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The Final Analysis of EXPAND: A Phase 1b, Open-Label, Dose-Finding Study of Ruxolitinib in Patients With Myelofibrosis and Low Platelet Count (50 × 10^9/L to < 100 × 10^9/L) at Baseline

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- **Jean-Jacques Kiladjian**: Membership on an entity's board of directors or advisory committees, Abbvie, AOP Orphan, Bristol-Myers Squibb, and Novartis
- **Alessandro M. Vannucchi:** Membership on an entity's board of directors or advisory committees, Blueprint and Incyte. Membership on an entity's board of directors or advisory committees and participation in speakers bureau, Abbvie, Bristol-Myers Squibb, Celgene and Novartis
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Introduction

- Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by cytopenia, splenomegaly and constitutional symptoms such as fatigue, weight loss, fever and night sweats[1-3]
- Ruxolitinib is a potent and selective oral JAK1/JAK2 inhibitor approved for the treatment of disease-related splenomegaly or symptoms in adult patients with primary MF, post-polycythemia vera or post-essential thrombocythemia MF.[4] In the US, ruxolitinib is also approved for the treatment of acute GvHD[4]
- Approval was based on the superior efficacy of ruxolitinib in improving splenomegaly and symptoms in MF patients as well as increasing survival and improving quality of life compared with placebo and best available therapy in the phase 3 COMFORT trials[5,6]
  - Patient eligibility in the COMFORT studies required baseline platelet counts ≥ 100 × 10^9/L, limiting safety and efficacy data in patients with lower platelet counts in spite of the high frequency of thrombocytopenia in MF

GvHD, graft vs host disease; JAK, Janus kinase.

1. Abdel-Wahab OI and Levine RL. *Annu Rev Med*. 2009;60:233–245. 2. Mesa RA, et al. *J Clin Oncol*. 2013;31:1285–1292. 3. Harrison CN, et al. *Ann Hematol*. 2017;96(10):1653–65. 4.. Jakafi, FDA PI. 5. Harrison CN, et al. *Leukemia*. 2016;30(8):1701-1707. 6. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55.

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Introduction (cont.)

- The EXPAND study aimed to establish the MSSD in patients with low baseline platelet count (50 to < 100 × 10^9/L) and evaluated the safety and tolerability of ruxolitinib in this population
  - Based on baseline platelet counts, the patients were assigned to stratum 1 (S1: 75 to 99 × 10^9/L) or stratum 2 (S2: 50 to 74 × 10^9/L)
  - Initially, a MSSD of 15 mg bid was established for S1 and 10 mg bid for S2. This was revised in the 24-week analysis, with the MSSD for both strata selected as 10 mg bid. In addition, a relevant clinical benefit was observed across all starting dose levels, including those patients who started treatment at the 10 mg bid dose[1]
  - Findings from the 48-week follow-up analysis supported the safety and effectiveness of a starting dose of 10 mg bid for patients with MF in S1, but were less conclusive for patients in S2[2]
- Here, we present the final results from the EXPAND study for the MSSD cohort

Bid, twice daily; MF, myelofibrosis; MSSD, maximum safe starting dose.

