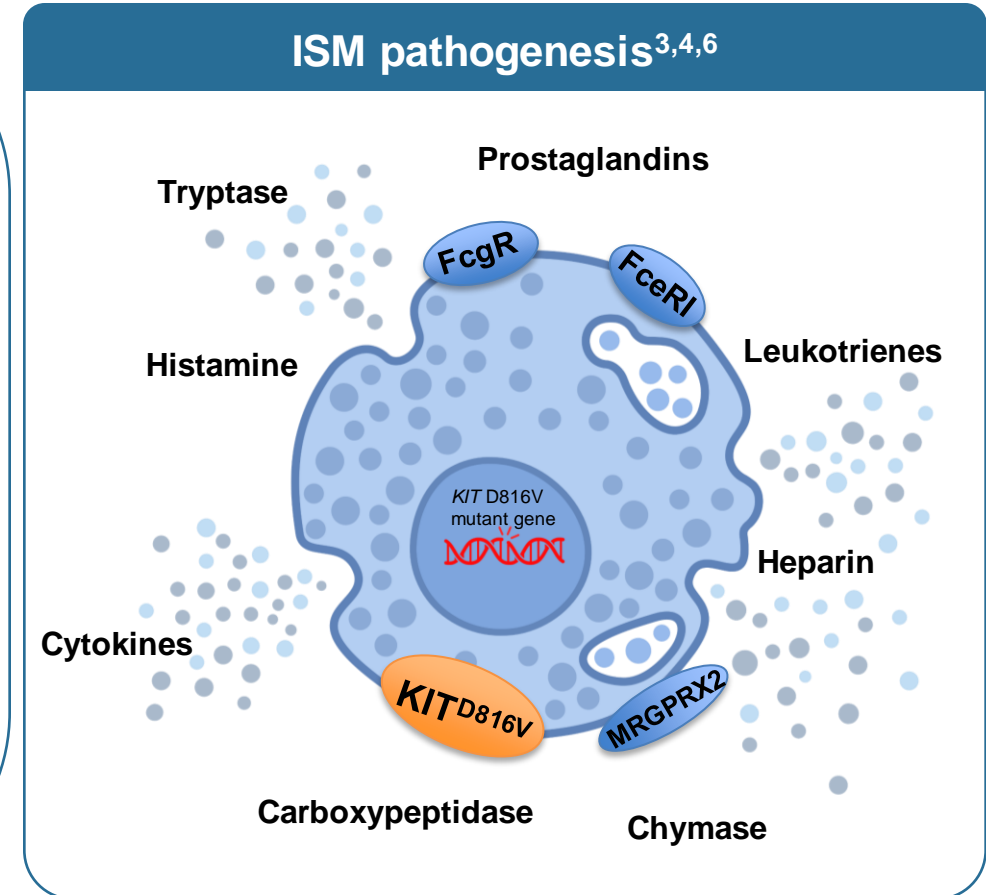
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Systemic mastocytosis (SM) is a clonal mast cell (MC) disease driven by the *KIT* D816V mutation^{1,2}

