PIONEER Part 2 Top-line Results

AYVAKIT® (avapritinib) in Non-Advanced Systemic Mastocytosis

August 17, 2022

R.S., living with systemic mastocytosis

Blueprint Medicines call participants

PREPARED REMARKS

Introduction	**Kate Haviland,** Chief Executive Officer
Positive PIONEER Part 2 Topline Results	**Becker Hewes, MD,** Chief Medical Officer
Investigator Commentary	**Mariana Castells, MD, PhD,** Director, Mastocytosis Center, Brigham and Women's Hospital
Q&A	**All**

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans to submit a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration (FDA) for AYVAKIT in non-advanced SM, with a subsequent submission of a type II variation marketing authorization application to the European Medicines Agency (EMA), plans and timing for presenting detailed data from the PIONEER trial of AYVAKIT in patients with non-advanced SM, and, expectations regarding the potential benefits of AYVAKIT in treating patients with non-advanced SM. The words “aim,” “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this presentation are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks and uncertainties related to the impact of the COVID-19 pandemic to Blueprint Medicines’ business, operations, strategy, goals and anticipated milestones, including Blueprint Medicines’ ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Blueprint Medicines’ ability and plans in continuing to establish and expand a commercial infrastructure, and successfully launching, marketing and selling current or future approved products; Blueprint Medicines’ ability to successfully expand the approved indications for AYVAKIT/AYVAKYT or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of AYVAKIT/AYVAKYT; Blueprint Medicines’ ability to successfully demonstrate the safety and efficacy of its drug candidates and gain approval of its drug candidates or of an approved product in an additional indication on a timely basis, if at all; the preclinical and clinical results for Blueprint Medicines’ drug candidates, which may not support further development of such drug candidates either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; the risk that “top-line" data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to confirmation, audit, and verification procedures that could result in material changes to the final data; the timing of the initiation of clinical trials and trial cohorts at clinical trial sites and patient enrollment rates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; Blueprint Medicines’ ability to obtain, maintain and enforce patent and other intellectual property protection for AYVAKIT/AYVAKYT or any drug candidates it is developing; Blueprint Medicines’ ability to develop and commercialize companion diagnostic tests for AYVAKIT/AYVAKYT, Blueprint Medicines' ability to successfully expand its operations, research platform and portfolio of therapeutic candidates, and the timing and costs thereof; and the success of Blueprint Medicines’ current and future collaborations, financing arrangements, partnerships or licensing arrangements. These and other risks and uncertainties are described in greater detail in the section entitled “Risk Factors” in Blueprint Medicines’ filings with the Securities and Exchange Commission (SEC), including Blueprint Medicines’ most recent Annual Report on Form 10-K, as supplemented by its most recent Quarterly Report on Form 10-Q and any other filings that Blueprint Medicines has made or may make with the SEC in the future. Any forward-looking statements contained in this presentation represent Blueprint Medicines’ views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date. Except as required by law, Blueprint Medicines explicitly disclaims any obligation to update any forward-looking statements.

AYVAKIT® (avapritinib) has the potential to be the first disease-modifying therapy for non-advanced SM

PIONEER 

POSITIVE TOPLINE RESULTS

FULL RESULTS EXPECTED AT UPCOMING MEDICAL CONFERENCE

SM, systemic mastocytosis

Not for promotional use.

Today's news reflects a decade of commitment and collaboration

OUR VISION TO IMPROVE SM PATIENT OUTCOMES

Advance the understanding of SM

- Generated robust datasets on SM disease burden in collaboration with patients, healthcare providers, and patient advocacy groups
- >100 scientific presentations and publications

Pioneer scientific and clinical innovation

- Designed the first precision therapy to specifically target KIT D816V, the underlying cause of SM
- Granted FDA breakthrough therapy designations for advanced and moderate-to-severe indolent SM
- Conducted the first and only positive registrational study in non-advanced SM

