



Clinical Data from SUMMIT Part 1b

Investor Webcast
February 23, 2024

Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

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Agenda and Speakers



Andrew Robbins
President and
Chief Executive Officer



Frank Siebenhaar, M.D.
Head, University Outpatient Clinic,
Institute of Allergology, Charite -
Universitätsmedizin Berlin




Jessica Sachs, M.D.
Chief Medical Officer

• Introduction and Corporate Overview	Andrew Robbins
• Review of SUMMIT Part 1b Data with Bezuclastinib in Nonadvanced Systemic Mastocytosis	Dr. Frank Siebenhaar
• Presentation Summary	Andrew Robbins
• Q&A	All

Multiple Clinical and Preclinical Programs with Upcoming Catalysts

Program	Indication	Early Stage Development	Late Stage Development	Regulatory Submission	Approval
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Clinical Programs

Bezuclastinib (KIT inhibitor)	Advanced Systemic Mastocytosis		• APEX Part 2 (Registration-Directed) <ul style="list-style-type: none">• Top-line results by mid-2025
	Nonadvanced Systemic Mastocytosis		• SUMMIT Part 2 (Registration-Directed) <ul style="list-style-type: none">• Top-line results by YE 2025
	Gastrointestinal Stromal Tumors		• PEAK Part 2 (Global Phase 3 trial) <ul style="list-style-type: none">• Top-line results by YE 2025

Research Programs

Indication	Hit ID	Lead Generation	Lead Optimization	Candidate Selected	IND Submission
ErbB2 mut					
FGFR2					
PI3Kα					
Target 4					
Target 5					
Target 6					

Objectives of Today's Presentation

- Review Summit Part 1b results, with a focus on newly announced RP2D 100 mg optimized formulation:
 - Well tolerated safety profile, generally consistent with placebo
 - Impressive pharmacodynamic effects, evidence of strong target engagement
 - 51% mean change in TSS with 70% of patients achieving $\geq 50\%$ reduction at week 12
 - 49% mean improvement in quality-of-life (McQoL) at week 12
- Introduce MS2D2, a novel, refined patient reported outcomes measure (PROM) for symptomatic severity in NonAdvSM patients
- Announce the initiation of SUMMIT Part 2, a 159-patient, registration-directed clinical trial of bezuclostinib vs. placebo in NonAdvSM patients
- Provide clinical context to the SUMMIT Part 1b findings
- Review upcoming milestones for Cogent Biosciences

Systemic Mastocytosis (SM) is a Rare and Debilitating Disease of Neoplastic Mast Cells with Significant Unmet Medical Need Remaining for New Therapies¹

- Nonadvanced SM (NonAdvSM)² includes smoldering SM (SSM),³ for which no therapies are approved, as well as indolent SM (ISM).
- Patients with NonAdvSM experience a variety of disabling, potentially serious and severe symptoms caused by mast cell degranulation, including life-threatening anaphylaxis.⁴
- Agents targeting KIT D816V are used to treat Advanced SM (AdvSM) and NonAdvSM, but unmet need remains.⁵⁻⁷
- Adverse events, such as cognitive impairment, bleeding, and edema, may limit dosing of other agents.

Development of MS2D2 Total Symptom Score

- Rigorous process, in accordance with FDA guidelines, was followed for the development of a novel patient reported outcomes measure (PROM)
- Literature review, patient and physician interviews, and data from SUMMIT Part 1 were used to design a reliable, valid and fit-for-purpose PROM
- Pending FDA approval, a comparison of week 24 mean absolute change from baseline in MS2D2 score between bezuclastinib and placebo will serve as the primary endpoint of SUMMIT Part 2

MS2D2 TSS Additions based on:

- Literature review
- Patient interviews
- SUMMIT Part 1 psychometric analysis

MS2D2 TSS

Itching
Flushing
Spots
Skin redness
Difficulty Concentrating
Difficulty Remembering
Nausea
Abdominal Pain
Headache
Bone Pain
Feeling Tiredness

MS2D2 TSS Exclusions based on:

- FDA feedback
- KOL advice
- SUMMIT Part 1 psychometric analysis

Brain Fog

Dizziness

Diarrhea Severity

Each of these items will be collected as part of MS2D2 secondary analyses in SUMMIT Part 2

MS2D2 TSS comprised of 11 items scored on 0-110 scale

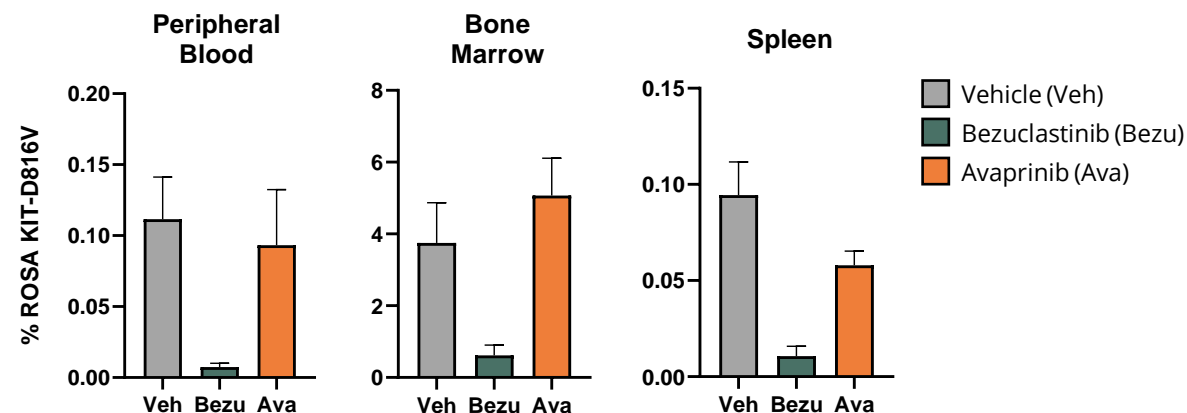
Nonclinical Data Suggests Optimal Activity Against Mastocytosis May Require Higher Exposures Than Clinically Tolerable With Available Therapy

- Mice engrafted with SCF-independent human ROSA^{KIT D816V} cells⁸ were treated daily for 8 weeks with a KIT inhibitor at doses matching clinical exposures observed in NonAdvSM patients
- Only bezuclastinib led to statistically significant decreases ($p < 0.05$) in mutant MC burden compared to vehicle
- At exposures comparable to those achieved in NonAdvSM patients, bezuclastinib led to statistically significant decreases ($P < 0.05$) in bone marrow and spleen compared to avapritinib

