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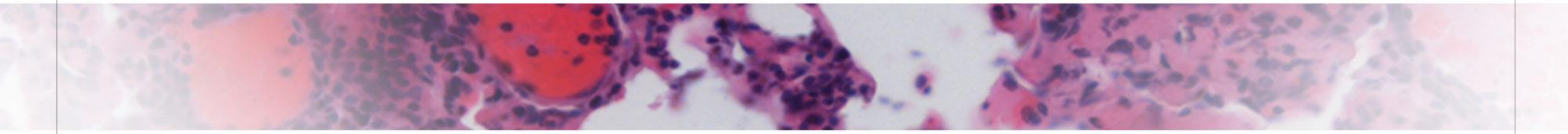

PIONEER part 2: a randomized, double-blind, placebo-controlled, phase 2 study to evaluate safety and efficacy of avapritinib in indolent systemic mastocytosis

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Disclosures

Dr. Akin has received consulting fees and research support from Blueprint Medicines Corporation and consulting fees from Novartis.

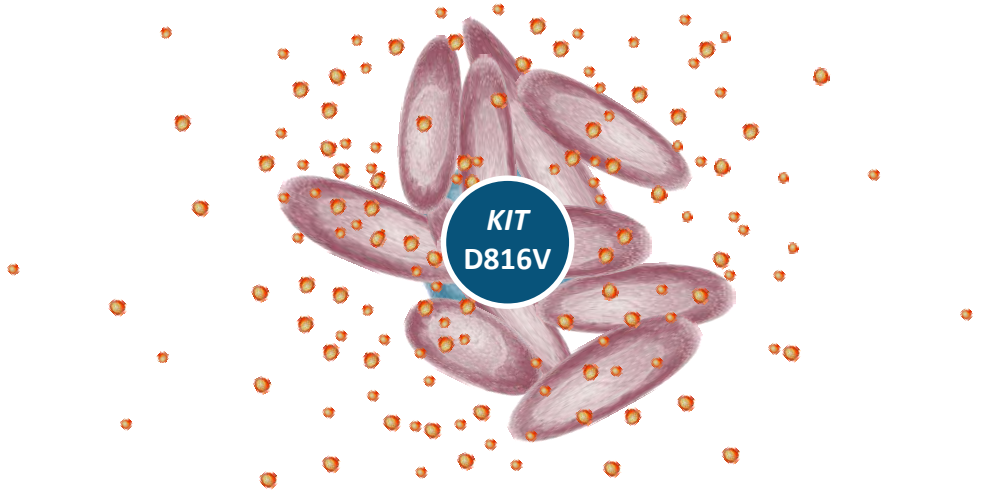
Study sponsored by Blueprint Medicines Corporation.

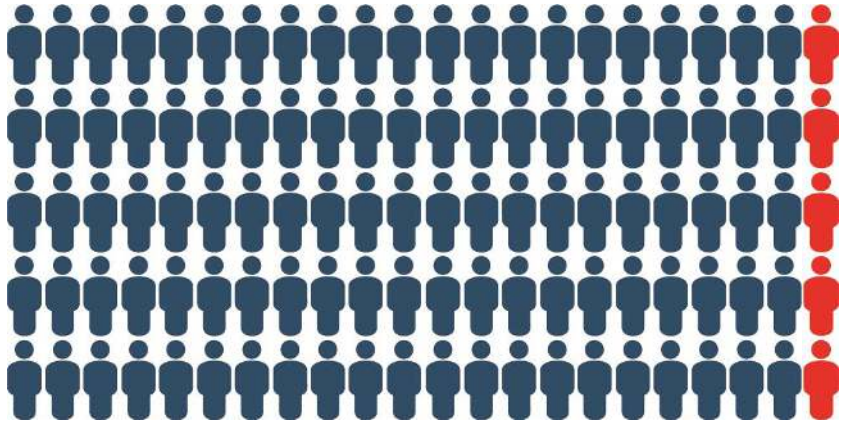
AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including *PDGFRA* D842V mutations.

In Europe, AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic gastrointestinal GIST harboring the *PDGFRA* D842V mutation.

Avapritinib is not approved as safe or effective for use in systemic mastocytosis or any other indication by the FDA, EMA, or any healthcare authority in any jurisdiction.