Deliver transformative medicines to patients

- AYVAKIT is approved for advanced SM in the U.S. and EU
- ~1000 patients with SM have received AYVAKIT in the clinical or commercial settings
- BLU-263 in development for mast cell disorders

SM, systemic mastocytosis; FDA, U.S. Food & Drug Administration; US, United States; EU, Europe

AYVAKIT demonstrated highly significant and clinically meaningful impact on the primary and all key secondary endpoints

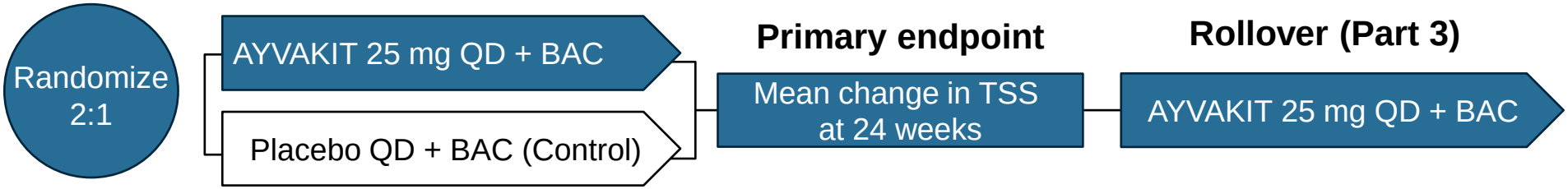
CLINICAL OUTCOME MEASURES		P VALUE[1]
Primary Endpoint	Mean Change in TSS	0.003
Secondary Endpoints[2]	≥30% Reduction in TSS	0.009
	≥50% Reduction in TSS	0.005
	Mean Change in Most Severe Symptom Score	0.015
	≥50% Reduction in Serum Tryptase	<0.0001
	≥50% Reduction in KIT D816V VAF	<0.0001
	≥50% Reduction in Bone Marrow MC Aggregates	<0.0001

Data cutoff as of June 23, 2022. 1. One-sided p-value < 0.025 indicates statistical significance. 2. For secondary endpoints, reductions in TSS and objective measures of mast cell burden represent proportion of patients with ≥30% and ≥50% reductions. All endpoints are key secondary endpoints, except for "Mean Change in Most Severe Symptom Score", which is an additional secondary endpoint. TSS, total symptom score; VAF, variant allele fraction; MC, mast cell

Positive PIONEER Part 2 Topline Results

Becker Hewes, MD, Chief Medical Officer

Largest clinical trial in non-advanced SM conducted to-date



Eligibility

- Age ≥18 years
- ISM confirmed by central pathology review
- No restriction on prior therapy
- Moderate-to-severe symptoms

Baseline Characteristics

	AYVAKIT	Control
Enrolled	141	71
TSS score, mean (SD)	50.2 (19.1)	52.4 (19.8)

- Similar between AYVAKIT and control arms
- Consistent with PIONEER Part 1
- Median BAC across both arms was 3 (range 0 – 11)

Data cutoff as of June 23, 2022. QD, once daily; BAC, best available care; TSS, total symptom score; SD, standard deviation

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Decreases in patient-reported symptoms and objective measures of disease burden

	AYVAKIT		Control
	PART 2: 24 weeks	**PART 3:** 48 weeks[1]	**PART 2:** 24 weeks
Mean Change in TSS [95 % CI]	**-15.6** [-18.6 – -12.6]	**-20.2** [-24.7 – -15.7]	**-9.2** [-13.1 – -5.2]

	AYVAKIT	Control
	PART 2: 24 weeks	**PART 2:** 24 weeks
≥50% Reduction in Serum Tryptase [95% CI]	**53.9%** [45.3 – 62.3]	**0.0%** [0.0 – 5.1]

Rapid and further deepening in mean TSS reduction observed in Part 3 when control switched over to receive AYVAKIT

1. After 24 weeks, all patients had the option to cross over into Part 3 and receive treatment with AYVAKIT 25 mg QD. TSS, total symptom score; CI, confidence interval.