Total Drug Exposure Ratio Measured in SM Mouse Model

	Mouse Plasma AUC ₀₋₂₄ (ng·hr/mL) ^a	NonAdvSM Clinical Plasma AUC ₀₋₂₄ (ng·hr/mL) ^b	Total Drug Exposure Ratio (mouse/clinic)
Bezuclastinib	11775	16900	0.7X
Avapritinib	2118	1548	1.4X

MC Burden in SM Mouse Model



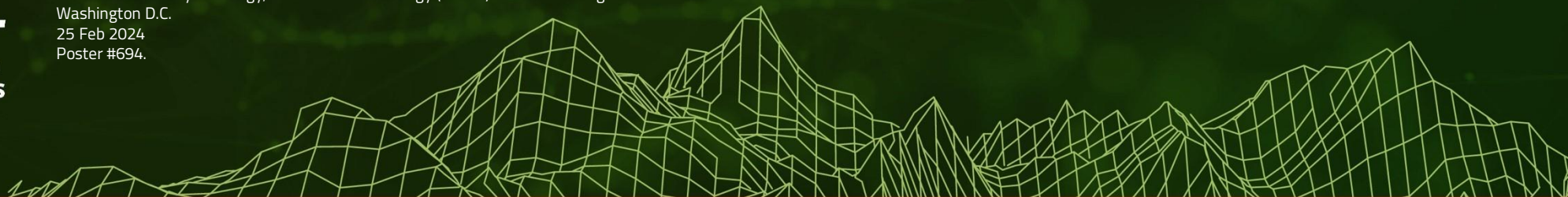
Initial Results from Summit: An Ongoing, 3-Part, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients with NonAdvanced Systemic Mastocytosis (NonAdvSM)

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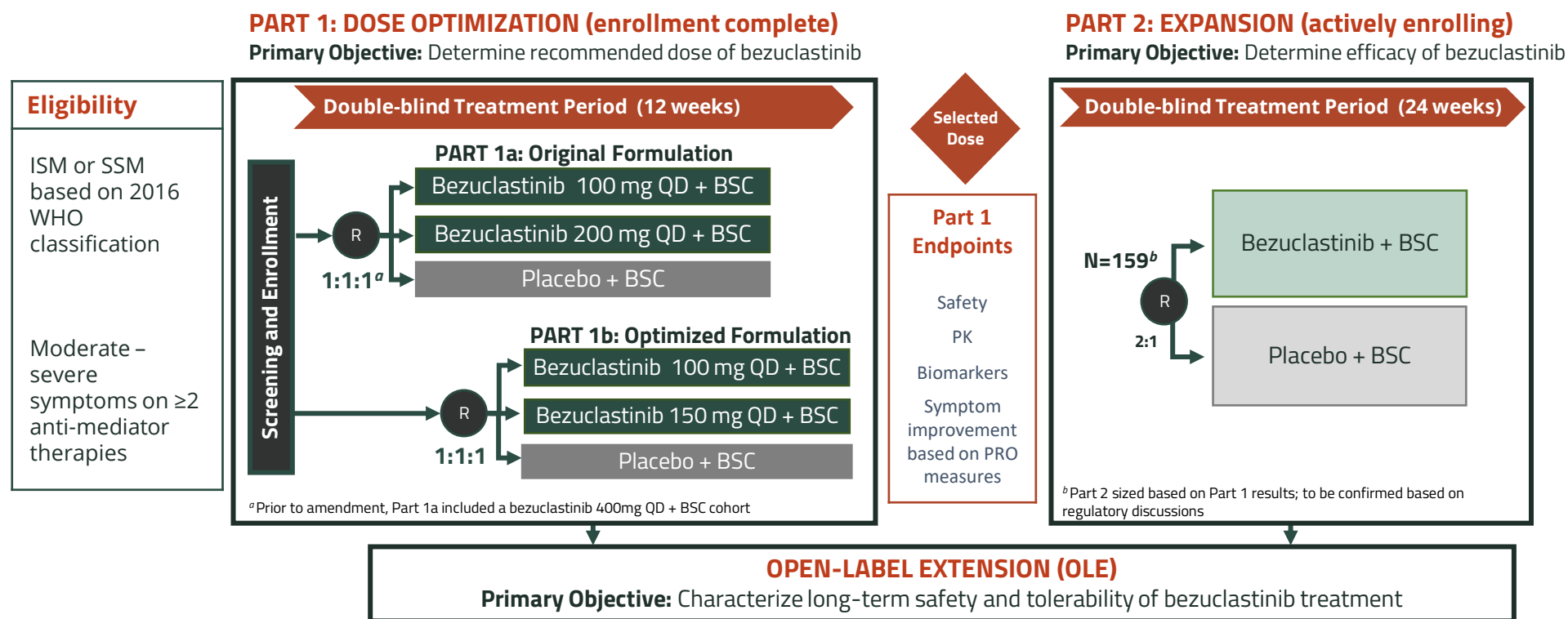
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American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting
Washington D.C.
25 Feb 2024
Poster #694.



SUMMIT: Phase 2 Clinical Study Evaluating Bezuclostinib in NonAdvSM



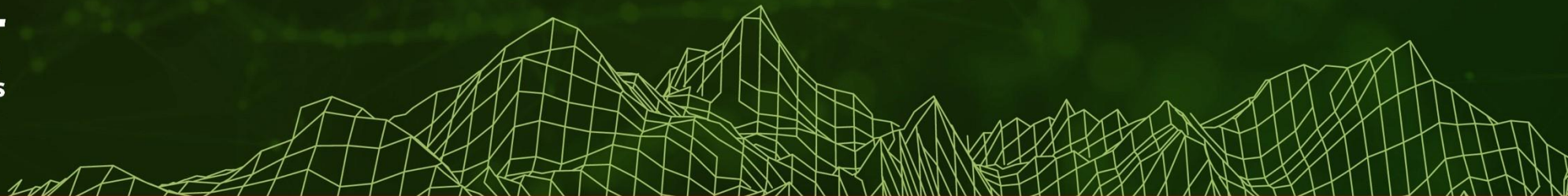
Summit Part 1 Enrolled NonAdvSM Patients with Moderate to Severe Disease

