EAACI Congress 2024

Valencia, Spain

31 May - 3 June

EAACI 2024 HYBRID VALENCIA

Revolutionising Patient Care
Through the Power of Data Science

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

#EAACIcongress

www.eaaci.org

Longer-Term Safety of Avapritinib in Indolent Systemic Mastocytosis: the Phase 2 PIONEER Study

Vito Sabato,[1] Jason Gotlib,[2] Mariana Castells,[3] Jens Panse,[4,5] Ivan Alvarez-Twose,[6] Deepti H. Radia,[7] Tsewang Tashi,[8] Cem Akin,[9] Cristina Bulai Livideanu,[10] Joseph Jurcic,[11] Hanneke Oude Elberink,[12] Paul Van Daele,[13] Sonia Cerquozzi,[14] Ingunn Dybedal,[15] Andreas Reiter,[16] Thanai Pongdee,[17] Stephane Barete,[18] Celalettin Ustun,[19] Phillipe Schafhausen,[20] Peter Vadas,[21] Prithviraj Bose,[22] Marcus Maurer,[23,24] Daniel J. DeAngelo,[25] Lindsay Rein,[26] Pankit Vachhani,[27] Massimo Triggiani,[28] Patrizia Bonadonna,[29] Karin Hartmann,[30,31] Sigurd Broesby-Olsen,[32] Mattias Mattsson,[33] Tracy George,[34] William Shomali,[35] Matthew Giannetti,[36] Kate Newberry,[37] Hui-Min Lin,[37] Ilda Bidollari,[37] Benjamin Lampson,[37] Frank Siebenhaar[23,24]

[1]Department of Immunology, Allergology and Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; [2]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [3]Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Oncology, Hematology, Hemostaseology, and Stem Cell Transplantation, University Hospital Aachen, Medical Faculty, RWTH Aachen University, Aachen, Germany; [5]Center for Integrated Oncology (CIO), Aachen, Bonn, Cologne, Düsseldorf (ABCD), Aachen, Germany; [6]Institute of Mastocytosis Studies of Castilla-La Mancha, Virgen del Valle Hospital, Toledo, Spain; [7]Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [9]University of Michigan, Ann Arbor, MI, USA; [10]Department of Dermatology, Expert Center of Mastocytosis (CEREMAST), Toulouse University Hospital, Toulouse, France; [11]Division of Hematology/Oncology, Columbia University Irving Medical Center, New York, USA; [12]Department of Allergology, University Medical Center, Groningen Research Institute Asthma and COPD, University of Groningen, Groningen, The Netherlands; [13]Department of Internal Medicine and Immunology, Erasmus Medical Center, Rotterdam, Netherlands; [14]Department of Medicine, University of Calgary, Calgary, AB, Canada; [15]Department of Hematology, Oslo University Hospital, Oslo, Norway; [16]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [17]Division of Allergic Diseases, Mayo Clinic, Rochester, MN, USA; [18]Unit of Dermatology, Reference Centre for Mastocytosis (CEREMAST) Pitié-Salpêtrière Hospital, AP-HP, Sorbonne Université, Paris, France; [19]Department of Internal Medicine, Division of Hematology, Oncology and Cell Therapy, Section of Bone Marrow Transplantation and Cellular Therapy, Rush Medical College Chicago, IL, USA; [20]Department of Oncology, Hematology, and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [21]Department of Medicine, Division of Clinical Immunology and Allergy, St. Michael's Hospital University of Toronto, Toronto, ON, Canada; [22]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [23]Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [24]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany; [25]Dana-Farber Cancer Institute, Boston, MA, USA; [26]Department of Medicine, Duke University, School of Medicine, Durham, NC, USA; [27]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA; [28]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy; [29]Allergy Unit and Asthma Center, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [30]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; [31]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [32]Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark; [33]Department of Hematology, Uppsala University Hospital and Department of Immunology, Genetics and Pathology, Uppsala Sweden; [34]Department of Pathology, University of Utah, Salt Lake City, UT, USA; [35]School of Medicine Stanford University School of Medicine, Stanford, CA, USA; [36]Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA, USA; [37]Blueprint Medicines Corporation, Cambridge, MA, USA.