- 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 cases⁵

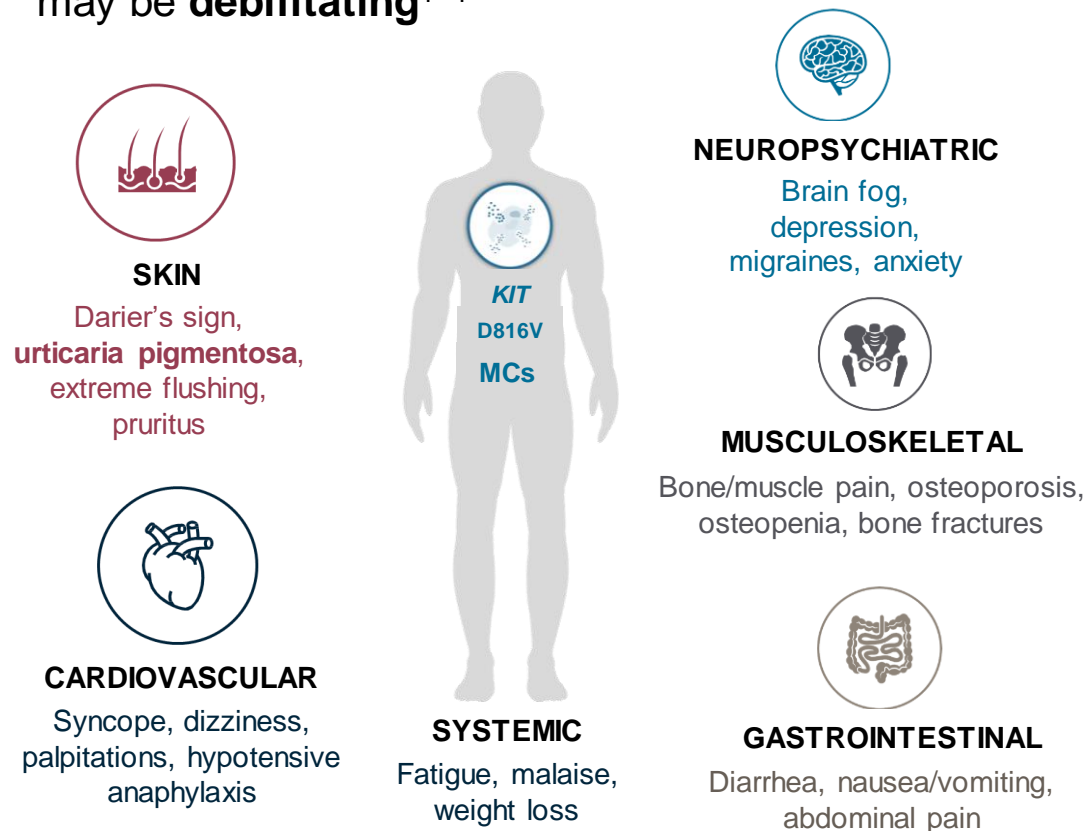


ISM, indolent systemic mastocytosis; MC, mast cell; SM, systemic mastocytosis.

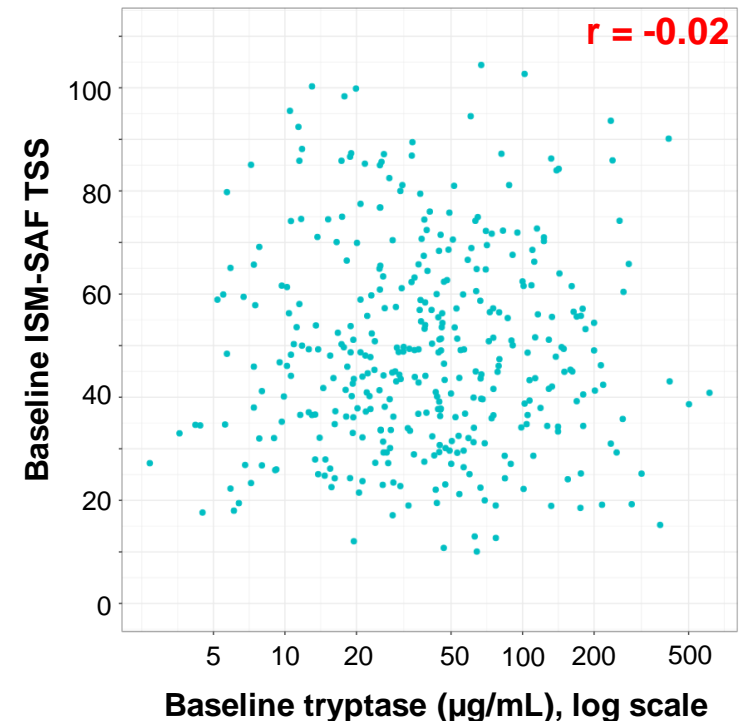
1. Kristensen T et al. *J Mol Diagn.* 2011;13:180–188; 2. Cohen SS et al. *Br J Haematol.* 2014;166:521–528; 3. Pardanani A et al. *Am J Hematol.* 2023;98:1097–1116; 4. Theoharides TC et al. *N Engl J Med.* 2015;373:163–172; 5. Mukherjee S et al. Presented at ASH 2022. Poster #3053; 6. Metcalfe DD et 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