Patient Demographics, Characteristics, and Disposition

Patient Demographics	Part 1a (N=20)	Part 1b (N=34)
Female, n (%)	15 (75)	21 (61.8)
Median Age in years, n (range)	50.5 (38 – 75)	52.0 (27-76)
ECOG PS, n (%)		
0	3 (15)	16 (47.1)
1	15 (75)	17 (50.0)
2	2 (10)	1 (2.9)
Clinical Characteristics	Part 1a (N=20)	Part 1b (N=34)
NonAdv Subtype per PI, n (%)		
Indolent SM (ISM)	18 (90)	33 (97)
Smoldering SM (SSM)	2 (10)	1 (3)
Median (range) MAS Total Score at Eligibility	45.56 (26.3 – 71.6)	43.44 (28.6 – 65.4)
Mast Cell Burden	Part 1a (N=20)	Part 1b (N=34)
KITD816V in Whole Blood, Positive, n (%)	15 (75)	28 (82.4)
Median KIT D816V VAF, % (range)	0.49 (BLD – 32.48)	0.085 (BLD - 19.58)
Median Bone Marrow MC Burden, % (range)	22.5 (1 – 80)	15 (2 – 50)
Median Serum Tryptase, ng/mL (range)	74.35 (10.2- 592.0)	37.15 (9.2 - 206.0)
<20 ng/mL, n (%)	3 (15)	7 (20.6)
≥20 ng/mL, n (%)	17 (85)	27 (79.4)

SM Therapy	Part 1a (N=20)	Part 1b (N=34)
Prior avapritinib, n (%)	1 (5.0)	1 (2.9)
Baseline Supportive Care Medications, Median (range)	3 (2-7)	2.5 (2 – 9)
H1 blockers, n (%)	19 (95)	30 (88.2)
H2 blockers, n (%)	18 (90)	27 (79.4)
Leukotriene receptor antagonists, n (%)	8 (40)	14 (41.2)
Proton pump inhibitors, n (%)	7 (35)	9 (26.5)
Cromolyn sodium, n (%)	4 (20)	3 (8.8)
Omalizumab, n (%)	3 (15)	1 (2.9)
Corticosteroids, n (%)	1 (5)	1 (2.9)
Patient Disposition	Part 1a (n=20)	Part 1b (N=34)
Months on Study (Part 1 + OLE), median (range)	7.03 (2.8 – 16.0)	4.09 (2.7-6.6)
Completed Part 1 (a or b), n (%)	20 (100)	34 (100)
On Study as of Data Cut-off, n (%)	18 (90)	33 (97.1)
Discontinued study, n (%)	2 (10)	1 (2.9)
AE, n (%)	1 (5)	1 (2.9)
Patient Decision, n (%)	1 (5)	0

Bezuclastinib 100 mg QD Optimized Formulation Selected as Summit Part 2 Dose Based on Part 1 Safety, PK, Biomarker and Efficacy Results



Encouraging Safety and Tolerability Profile for Bezuclastinib 100 mg Dose in Part 1b

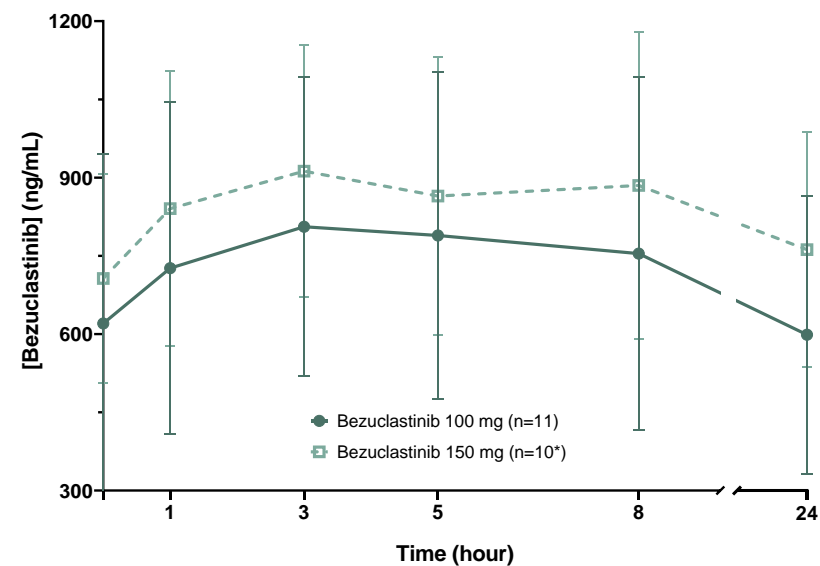
- The majority of TEAEs were low grade and reversible without dose modification
- No bleeding or cognitive impairment events reported across bezuclastinib cohorts
- No dose reductions at 100mg cohort; two dose reductions at 150mg: Gr1 ALT, Gr2 abdominal pain
- Only one SAE reported in bezuclastinib cohorts (150mg patient experienced ALT/AST increase that led to discontinuation)

All TEAEs Occurring >1 Patient in Any Cohort in Part 1b

Preferred Term	Placebo (n=12)		Bezuclastinib			
			100mg QD (n=11)		150mg QD (n=11)	
	Gr 1/2	Gr 3+	Gr 1/2	Gr 3+	Gr 1/2	Gr 3+
Hair color changes	-	-	3	-	7	-
Diarrhea	2	-	2	-	2	-
Nausea	3	-	3	-	1	-
Taste disorder [#]	-	-	1	-	2	-
Dizziness	2	-	-	-	2	-
Fatigue	1	-	-	-	2	-
Noncardiac chest pain	1	-	-	-	2	-
ALT/AST increased [#]	1	-	-	-	1	1*
Neutropenia [#]	-	-	-	-	1	1*
COVID-19	3	-	1	-	-	-
Insomnia	2	-	-	-	-	-
Decreased appetite	2	-	-	-	-	-
Vomiting	2	-	-	-	-	-
Urticaria	2	-	-	-	-	-
Palpitations	2	-	-	-	-	-

Bezuclastinib Demonstrated Dose Dependent Increase in Mean Steady State Exposure

Summit Part 1b: Mean (± SD) Concentration on C2D1 (Steady State)



Comparable Exposures for Low and High Dose Across Part 1a and 1b

	Dose (mg), Study Part	N	Mean S.S. AUC _{0-24h} (ng.h/mL)
Low Dose	100, 1a	7	16900
	100, 1b	11	16900
High Dose	200, 1a	5	19200
	150, 1b	10*	19700

*Excludes one patient with undetectable trough and anomalous low C2D1 exposure

Bezuclastinib Elicited Deep Reductions Across Markers of Mast Cell Burden Within 12 Weeks