AYVAKIT was well-tolerated with a safety profile favorable to control

	AYVAKIT	Control
AEs, n (%)	128 (90.8)	66 (93.0)
SAEs, n (%)	7 (5.0)	8 (11.3)
Discontinuation due to TRAEs, n (%)	1 (0.7)	0 (0.0)
TRAEs in ≥5% of AYVAKIT patients, by preferred term		
Headache, n (%)	11 (7.8)	7 (9.9)
Nausea, n (%)	9 (6.4)	6 (8.5)
Peripheral edema, n (%)	9 (6.4)	1 (1.4)
Periorbital edema, n (%)	9 (6.4)	2 (2.8)

- No ICB events
- Lower rate of cognitive effect AEs[1] reported for AYVAKIT (2.8%) vs. control (4.2%)
- No Grade 3 cognitive effect AEs[1] for AYVAKIT (0%) vs. control (1.4%)
- In the AYVAKIT arm, 93.0% of edema AEs were Grade 1, with remainder Grade 2
- Higher Part 2 completion rate for AYVAKIT (96.5%) vs. control (93.0%)

Data cutoff as of June 23, 2022. 1. Cognitive effect AEs refer to 17 pooled terms identified across AYVAKIT clinical studies. AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event; ICB, intracranial bleed

Investigator Commentary

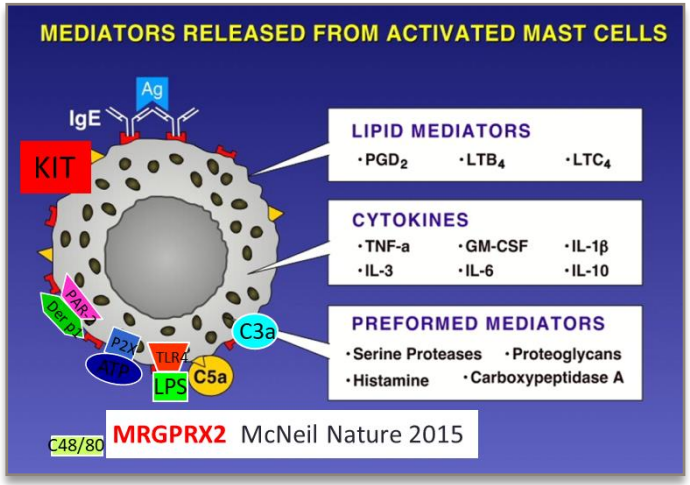
Mariana Castells, MD, PhD,
Director, Mastocytosis Center
Brigham and Women's Hospital

Dr. Mariana Castells, MD, PhD

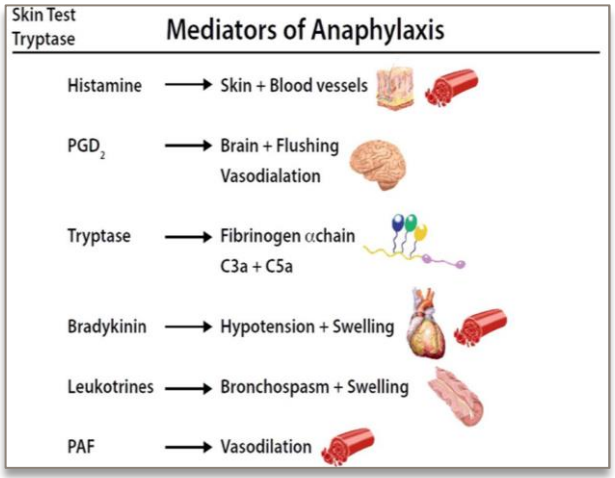
- Brigham and Women's Hospital
  - Director, Mastocytosis Center; database includes > 2,000 SM patients
  - Director, Drug Hypersensitivity and Desensitization Center; Allergy and Clinical Immunology Training Program
- Professor, Harvard Medical School
- Board of Directors: AAAAI, ABAI
  - AAAAI Foundation Research Chair
- Clinical interests: drug allergy, anaphylaxis, mast cell activation disorders, urticaria, immune deficiencies, food and environmental allergies, and asthma

SM, systemic mastocytosis; AAAAI, American Academy of Allergy, Asthma & Immunology; ABAI, American Board of Allergy and Immunology.