Systemic mastocytosis is a rare, clonal mast cell neoplasm driven by *KIT* D816V[1]





- **Mast cell hyperactivation and proliferation**[2,3]
- **Debilitating** mediator symptoms in **skin**, **gastrointestinal,** and **neurological symptoms**[2,3]
- Significant symptom-directed polypharmacy, including mast cell stabilizers, antihistamines, LTRAs, and anti-IgE[2,3]
- **No targeted approved therapies** to reduce disease burden; significant use of symptom-directed polypharmacy[2,3]

Approximately 1:10,000 people worldwide have SM[4,5]

~5% AdvSM

Organ damage and decreased survival

~95% non-AdvSM

Indolent and smoldering SM

Suffer **long-term** with significant morbidity and **poor quality of life**[2,3,6]

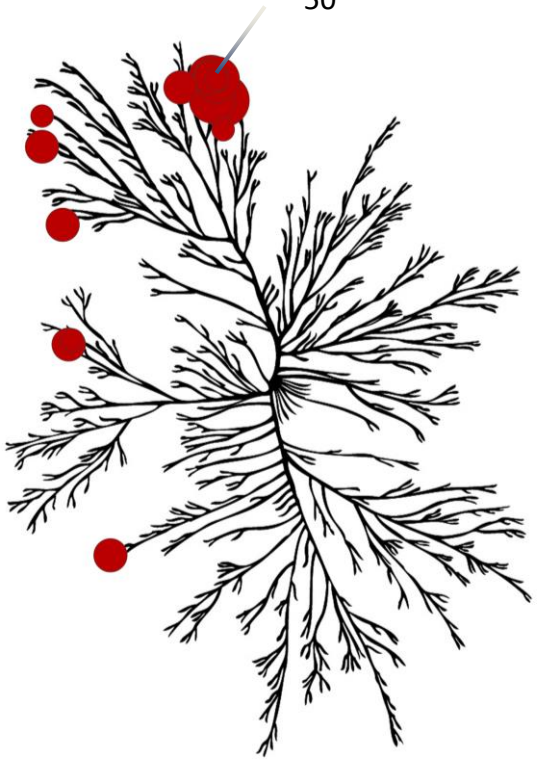
AdvSM, advanced systemic mastocytosis; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist; SM, systemic mastocytosis.

1. Verstovsek S et al. *Eur J Haematol*. 2013;90:89–98; 2. Rossignol J et al. *F1000Research*. 2019;8; 3. Pardanani A. *Am J Hematol*. 2019;94:363–377; 4. Czarny J et al. *Adv Dermatol Allergol.* 2018;35:541–545; 5. Cohen SS et al. *Br J Haematol.* 2014;166:521–528; 6. Valent P et al. *Int J Mol Sci*. 2019;20;789.

Avapritinib targets KIT D816V with objective and symptomatic responses in patients with systemic mastocytosis

Highly potent against KIT D816V

Biochemical IC_{50}=0.27 nM[1]



Highly selective kinome profile

Objective responses in AdvSM

Phase 1 EXPLORER trial

77% confirmed ORR at ≥12 weeks[2]
in AdvSM at ≥200 mg once daily

Responses deepen over time

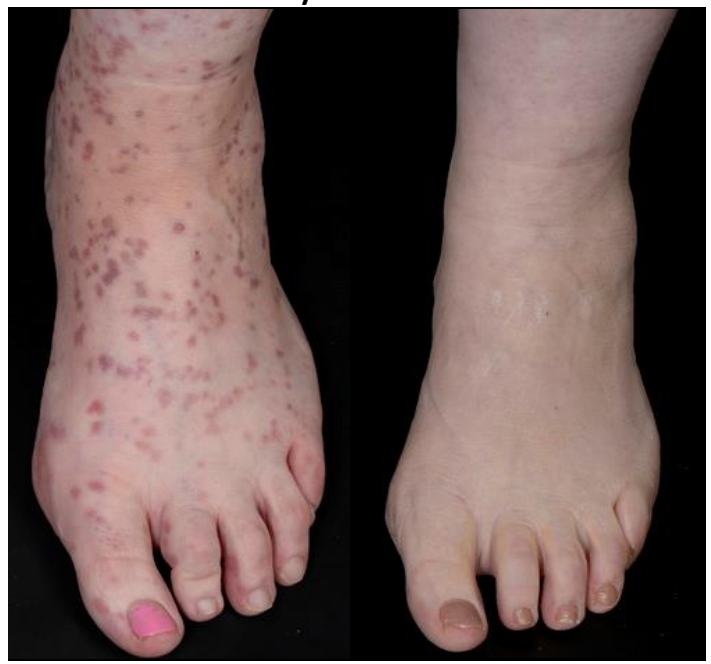
FDA Breakthrough Designation for AdvSM

Registration-enabling PATHFINDER trial in AdvSM is currently ongoing

Efficacy against AdvSM symptoms

Significant reduction in AdvSM-SAF TSS[3]

Potential for **resolution** of mastocytosis in skin[2]



Baseline On study

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. AdvSM, advanced systemic mastocytosis; AdvSM-SAF, Advanced Systemic Mastocytosis-Symptom Assessment Form; FDA, Food and Drug Administration; IC_{50}, half-maximal inhibitory concentration; ORR, overall response rate; TSS, total symptom score.