Serum Tryptase

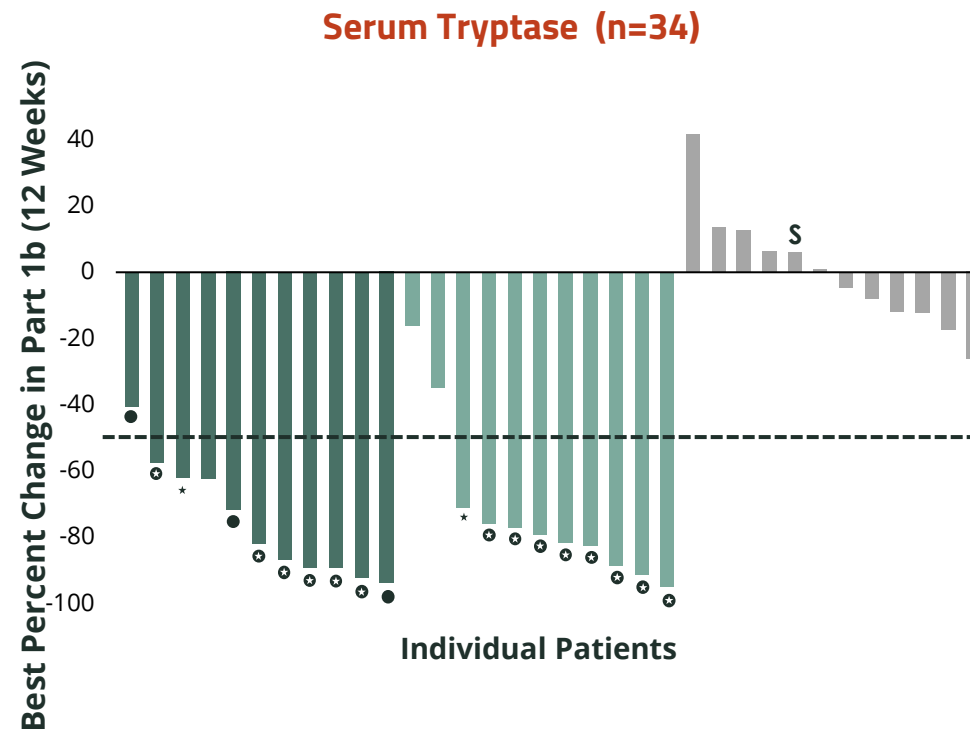
- Of patients with baseline tryptase $\geq 20\text{ng/mL}$, nearly all patients treated with bezuclastinib achieved $<20\text{ng/mL}$ (100% on 100 mg, 89% on 150 mg, 0% on placebo)
 - Overall, mean time to tryptase $<20\text{ng/mL}$ was 4.5 weeks for patients treated with bezuclastinib
- Of patients with baseline tryptase $\geq 11.4\text{ng/mL}$: 70% on 100mg, 90% on 150mg and 0% on placebo achieved $<11.4\text{ng/mL}$

KIT D816V VAF

- Among patients with detectable KIT D816V at baseline: 100% on 100mg, 89% on 150mg and 0% on placebo achieved at least 50% reduction or undetectable KIT D816V at Week 12

Bone Marrow Mast Cells (BM MC)

- Among patients with evaluable BM: 86% on 100mg, 78% on 150mg and 40% on placebo achieved $\geq 50\%$ reduction in BM MC at Week 12
 - Mean % change from baseline in BM MC at Week 12 for patients treated with bezuclastinib 100mg was -70% vs -30% on placebo



■ Bezuclastinib 100 mg
■ Bezuclastinib 150 mg
■ Placebo
s Smoldering SM

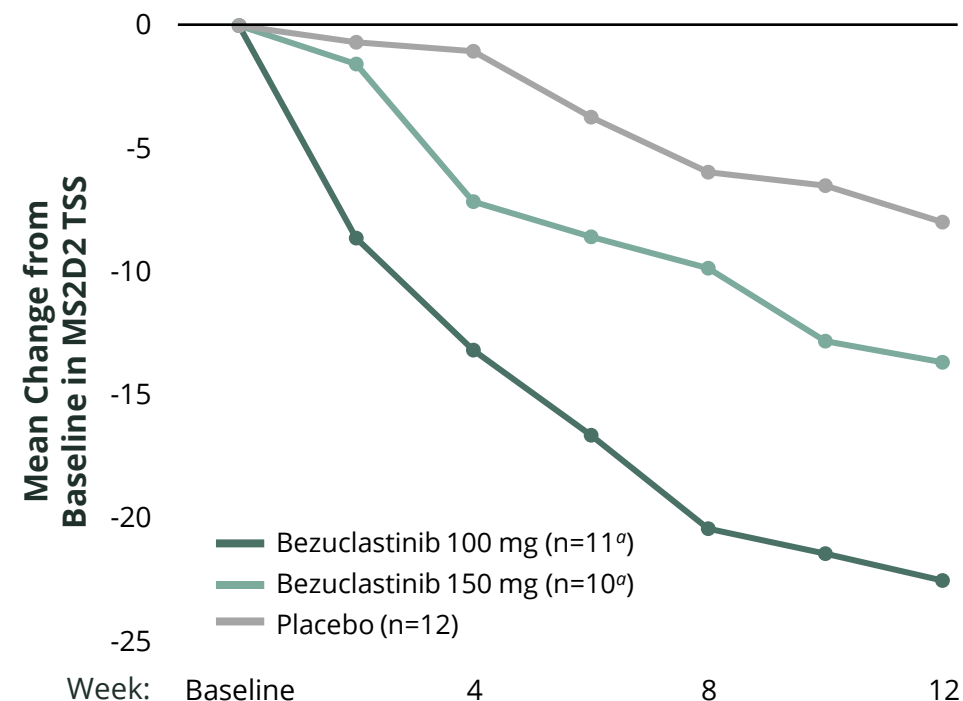
Serum Tryptase Outcomes

- Achieved $<20\text{ng/mL}$ [†]
- ★ Achieved $<11.4\text{ng/mL}$ [†]
- ⊛ Achieved both[†]

Patients Treated With Bezuclastinib 100 mg Reported Rapid and Significant Improvement in Symptom Severity

- 51% mean improvement in overall symptom severity (MS2D2 TSS) from baseline at Week 12 for patients receiving 100 mg bezuclastinib vs. 18% improvement for placebo patients
- Patients treated with 100 mg bezuclastinib reported a significant reduction in total symptom severity vs. placebo at Week 12 (-23.78 vs. -9.03; $p=0.0003$)
- 70% of patients treated with 100 mg bezuclastinib achieved $\geq 50\%$ reduction in MS2D2 TSS at Week 12 vs. 8% placebo patients