Upon activation of mast cells, proinflammatory mediators are released

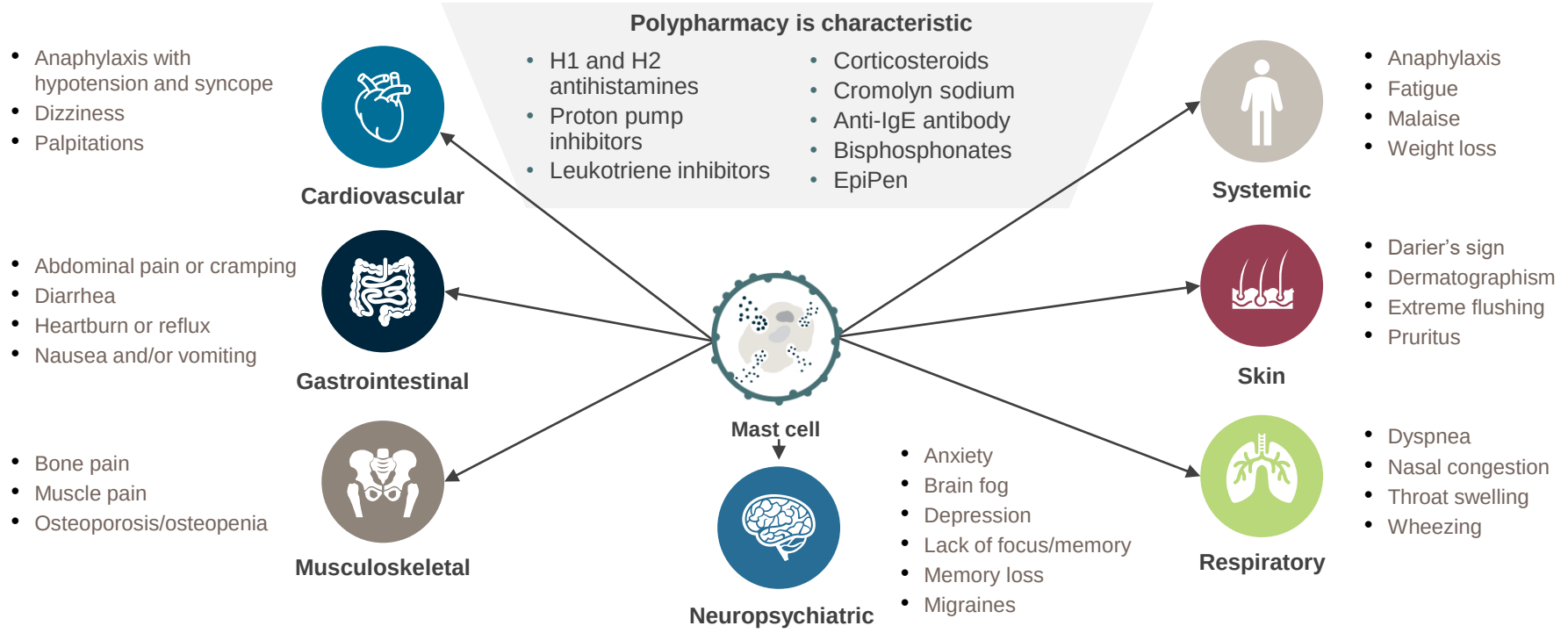


	Mediator(s)	Measured in mastocytosis
Systemic		
Vasodilation/hypotension	Histamine	+
	Prostaglandin D2	+
Hypertension	Chymase	–
Fatigue/cachexia/weight loss	TNF-α	+
Fever	IL-6	+
	IL-1	–
Fibrosis	IL-1	–
	IL-13	–
	TGF-β	–
Skin		
Flushing	Histamine	+
	Prostaglandin D2	+
Urticaria/angioedema	Histamine	+
	Prostaglandin D2	+
	Leukotriene C4	–
Gastrointestinal		
Abdominal pain	Histamine	+
Peptic		
Colic		
Diarrhea	Histamine	+
Malabsorption		
Bone		
Bone pain		
Osteoporosis/osteopenia	IL-6	+
	Heparin	–
	Tryptase	+
	TGF-β	–
Central nervous system		
Mixed CNS syndrome	Prostaglandin D2	+
	Histamine	+