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

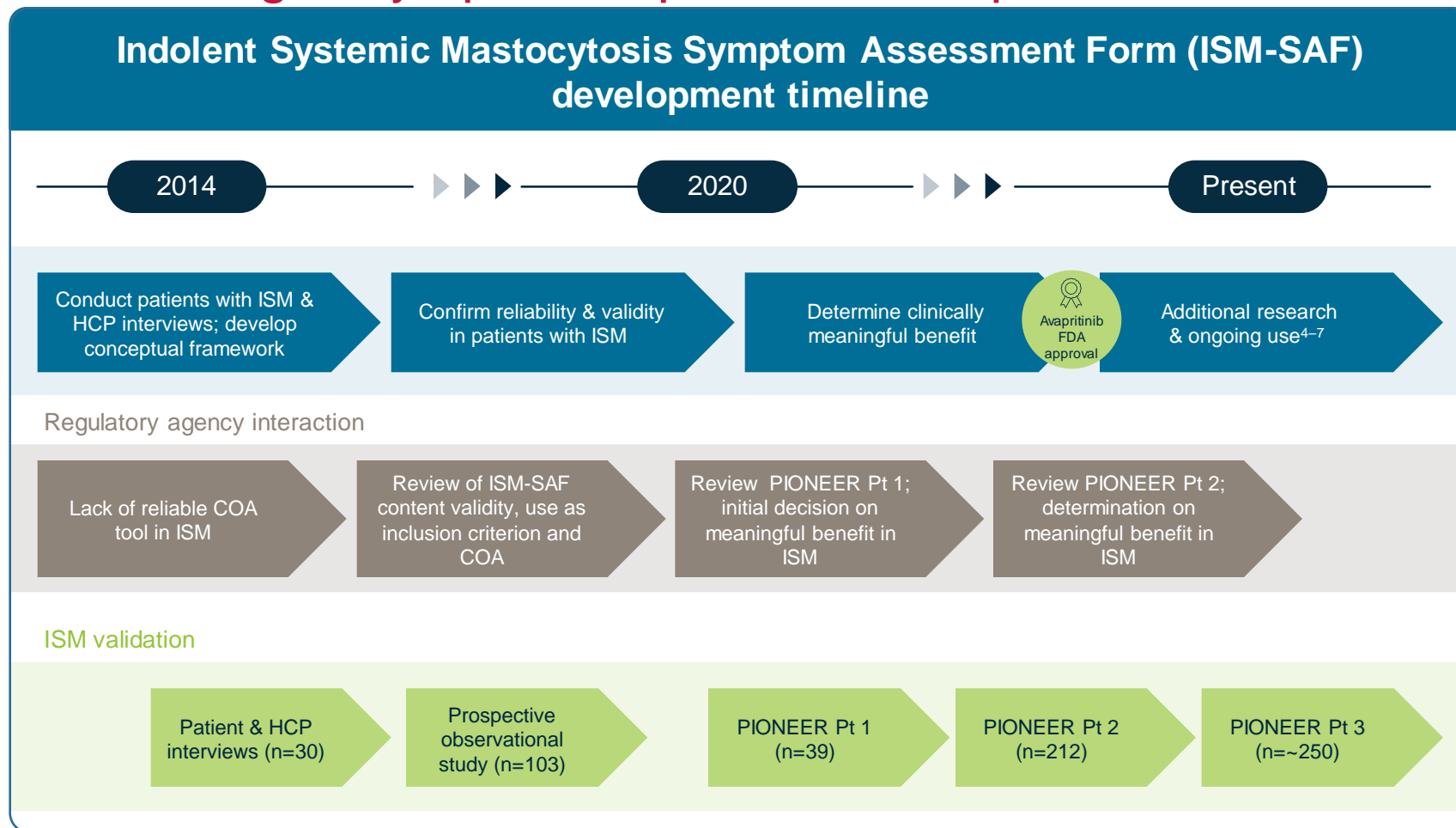


^abased on patients with baseline assessments from PIONEER and HARBOR studies

- 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 ISM¹⁻³



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

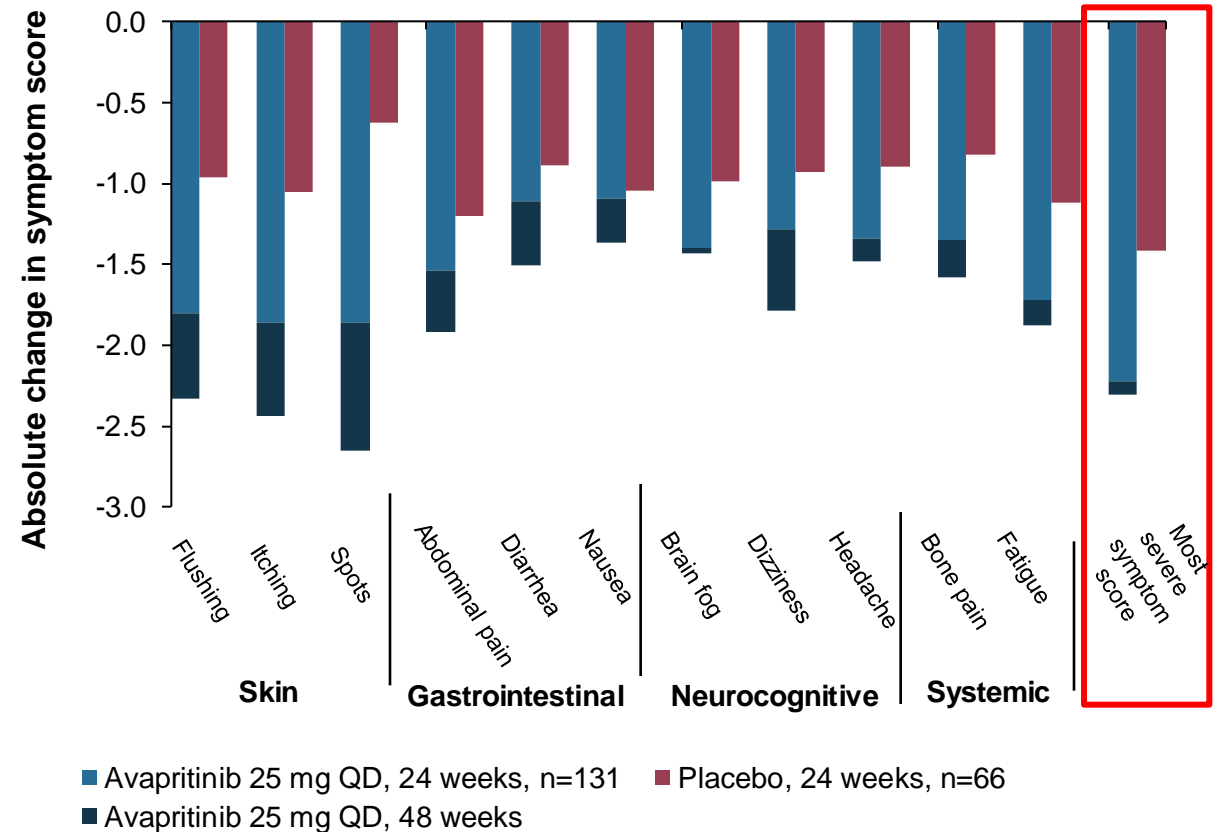
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Targeting KIT D816V in Indolent Systemic Mastocytosis results in deepening symptom improvement

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 placebo¹
- Avapritinib improved symptoms and biomarkers of MC burden¹
- 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