1. Evans EK et al. *Sci Transl Med*. 2017;9:eaao1690; 2. Radia D et al. Presented at the 24th European Hematology Association Congress, Amsterdam, Netherlands, July 13–16, 2019; 3. Gotlib JR et al. *Blood*. 2018;132 (suppl 1):351.

PIONEER (NCT03731260): An international, multicenter, randomized, double-blind, placebo-controlled, phase 2 study

Objective: determine the safety and efficacy of avapritinib in patients with indolent SM and symptoms inadequately controlled by BSC

PIONEER PART 1[1]

- Assessed safety profile
- Determined pharmacokinetic profile
- Identified recommended phase 2 dose: 25 mg QD in continuous 28-day cycles

PIONEER PART 2

- Assess safety profile
- Determine efficacy of avapritinib at recommended phase 2 dose (25 mg QD)

BSC, best supportive care; QD, once daily.

1. Akin C et al. Presented at the 62nd American Society of Hematology Annual Meeting. December 5–8, 2020. Abstract 1248.

Key eligibility criteria

Inclusion criteria

- Age ≥18 years
- ECOG PS 0–2
- Indolent SM confirmed by central pathology review of bone marrow biopsy and central review of B- and C-findings according to WHO criteria
- Moderate-to-severe symptoms based on ISM-SAF[a] minimum mean TSS over the 14-day eligibility screening period
- Failure to achieve symptom control for ≥1 baseline symptom measured by ISM-SAF with ≥2 therapies considered BSC

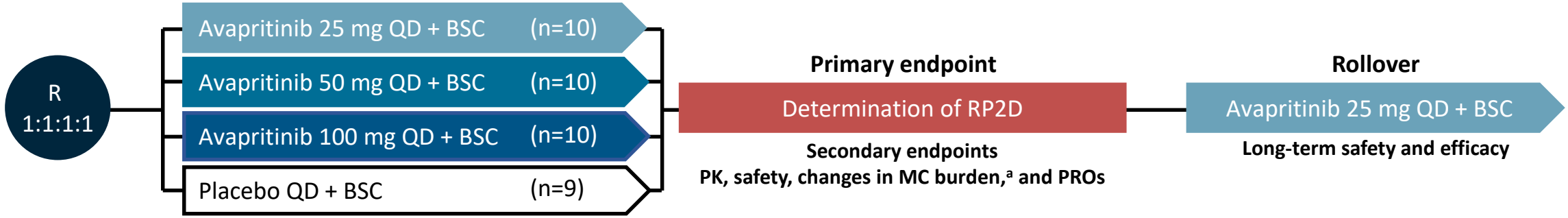
Exclusion criteria

- Diagnosis with other WHO SM subclassifications: cutaneous mastocytosis only, smoldering SM, SM with associated hematologic neoplasm, aggressive SM, mast cell leukemia, or mast cell sarcoma
- Any anti-neoplastic therapy <28 days or TKI therapy <14 days before the ISM-SAF eligibility TSS assessment

[a]The ISM-SAF TSS is composed of 11 individual 24-hour recall patient-reported symptoms (score 0–110 total) within the gastrointestinal, skin, and neurologic domains plus bone pain and fatigue, using a 14-day moving average.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; TKI, tyrosine kinase inhibitor; WHO, World Health Organization.

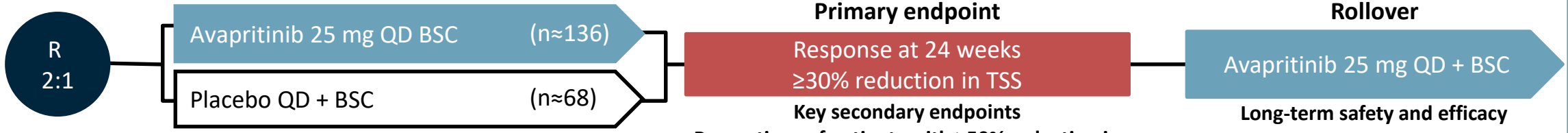
PIONEER study design

Part 1: Dose escalation (fully enrolled)