1. Castells M, Austen KF. *Int Arch Allergy Immunol*. 2002 Feb;127(2):147-52. 2. Castells M. *J Allergy and Clin Immunol.* 2017 Aug;140(2):321-333.

Uncontrolled mast cell activation in SM causes severe and unpredictable symptoms across multiple organ systems[1-3]



1. Theoharides TC et al. *N Engl J Med.* 2015;373(2):163-172. 2. Gilreath JA et al. *Clin Pharmacol*. 2019;11:77-92. 3. Jennings SV et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. 4. Amin K. *Respir Med.* 2012;106(1):9-14. SM, systemic mastocytosis.

Case study #1 in a patient with significant skin and GI involvement

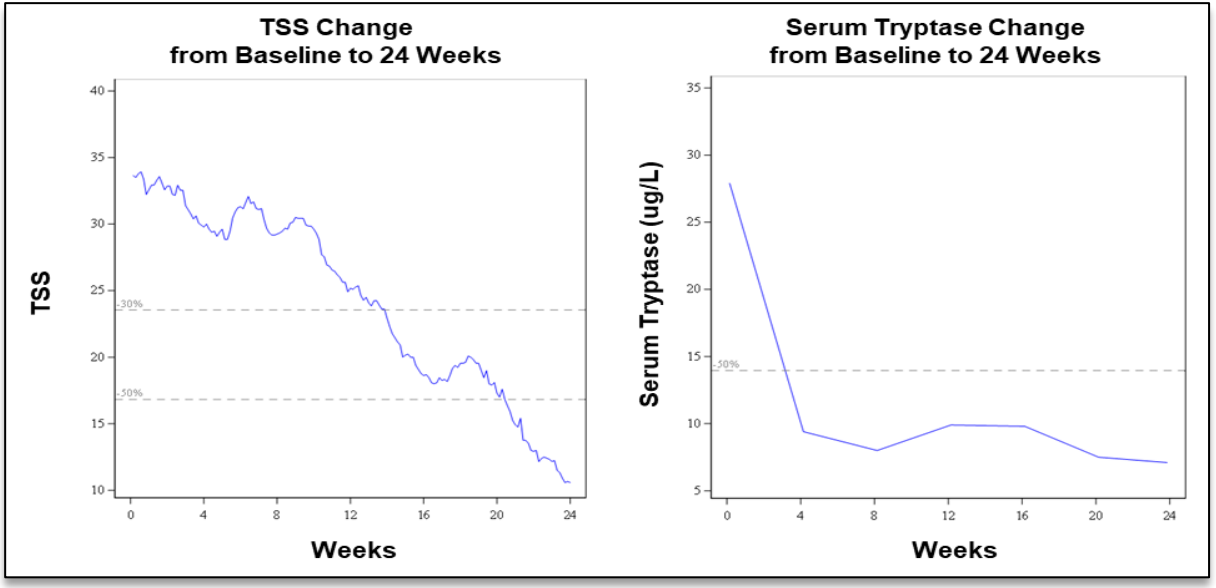
First symptoms in 2009
ISM diagnosis in 2011
KIT D816V positive

Severe ongoing symptoms; highly reduced QoL

- **Skin**: lesions > 80%; triggered by sun, exercise, alcohol, stress, medical procedures
- **GI**: recurrent, unpredictable heartburn, diarrhea, nausea

Ranitidine; famotidine; omalizumab; cetirizine; Benadryl, Epipen

MEANINGFUL REDUCTIONS IN TSS AND SERUM TRYPTASE AT 24 WEEKS



23-point TSS reduction

75% reduction in serum tryptase

After almost two years on AYVAKIT, patient reports "life changing" improvement, including continued improvement in QoL, no new symptoms, and reduction in polypharmacy. This patient remains on AYVAKIT today.