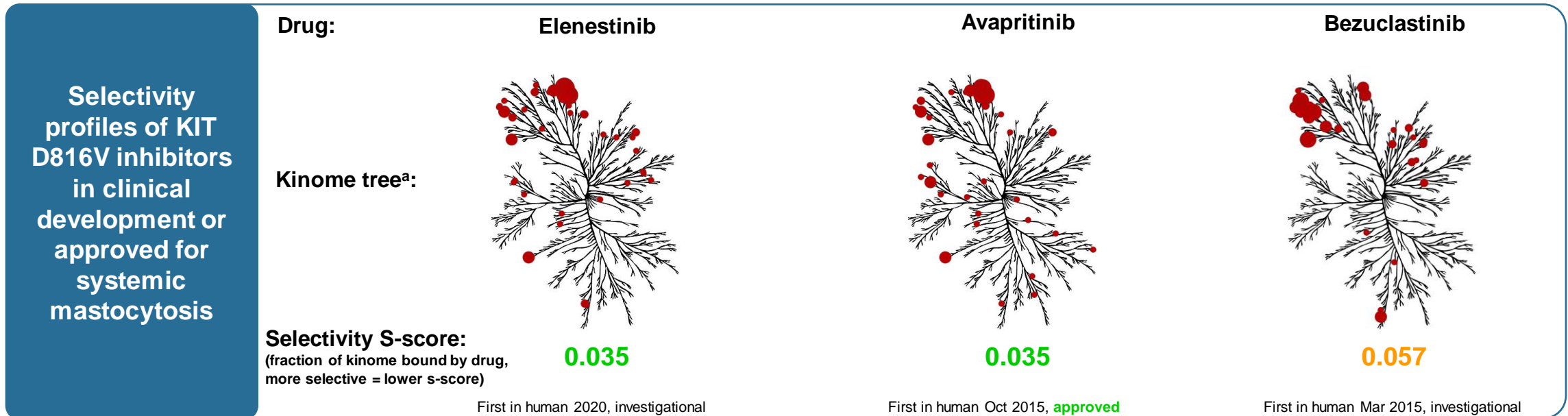


^aNCT03731260.
Gotlib J et al. *NEJM Evidence*. 2023;2

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
- **Well-characterized** product formulation allowing for **once-daily** (QD) dosing^{1,2}