EAACI
EUROPEAN academy of allergy and clinical immunology

EAACI Annual Meeting, Valencia, Spain; 31 May – 03 June 2024

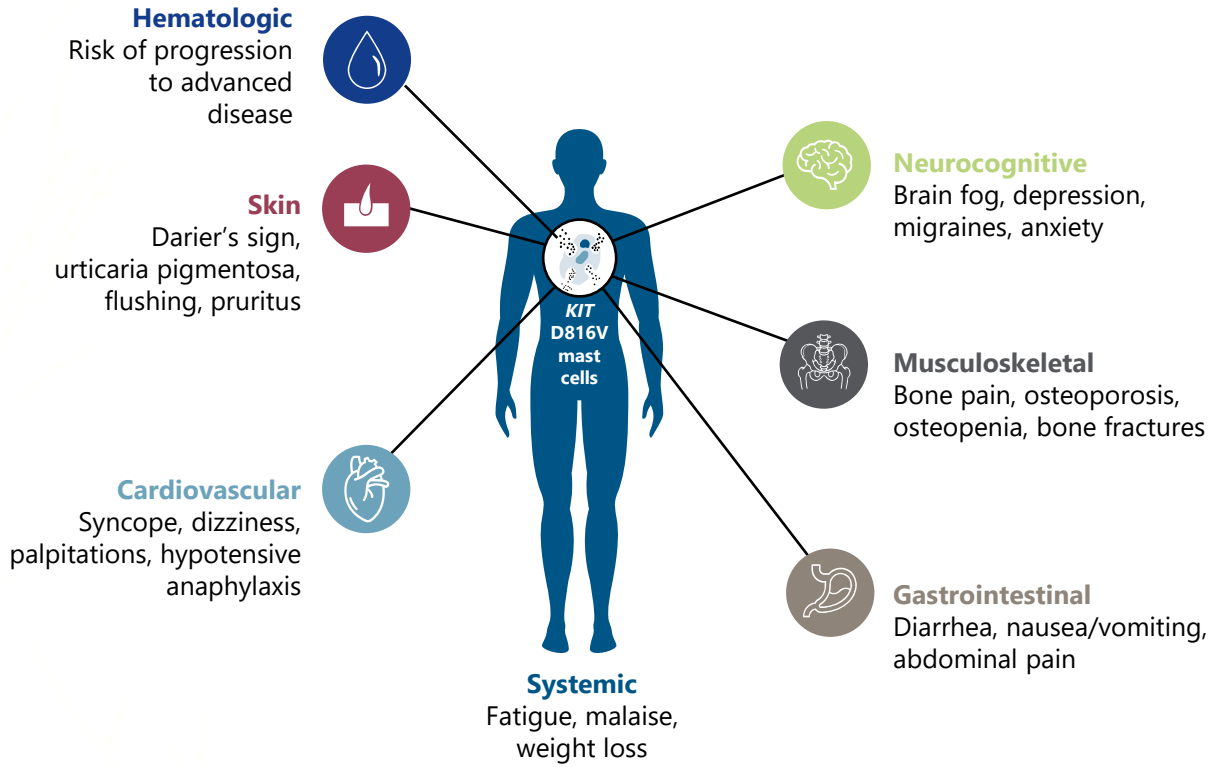
www.eaaci.org
#EAACIcongress

Disclosures

- Dr Sabato's institution has received funding from Blueprint Medicines Corporation for clinical trials

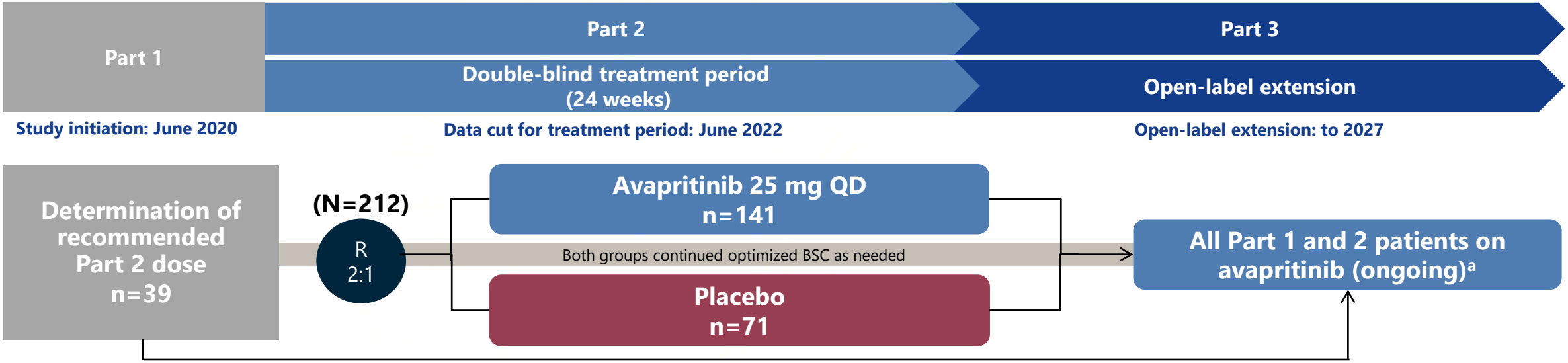
Indolent systemic mastocytosis: a *KIT* D816V-driven disease with substantial impact on quality of life