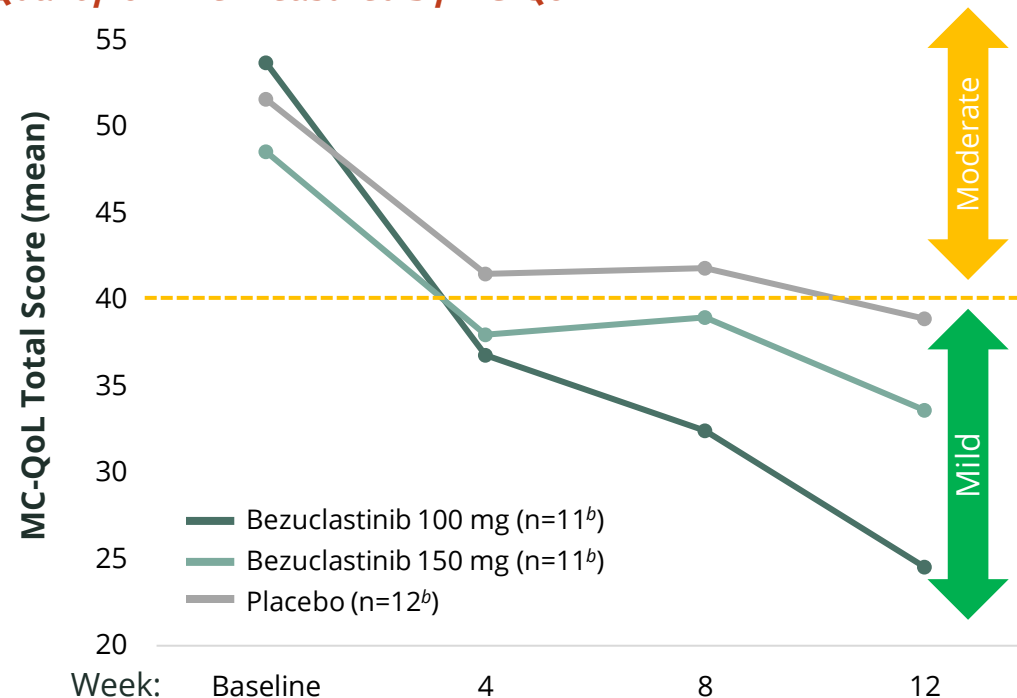
Symptom Severity Measured by MS2D2



Patients Treated With Bezucclastinib 100 mg Reported Rapid and Significant Improvement in Quality of Life

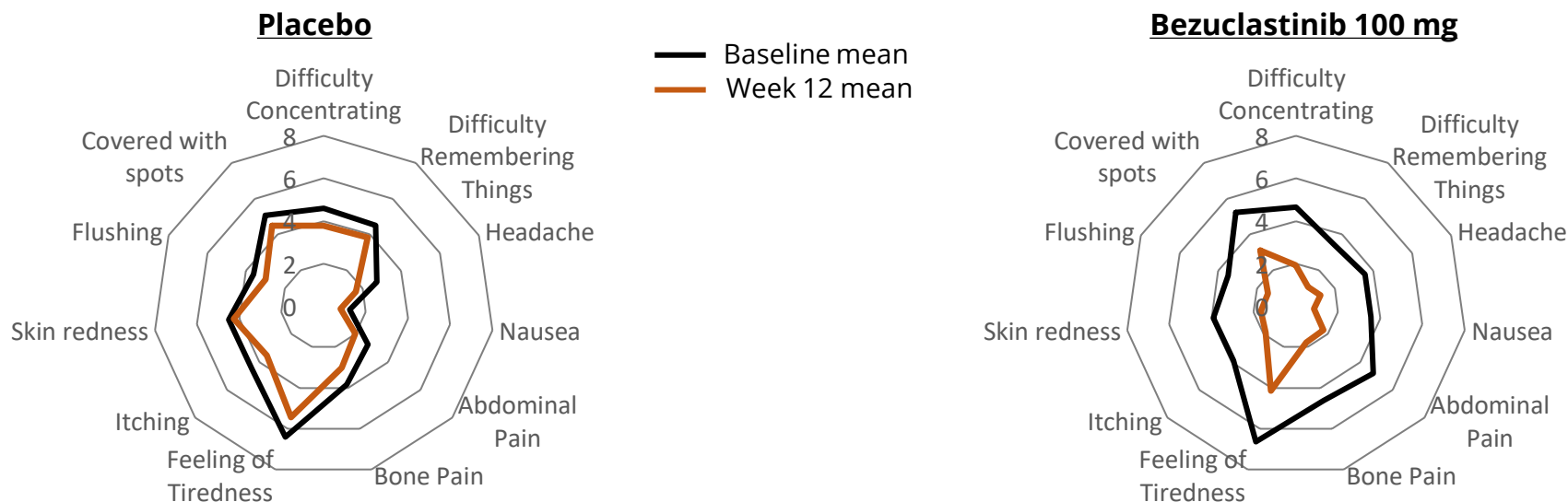
- 49% mean improvement in quality of life (MC-QoL) from baseline at Week 12 in patients treated with 100 mg bezucclastinib vs 24% for placebo
- Patients reported a significant improvement in quality of life after 12 weeks of bezucclastinib 100mg QD compared to placebo (-24.86 vs. -12.39, $p=0.046$)

Quality-of-Life Measured by MC-QoL^a

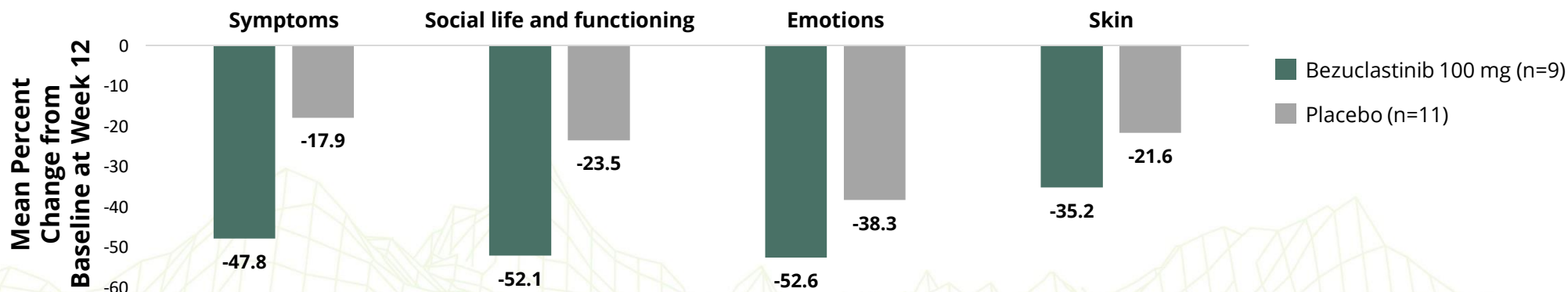


Bezuclastinib 100mg Demonstrated Improvement Compared to Placebo Across Symptoms of SM