	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

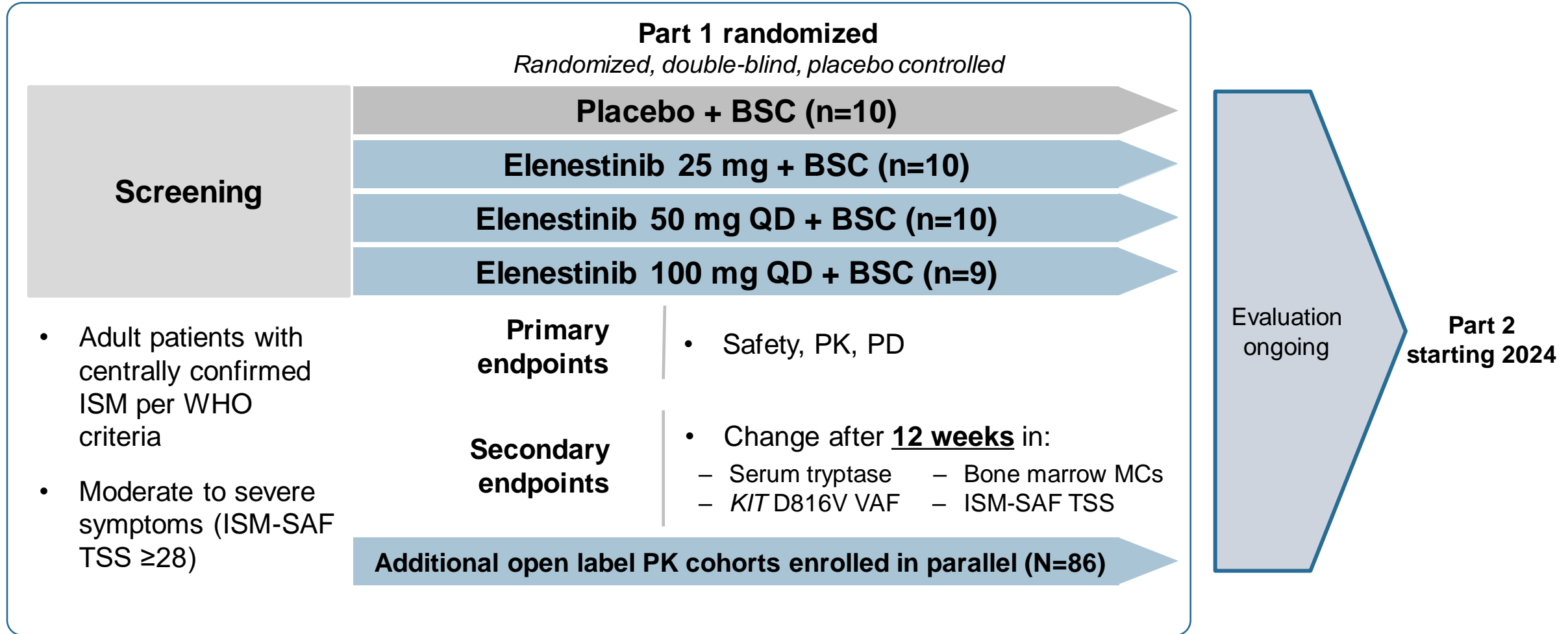


^aKinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.

IC₅₀, 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



^aNCT04910685.

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 <i>KIT</i> 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)

^aBy central assessment; ^bCategories 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

^aIncluding one event each of anaphylaxis, hypertension, esophageal candidiasis at 50 mg (all unrelated); one event each of leukopenia (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

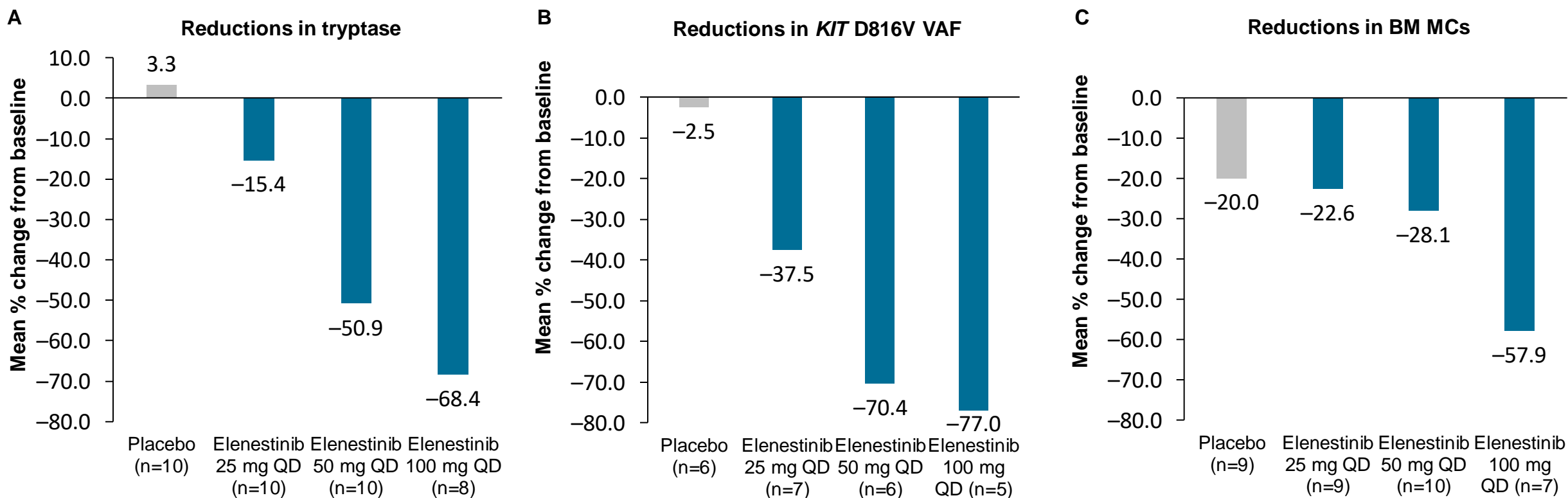
Adverse event ^a	Placebo (n=10)		Elenestinib 25 mg QD (n=10)		Elenestinib 50 mg QD (n=10)		Elenestinib 100 mg QD (n=9)	
	Any-cause	Treatment-related	Any-cause	Treatment-related	Any-cause	Treatment-related	Any-cause	Treatment-related ^b
Headache	2	0	2	2	3	1	2	0
Arthralgia	1	0	3	1	2	0	1	0
COVID-19	2	0	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. ^aAEs are presented from highest to lowest incidence in reference to any-grade TEAEs in all treated patients (N=39). ^bThe only related grade 3 AE was leukopenia (at a 100-mg dose). AST, aspartate aminotransferase.