- Systemic mastocytosis (SM) is driven by aberrant mast cells carrying a *KIT* D816V mutation in >95% of cases[1,2]
- Indolent systemic mastocytosis (ISM) is the most common subtype of SM, and over time, patients can progress to advanced disease in 5–19% of cases[3–5]
- Clinical manifestations of ISM are caused by the aberrant *KIT* D816V-mutant mast cells and most commonly include cutaneous, gastrointestinal, and neurocognitive symptoms, which may be unpredictable and debilitating[7–9]



1. Kristensen T et al. *J Mol Diagn*. 2011;13:180–188; 2. Ungerstedt J et al. *Cancers*. 2022;14:3942; 3. Mukherjee S et al. Presented at ASH 2022. Poster #3053; 4. Escribano L et al. *J Allergy Clin Immunol*. 2009;124(3):514–521; 5. Trizuljak J et al. *Allergy* 2020;75(8):1927–1938; 7. Mesa RA et al. *Cancer*. 2022;128:3691–3699; 8. van Anrooij B. et al. *Allergy*. 2016;71:1585–1593; 9. Hartmann K et al. *J Allergy Clin Immunol*. 2016;137:35–45

The PIONEER trial examined avapritinib, a potent and selective KIT D816V inhibitor, as a treatment for ISM[1,2]

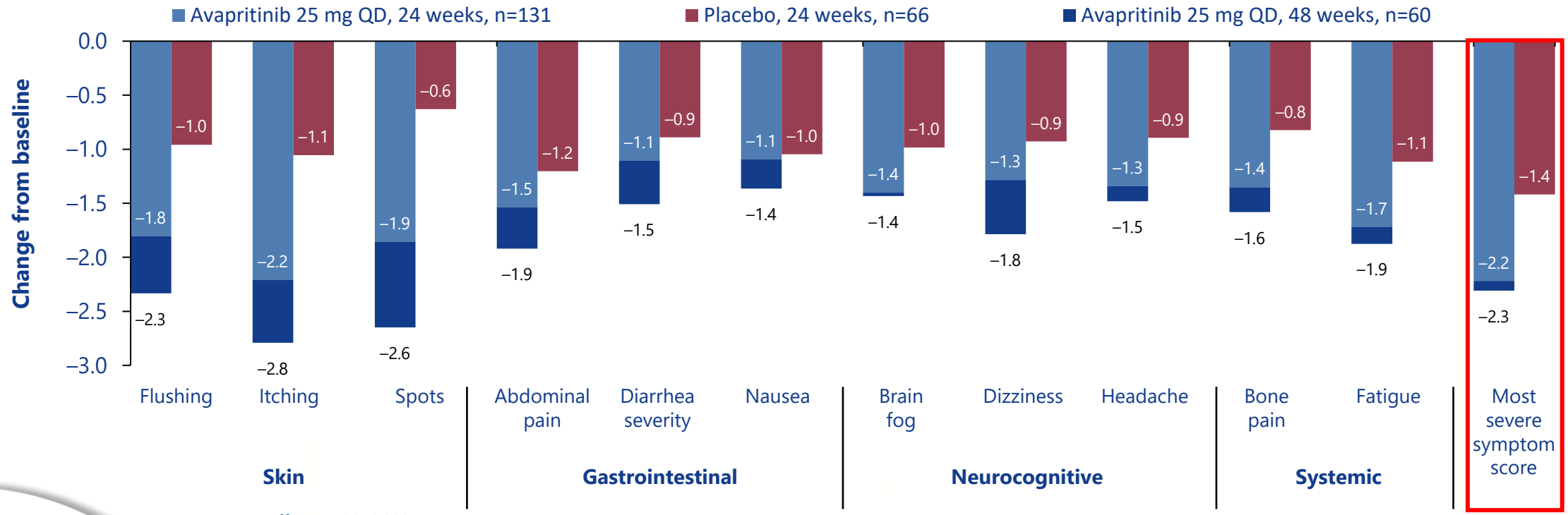


- **Primary endpoint**: avapritinib safety and efficacy
- Basis of **US FDA and EMA approvals** of avapritinib for adults with ISM
  - *May 2023 FDA approval; December 2023 EMA approval for ISM*
- Full data previously presented[1,2]