Greater Improvement Observed in the MS2D2 TSS With 12 Weeks of Bezuclastinib 100 mg vs Placebo



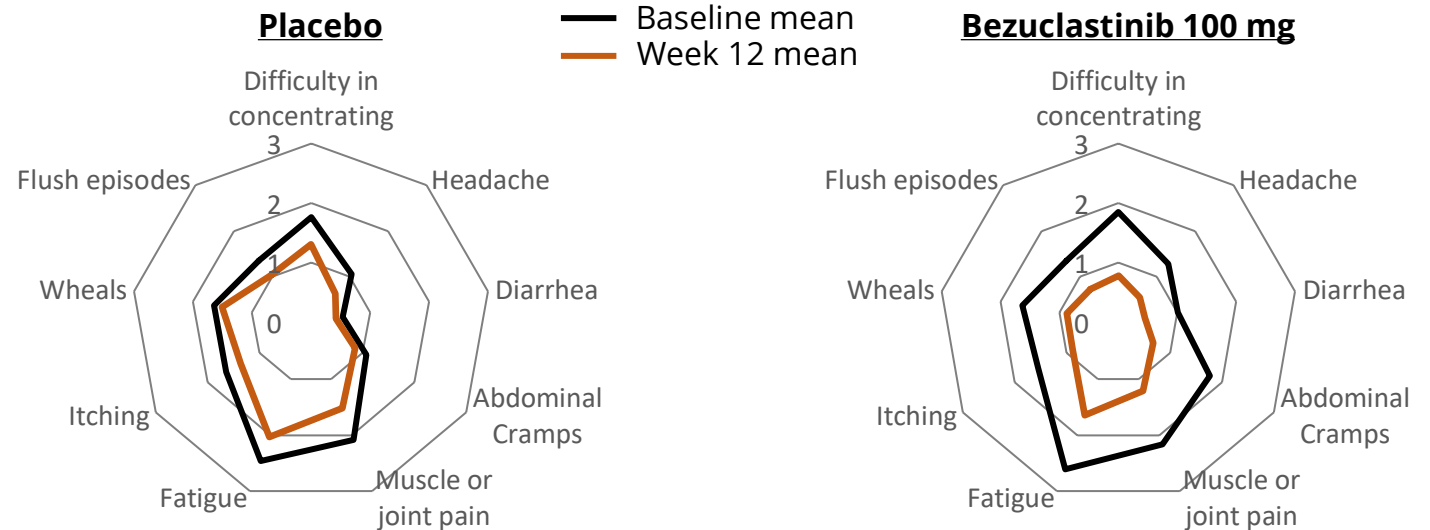
Health-Related QoL Across All MC-QoL^a Domains Improved With 12 Weeks of Bezuclastinib 100mg vs Placebo



Bezuclastinib 100 mg Demonstrated Improvement Compared to Placebo Across Symptoms of SM

Bezuclastinib 100 mg Improved Symptom Severity, As Measured by the Mastocytosis Activity Score^a (MAS), Compared to Placebo

- 41% mean improvement from baseline in MAS at Week 12 for patients receiving 100 mg bezuclastinib vs. 21% improvement for placebo
- 50% of patients treated with 100 mg bezuclastinib achieved $\geq 50\%$ improvement in MAS at week 12 vs. 0% placebo patients



Conclusions: Totality of Results from Summit Part 1 Support 100 mg QD as the Optimal Dose of Bezuclostinib for Patients With NonAdvSM

In Part 1b, bezuclostinib 100mg QD resulted in:

- Safety and tolerability profile generally consistent with placebo results
 - No bleeding, cognitive impairment, or edema AEs reported
 - No dose reductions or discontinuations due to AEs
- Rapid reductions across markers of mast cell burden, supported by KIT D816V mechanism and exposure evidence from nonclinical studies
- Significant improvement versus placebo at 12 weeks in both symptom severity and quality of life, based on mean change from baseline in MS2D2 and MC-QoL total scores which corresponds to:
 - 51% reduction in symptom severity (measured by MS2D2)
 - 49% improvement in health-related quality-of-life (measured by MC-QoL)
- 70% of patients achieving $\geq 50\%$ improvement in symptom severity versus 8% on placebo, as measured by MS2D2