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

- Patients receiving elenestininib 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

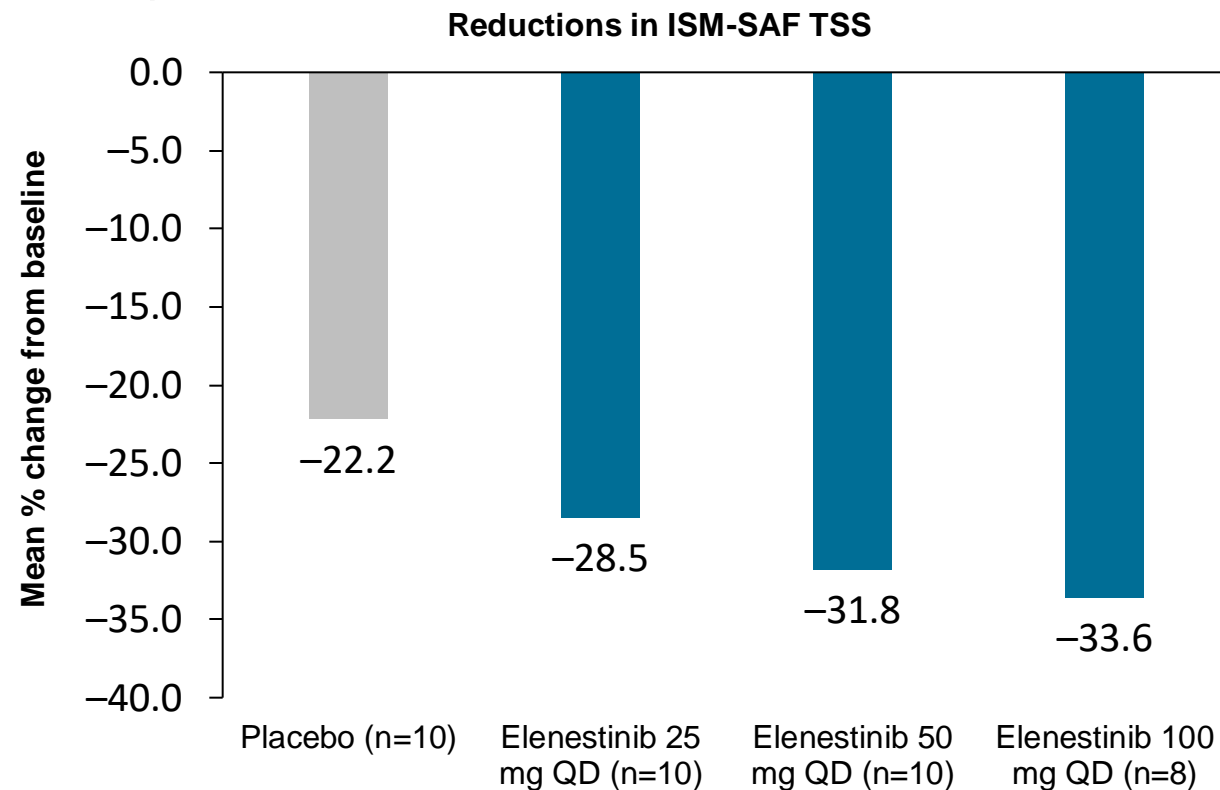


BM, bone marrow.



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



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