1. Vannucchi AM, et al. *Blood*. 2015;126:2817. 2. Vannucchi AM, et al. *Haematologica*. 2019;104(5):947-954.

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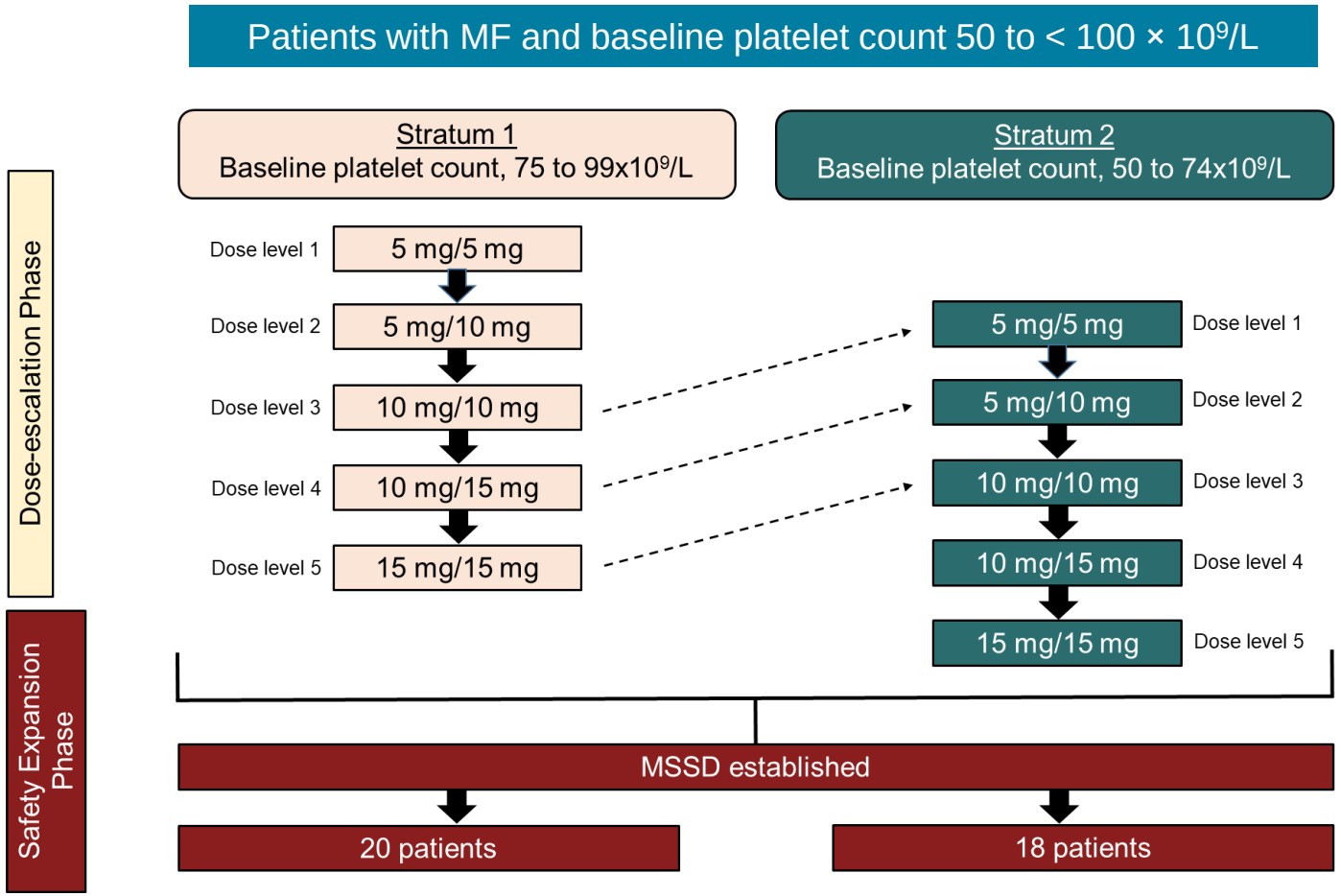
Methods – EXPAND study design

- EXPAND (NCT01317875) is a phase 1b, open-label, multicenter, dose-finding study of ruxolitinib
- **Primary end point:** MSSD
- **Secondary end points:** safety and efficacy
  - Based on baseline platelet counts, the patients were assigned to stratum 1 (S1: 75 to 99 × 10^9/L) or stratum 2 (S2: 50 to 74 × 10^9/L)



MF, myelofibrosis; MSSD, maximum safe starting dose.
Dotted arrows represent each dose level in stratum 2, which will open to patients only if both that dose level and the following one have been deemed safe in stratum 1.

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Patient disposition (MSSD cohort)

n (%)	Stratum 1 N=20	Stratum 2 N=18
Subjects enrolled		
Completed treatment period	10 (50.0)	3 (16.7)
Discontinued from treatment period	10 (50.0)	15 (83.3)
Reason for discontinuation		
Adverse event	2 (10.0)	6 (33.3)
Physician decision	1 (5.0)	3 (16.7)
Progressive disease	3 (15.0)	1 (5.6)
Death	0	3 (16.7)
Other	2 (10.0)	0
Withdrawal by subject	0	2 (11.1)
Lack of efficacy	1 (5.0)	0
Non-compliance with study drug	1 (5.0)	0

Reasons for patient discontinuation were assessed by investigators.
MSSD, maximum safe starting dose.