[a]n=226, includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg QD.
BSC, best supportive care; QD, once daily.
1. Castells M et al. Presented at AAAAI 2023. Oral #627; 2. Gotlib J et al. *NEJM Evidence* 2023;2(6):EVIDoa2200339

PIONEER was the first successful randomized controlled trial of a KIT D816V-targeting agent in ISM that addresses the breadth of symptoms in patients with ISM[1,2]

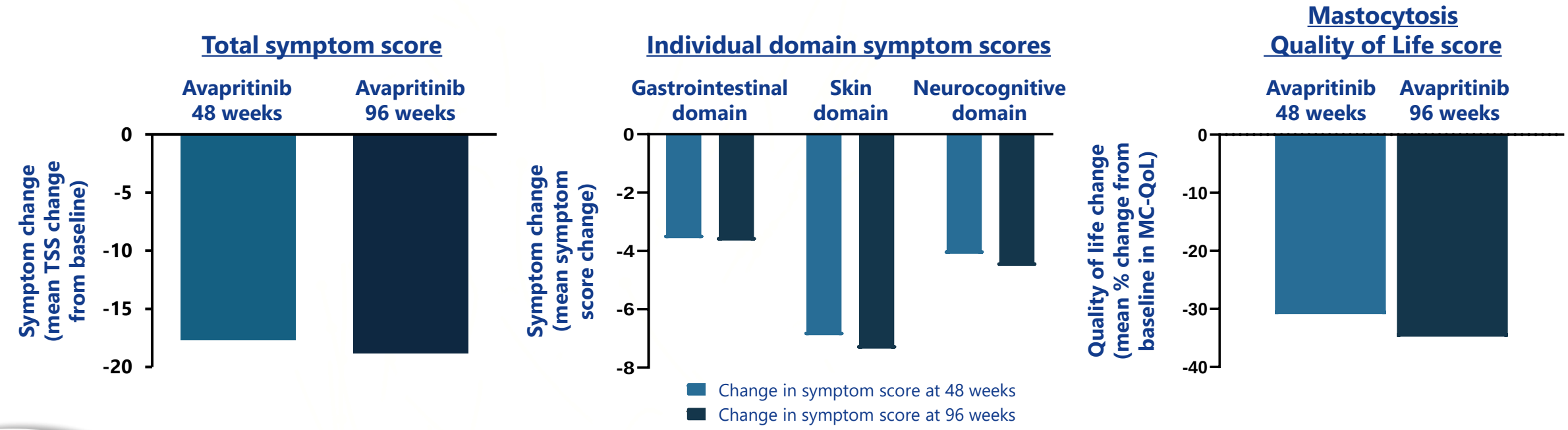
Mean absolute change from baseline up to 48 weeks in individual symptoms per the ISM-SAF (0–10), by treatment group



Data cut-off: June 23, 2022.
ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form.
1. Castells M et al. Presented at AAAAI 2023. Oral #627; 2. Gotlib J et al. *NEJM Evidence* 2023;2(6):EVIDoa2200339