Summit Part 2 is expected to include 159 patients and is actively enrolling



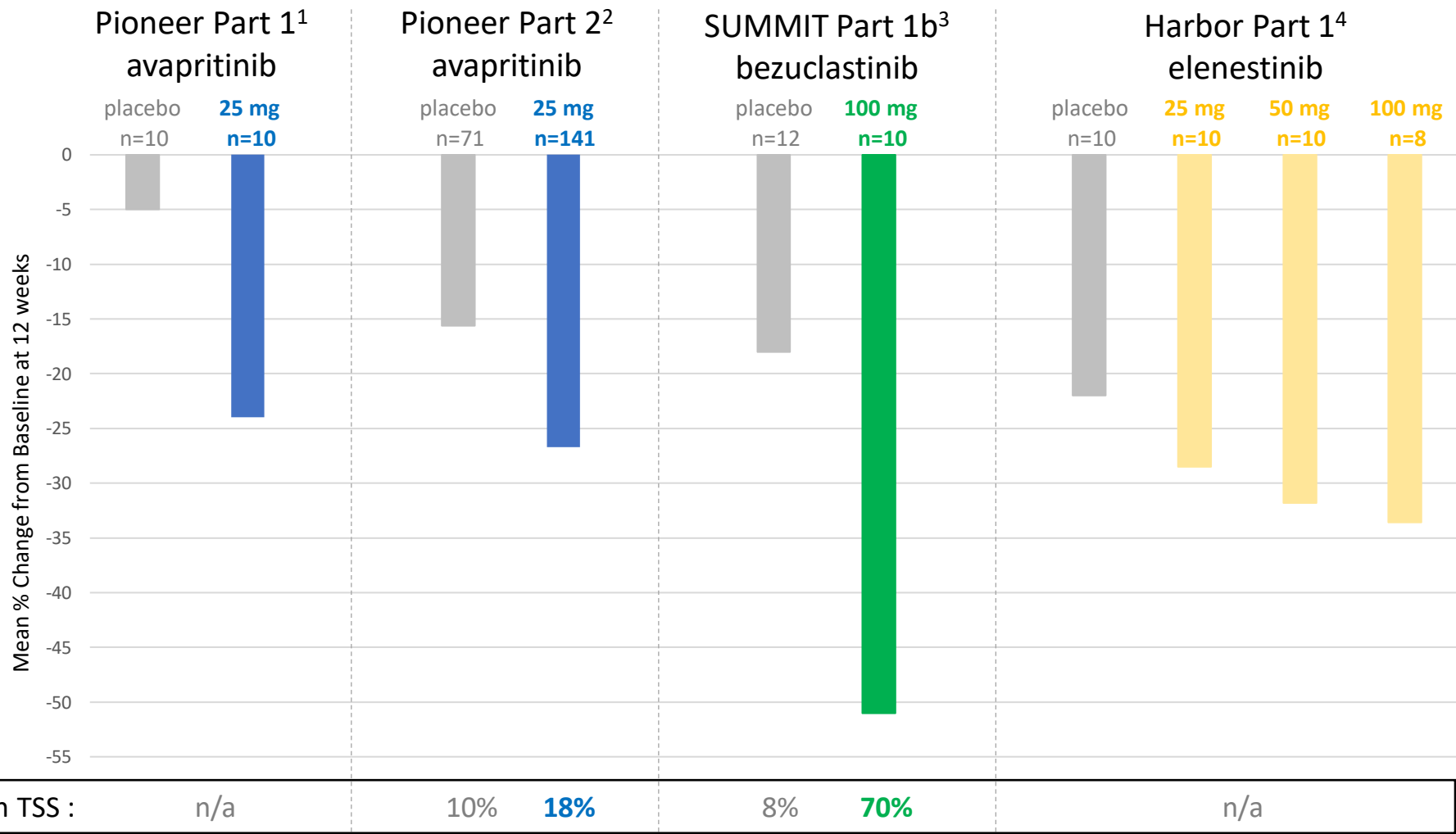
Additional Thoughts on SUMMIT Results

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Precision therapies for genetically defined diseases

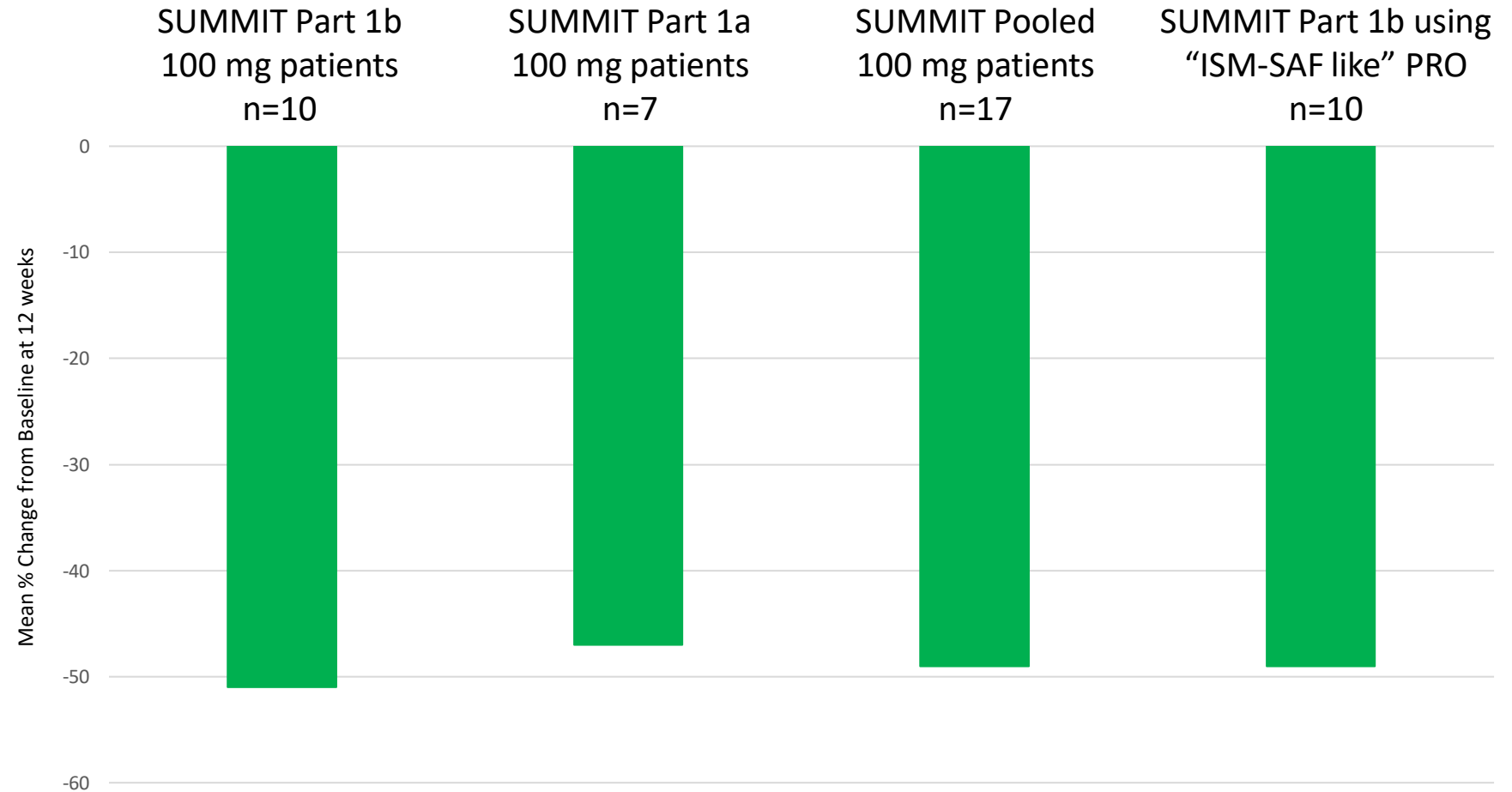
NonAdvSM Clinical Results: Symptomatic Severity Reduction – Week 12 Means