Data cutoff as of June 23, 2022. ISM, indolent systemic mastocytosis; GI, gastrointestinal; TSS, total symptom score; QoL, quality of life

Case study #2 in a patient heavily pretreated with cytoreductive therapies and ongoing polypharmacy

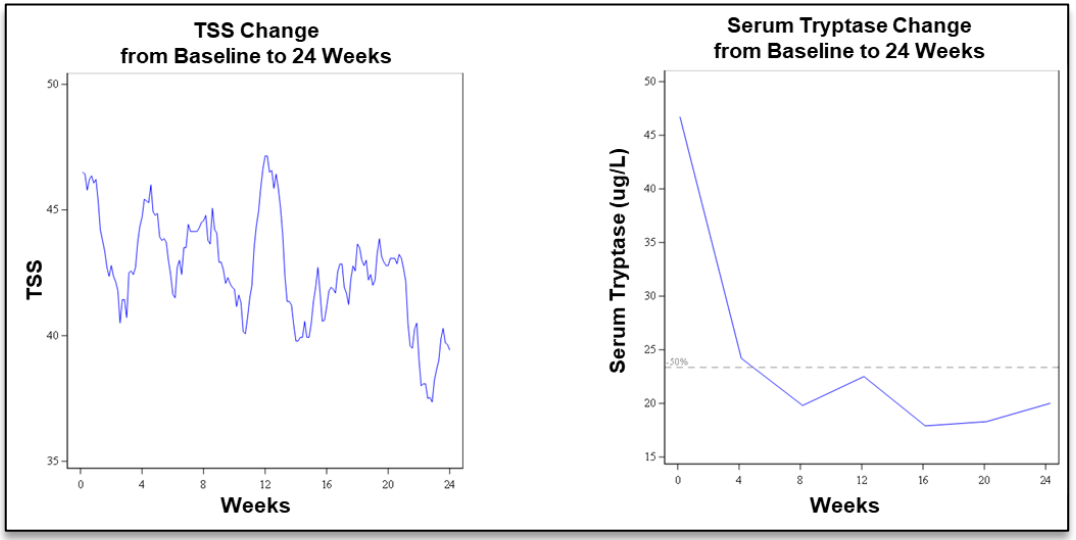
First symptoms in childhood
KIT D816V positive

Severe and progressing symptoms

- **Skin**: Chest/back lesions grew and spread 2000 – 2010; lesions flare with triggers; episodes of flushing, hiving, redness, swelling
- **GI**: restricted diet to control pain, bloating, diarrhea, nausea, vomiting

Cromolyn, doxepin, cimetidine, hydroxyzine, Benadryl, EpiPen, prednisone; prior montelukast, omalizumab, hydroxyurea, interferon alpha

MEANINGFUL REDUCTIONS IN TSS AND SERUM TRYPTASE AT 24 WEEKS



7-point TSS reduction

57% reduction in serum tryptase

Patient reports drastic symptom improvement including reduction in baseline skin lesions, rare GI symptoms, and consistent improvement in bone pain. This patient remains on AYVAKIT today.

Data cutoff as of June 23, 2022. GI, gastrointestinal; TSS, total symptom score

PIONEER Part 2 positive topline results

1	AYVAKIT demonstrated highly significant and clinically meaningful impact on the primary and all key secondary endpoints
2	AYVAKIT was well-tolerated with a safety profile favorable to control
3	Decreases in patient-reported and objective measures of disease burden demonstrate clinically meaningful, disease-modifying benefit of AYVAKIT
4	Detailed results expected to be presented at a future scientific congress
5	Plan to submit sNDA by end of the year

Data cutoff as of June 23, 2022. sNDA, supplemental new drug application

Thank you