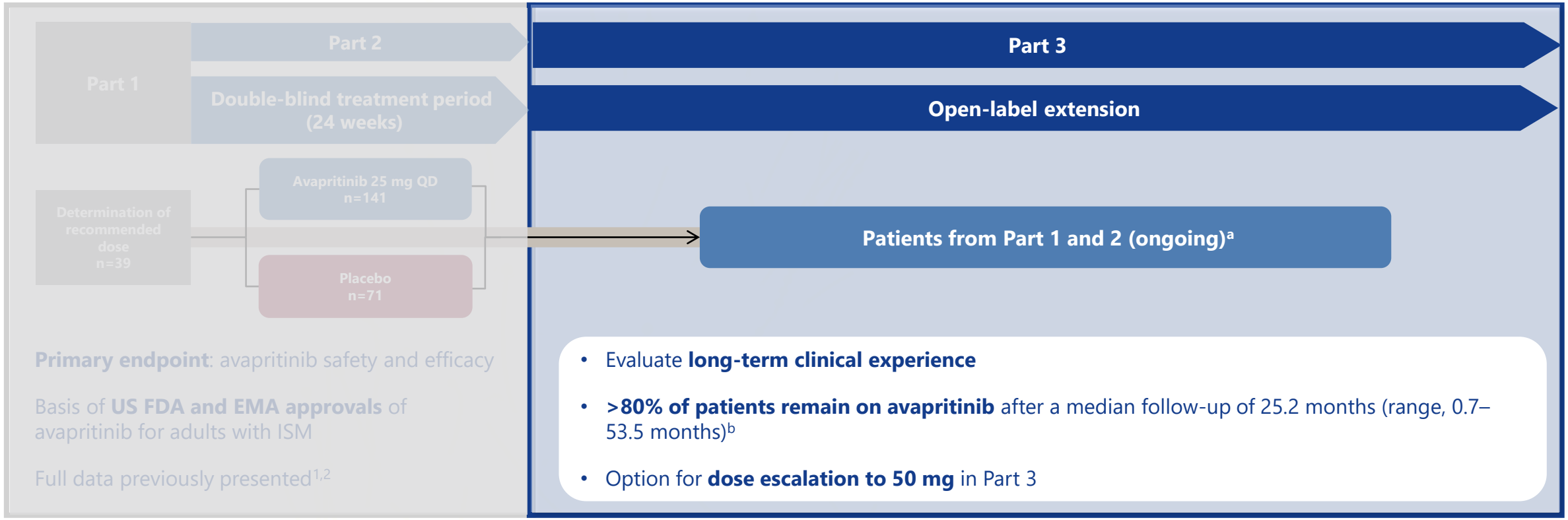
Longer-term efficacy data with median 2 years of follow-up demonstrate durable improvements in symptoms and quality of life

- The mean change (standard deviation) in total symptom score (TSS) was –17.66 (19.32) at Week 48, and –18.80 (22.46) at Week 96 in the on-study patients that received avapritinib 25 mg QD, with continued responses seen in all symptom domains



Data cut-off: November 17, 2023.
MC-QoL score, Mastocytosis Quality of Life score; TSS, total symptom score.

The open-label extension on PIONEER (Part 3) allows for characterization of longer-term experience with avapritinib



[a]Includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg QD. [b]Data cut-off: November 17, 2023.

Baseline demographics of 226 patients exposed to avapritinib 25 mg QD in Parts 1, 2, or 3

Patient demographic	On-study patients who received avapritinib 25 mg QD (n=226)
Age (years), median (range)	49.8 (18–79)
Female, n (%)	166 (73)
Baseline BMI (kg/m^2), median (range)	28.1 (17.6–51.4)
Medical history of anaphylaxis, n (%)	36 (16)
ISM symptom burden	
Baseline TSS, mean (SD)	48.1 (19.5)
Mast cell burden	
Median (range) serum tryptase (central), ng/mL	39.2 (3.6–590.4)
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–60.0)
Median (range) *KIT* D816V VAF in peripheral blood, %	0.39 (undetectable–41.29)
Duration of avapritinib therapy	
≥12 months, n (%)	205 (91)
≥24 months, n (%)	132 (58)
≥36 months, n (%)	17 (8)
≥48 months, n (%)	7 (3)

Data cut: November 17, 2023.
BMI, body mass index; SD, standard deviation; VAF, variant allele frequency.

The safety profile of avapritinib remained favorable with longer-term follow-up of two years

Longer-term safety conclusions

- No new safety concerns were identified with longer treatment exposure
- Grade ≥3 treatment-related AEs remain limited
- There continues to be a low rate of treatment discontinuation due to treatment-related AEs
- The most frequently reported AE associated with treatment was edema, with the majority of edema events being Grade 1