- Results shown from RP2D for avapritinib and bezuclostinib; elenestininb RP2D yet to be announced
- Symptomatic severity assessed using ISM-SAF (avapritinib & elenestininb) and MS2D2 (bezuclostinib), each fit-for-purpose PROMs designed to measure NonAdvSM symptoms
- Pioneer 2, SUMMIT and Harbor Part 1 conducted with patients blinded to laboratory values (eg. serum tryptase) – placebo effect reported appears consistent across studies



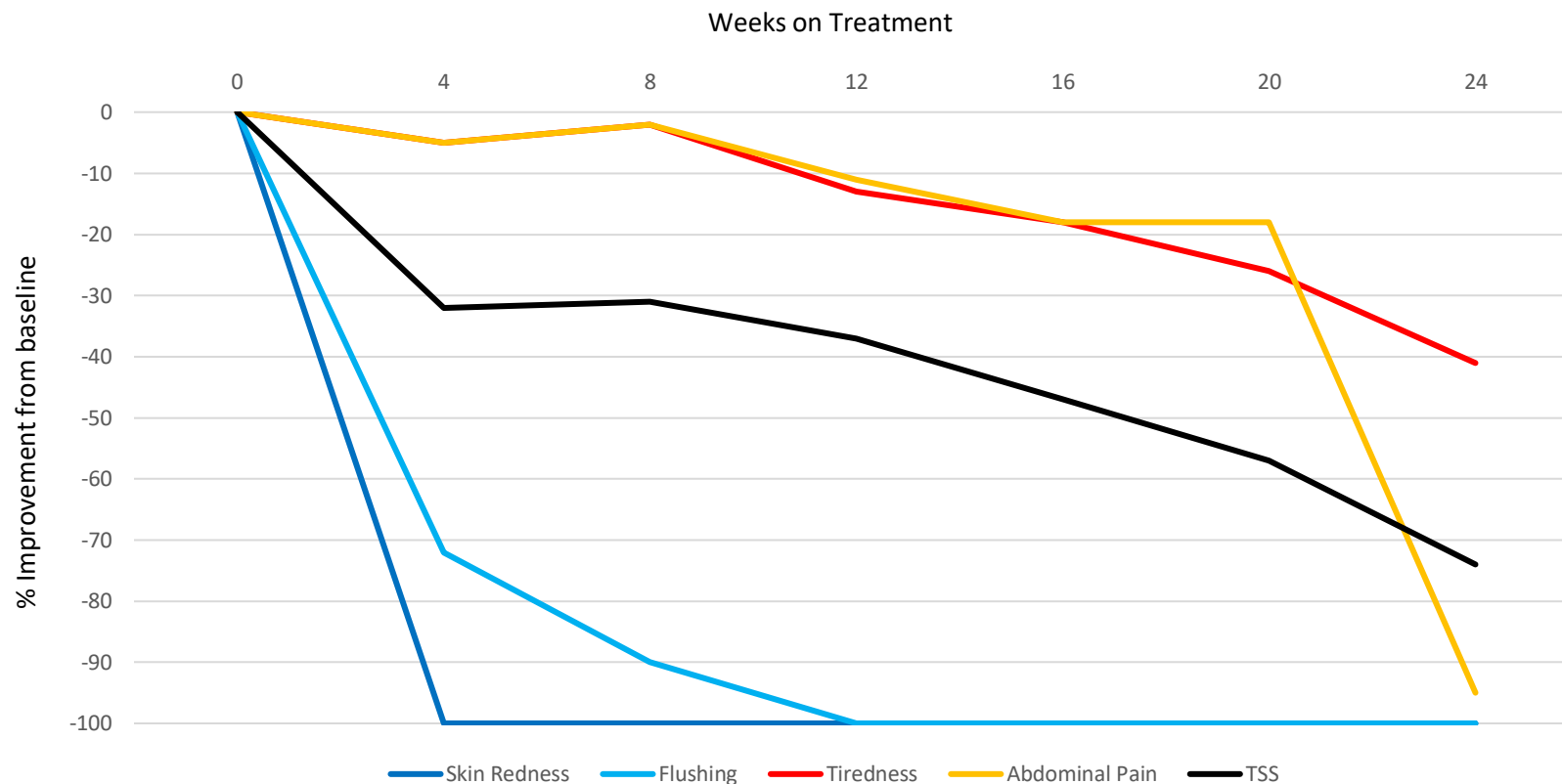
Consistent Magnitude of Symptomatic Improvement for Patients Receiving 100 mg Bezuclostinib

- 100 mg bezuclostinib patients reported very similar symptomatic improvement (week 12 mean change TSS) across SUMMIT 1a and 1b
- Constructing a scoring system using the same symptoms as ISM-SAF results in consistent week 12 mean change in TSS vs. MS2D2
- Improvements across domains in SUMMIT Part 1 support finding that magnitude of effect is not sensitive to item selection in TSS



Optimizing Dose in NonAdvSM is Critical as Adverse Events May Confound TSS

- 52yr old patient receiving 150 mg bezuclastinib in Part 1b
- Serum tryptase reduced from 74.1 ng/ml baseline to 8.6 ng/ml at week 12
- Skin symptoms resolved quickly, but TSS at week 12 only -37% due to persistent tiredness and Gr 2 abdominal pain
- Dose reduced to 100 mg at week 20. Following dose reduction, rapid elimination of abdominal pain, improvement in tiredness and resulting TSS of -73% by week 24





Cogent Summary

Real Challenges. Real Solutions.

Precision therapies for genetically defined diseases

Bezuclastinib Offers Best-in-Class KIT Inhibitor Opportunity



Registration-directed study in ISM
bezuclastinib vs. placebo
n=159, 24 week MS2D2 primary endpoint



Phase 3 study in 2nd-line GIST
bezuclastinib +/- sunitinib
n=388, mPFS primary endpoint



Registration-directed study in ASM
bezuclastinib monotherapy
n=65, ORR primary endpoint

← 2024 → ← 2025 →



\$1.5 billion US annual market opportunity; SUMMIT Part 1b results provide path to market leadership

\$700 million US annual market opportunity, no competition for broad 2nd-line GIST population

\$300 million US annual market opportunity; avapritinib safety/tolerability concerns provides path to market leadership

Recent \$225M fundraising provides cash runway into 2027, more than 12 months after results from all three registration trials expected; aggregate US annual sales opportunity \$2.5 billion with limited competition



LPFV: last patient, first visit signifies end of enrollment period
TLR: top-line results from primary endpoint of trial



Q&A

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