Part 2: Pivotal efficacy (enrolling)

30% or greater reduction in ISM-SAF TSS determined as clinically important response[1]



Randomization is stratified by serum tryptase levels at screening (<20 ng/mL[b] vs ≥20 ng/mL)

- Patients who complete PIONEER part 1 or part 2 will be eligible to enter an open-label extension (rollover) to evaluate the long-term safety and efficacy of avapritinib 25 mg QD

[a]Measured by reduction of serum tryptase, peripheral blood *KIT* D816V allele fraction and BM MCs. [b]Enrollment will be capped at approximately 20% of patients.
BM, bone marrow; MC, mast cell; PK, pharmacokinetics; PROs, patient reported outcomes; R, randomize; RP2D, recommended phase 2 dose.
1. Shields A et al. *Value Health*. 2019;22(Suppl 3):S867–S868.

PIONEER part 2 target enrollment is 204 patients at ~50 sites across Europe and North America

Europe	
Belgium	• Antwerp University Hospital (UZA), Edegem
Denmark	• Odense University Hospital, Odense
France	• Pitié-Salpêtrière Hospital, Paris • Hôpitaux Universitaires de Marseille Timone, Marseille • Centre Hospitalier Universitaire de Toulouse, Toulouse
Germany	• Technischen Universität München, München • Charité-Universitätsmedizin Berlin, Berlin • Universitätsklinikum Aachen, Aachen • Universitätsmedizin Mannheim, Mannheim • Hubertus Wald Tumorzentrum, Universitäres Cancer Center, Hamburg • Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz • Universität zu Lübeck, Lübeck
Italy	• Azienda Ospedaliera Universitaria Integrata Verona, Verona • Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan • Azienda Ospedaliero-Universitaria di Bologna, Bologna • Azienda Ospedaliera Universitaria San Giovanni di Dio Ruggi d'Aragona, Salerno
Netherlands	• Universitair medisch Centrum Groningen, Groningen • Erasmus Medisch Centrum, Rotterdam
Norway	• Oslo Universitetssykehus, Oslo • Haukeland universitetssjukehus, Bergen
Spain	• Instituto de Estudios de Mastocitosis de Castilla-La Mancha, Toledo • Hospital Universitari Vall d'Hebron, Barcelona
Sweden	• Akademiska Sjukhuset, Uppsala • Karolinska Universitetssjukhuset, Huddinge
Switzerland	• University of Basel, Basel
UK	• Beatson West of Scotland Cancer Centre, Glasgow • Guy's and St Thomas' NHS Foundation Trust, London

North America	
Canada	• Tom Baker Cancer Center, Alberta Health Services, Calgary, Alberta • University of Alberta, Edmonton, Alberta • St. Michaels Hospital, Toronto, Ontario
USA	• The Kirklin Clinic of University of Alabama at Birmingham Hospital, Birmingham, Alabama • Mayo Clinic, Phoenix, Arizona • Stanford Cancer Institute, Palo Alto, California • H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida • Winship Cancer Institute, Emory University, Atlanta, Georgia • Rush University, Chicago, Illinois • University of Kansas Cancer Center, Westwood, Kansas • Brigham and Women's Hospital, Boston, Massachusetts • Dana-Farber Cancer Institute, Boston, Massachusetts • University of Michigan, Ann Arbor, Michigan • Mayo Clinic, Rochester, Minnesota • Washington University School of Medicine, St. Louis, Missouri • Columbia University Medical Center, New York, New York • Memorial Sloan-Kettering Cancer Center MSKCC, New York, New York • Duke University, Durham, North Carolina • Case Western Reserve University, Cleveland, Ohio • The University of Texas Health Science Center at San Antonio, San Antonio, Texas • University of Utah, Salt Lake City, Utah • Virginia Commonwealth University, Richmond, Virginia • University of Washington, Seattle, Washington

- Enrolling 204 patients in PIONEER part 2 is predicted to provide >97% power to detect superiority of avapritinib compared with placebo using a 2-sample Fisher Exact test, with a 1-sided type I error rate of 0.025, for the primary endpoint at Week 24
- Contact medinfo@blueprintmedicines.com for more information on study sites and enrollment

Acknowledgments

- Participating patients and families
- Avapritinib investigators and research coordinators
- Colleagues at Blueprint Medicines Corporation

- Medical writing support and editorial support were provided by Deborah Cantu, PhD, and Travis Taylor, BA, both of Paragon, UK, supported by Blueprint Medicines Corporation, Cambridge, MA