	Randomized controlled part 2[a]		All patients who received avapritinib 25 mg QD during Parts 1, 2, or 3 (N=226)[b]
	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	
Median length of follow-up (months)[c]	5.5	5.5	25.2
Any AEs, n (%)	128 (91)	66 (93)	223 (99)
Any treatment-related AEs, n (%)	77 (55)	32 (45)	158 (70)
Grade ≥3 AEs	30 (21)	15 (21)	94 (42)
Grade ≥3 treatment-related AEs	3 (2)	2 (3)	13 (6)
Serious adverse events[d]	7 (5)	8 (11)	38 (17)
Treatment-related serious adverse events[e]	0 (0)	0 (0)	3 (1)
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	26 (12)
Headache	11 (8)	7 (10)	21 (9)
Periorbital edema	9 (6)	2 (3)	20 (9)
Nausea	9 (6)	6 (8)	18 (8)
Diarrhea	4 (3)	2 (3)	13 (6)
Fatigue	6 (4)	2 (3)	13 (6)
Alopecia	5 (4)	3 (4)	12 (5)
Dizziness	4 (3)	5 (7)	10 (4)
TRAEs leading to discontinuation	2 (1)	1 (1)	6 (3)

[a]Data cut: June 23, 2022. [b]Data cut: November 17, 2023. [c]Reflects median length of follow up during the indicated study period; 89% of patients receiving avapritinib and 88% of patients receiving placebo in Part 2 rolled over to Part 3. [d]One death (Grade 5 serious adverse event) occurred on study unrelated to treatment. The patient had a medical history of atrial fibrillation, and the event was assessed as due to anaphylaxis in the context of atrial fibrillation. [e]Serious TRAEs included diarrhea (1), gastric hemorrhage (1), and peripheral edema (1).
AEs, adverse events; TRAEs, treatment-related adverse events.

At baseline, patients who dose escalated to 50 mg QD had higher mast cell burden

Patient demographic	Patients who did not dose escalate (n=198)	Patients who dose escalated (n=28)	*P*-value
Age (years), median (range)	51.0 (18–79)	48.2 (22–72)	0.46
Female, n (%)	144 (73)	22 (79)	0.65
ISM symptom burden			
Baseline TSS score, mean (SD)	47.1 (19.7)	54.7 (16.9)	0.04
Mast cell burden			
Median (range) serum tryptase (central), ng/mL	37.5 (3.6–590.4)	55.3 (13.0–444.0)	0.02
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–60.0)	10.0 (3.0–50.0)	0.003
Median (range) *KIT* D816V VAF in peripheral blood, %	0.28 (0.00–29.2)	1.14 (0.01–41.29)	0.006

Data cut: November 17, 2023.

Early data demonstrates promising efficacy and safety of avapritinib 50 mg QD in a select subset of patients with ISM

- 28 patients (12%) who received avapritinib 25 mg in PIONEER parts 1 or 2 (n=226) have escalated to 50 mg
- Median time on avapritinib at the 50-mg dose level is 4.7 months (range, 0.5–16.7)

Early safety

- The only TRAE occurring in >1 patient after initiation of the 50 mg dose was peripheral edema (n=4)

Early efficacy

- 21 out of 21 patients who completed two cycles of avapritinib 50 mg had a stable-to-improved TSS (18 with improvement in TSS, 3 with stable TSS)[a]
- No patients have discontinued after protocol-defined dose escalation

[a]Defined as <10% increase in TSS.
Data cut: November 17, 2023.

Summary

- Patients with ISM can suffer from a wide range of debilitating symptoms often not adequately controlled by BSC medications
- PIONEER is the first randomized, double-blind, placebo-controlled trial of a highly selective KIT D816V-targeting agent in patients with ISM and led to the EMA and FDA approval of avapritinib for the treatment of this disease
- Avapritinib achieved durable improvements in overall symptom scores, symptom domain scores, and quality of life measures through 96 weeks
- Avapritinib was generally well-tolerated with a longer-term safety profile consistent with previously reported results and no new safety concerns identified after a median follow-up of 2 years on therapy
- Avapritinib at a dose of 50 mg QD has promising early efficacy and safety, and thus, may represent an option for some patients with ISM, potentially for those with high disease burden at baseline

Conclusion

- Avapritinib selectively targets KIT D816V, the underlying driver of disease
- Avapritinib maintains a favorable benefit-risk profile in ISM after a median of 2 years of therapy

Acknowledgements

- We thank the patients and their families for making the PIONEER study possible
- We also thank the investigators and clinical trial teams who participated in the study
- Medical writing support was provided by Akanksha Srivastava, MSc, and Travis Taylor, BA, of Paragon (a division of Prime, Knutsford, UK). Funded by Blueprint Medicines Corporation. The sponsor reviewed and provided feedback on the presentation. However, the authors had full editorial control and provided final approval of all content