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Baseline patient characteristics (MSSD cohort) 1/2

- Of 69 treated patients, 38 received ruxolitinib at the MSSD of 10 mg bid (S1, n=20; S2, n=18)
- Baseline characteristics were indicative of advanced disease in both strata

Demographic variable/disease characteristic	MSSD cohort	
	Stratum 1 N=20	Stratum 2 N=18
Age, median (range), years	64.5 (27-81)	66.5 (46-86)
Age ≥65 years, n (%)	10 (50.0)	11 (61.1)
Sex, n (%)		
Male	8 (40.0)	11 (61.1)
Female	12 (60.0)	7 (38.9)
MF subtype, n (%)		
PMF	18 (90.0)	13 (72.2)
PPV-MF	1 (5.0)	3 (16.7)
PET-MF	1 (5.0)	2 (11.1)
Spleen length, median (range), cm	10.5 (5-25)	12.0 (4-33)

Bid, twice daily; MSSD, maximum safe starting dose; MF, myelofibrosis; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera.

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Baseline patient characteristics (MSSD cohort) 2/2

Demographic variable/disease characteristic	MSSD cohort	
	Stratum 1 N=20	Stratum 2 N=18
***JAK2* mutation,** n (%)		
Positive	19 (95.0)	12 (66.7)
Negative	1 (5.0)	5 (27.8)
Not assessed	0	1 (5.6)
IWG risk level at screening, n (%)		
Int-1	10 (50.0)	2 (11.1)
Int-2	8 (40.0)	8 (44.4)
High risk	2 (10.0)	8 (44.4)
Time since initial diagnosis, median (range), months	19.1 (1.7-190.0)	39.5 (1.3-335.6)
Hemoglobin, median (range), g/L	107.5 (51-155)	104.0 (58-150)
Baseline platelet count, median (range), $x10^9$/L	83.0 (40-132)	57.5 (50-81)

Int, intermediate; IWG, International Working Group; JAK, Janus kinase; MSSD, maximum safe starting dose.

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Exposure to study drug – MSSD cohort

	Stratum 1 N=20	Stratum 2 N=18
Duration of exposure to study drug, median (range), weeks	155.0 (4.3, 210.0)	83.2 (4.4, 161.1)
Relative dose intensity, median, (range), %	97.6 (53, 104)	55.3 (28,102)
Dose reductions/interruptions, n (%)		
Patients without dose reduction/interruption	8 (40.0)	2 (11.1)
Patients with at least one dose reduction/interruption	12 (60.0)	16 (88.9)
Patients with only one dose reduction/interruption	4 (20.0)	5 (27.8)
Patients with more than one dose reduction/interruption	8 (40.0)	11 (61.1)

The majority of patients had at least one dose reduction/interruption

MSSD, maximum safe starting dose.

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Adverse events regardless of study drug relationship occurring in ≥20% of patients - MSSD cohort (1/2)

- Reported AEs and AE frequency were consistent with the known safety profile of ruxolitinib.

	Stratum 1 N=20		Stratum 2 N=18	
n, (%)	All grades	Grade ≥3	All grades	Grade ≥3
Anemia	11 (55.0)	5 (25.0)	8 (44.4)	3 (16.7)
Thrombocytopenia	10 (50.0)	8 (40.0)	14 (77.8)	14 (77.8)
Diarrhea	6 (30.0)	1 (5.0)	5 (27.8)	0
Pyrexia	6 (30.0)	0	4 (22.2)	1 (5.6)
Ecchymosis	6 (30.0)	0	2 (11.1)	0
Platelet count decreased	6 (30.0)	5 (25.0)	1 (5.6)	1 (5.6)
Abdominal pain	5 (25.0)	0	4 (22.2)	0
White blood cell count decreased	5 (25.0)	2 (10.0)	1 (5.6)	0
Epistaxis	5 (25.0)	0	0	0
Nasopharyngitis	4 (20.0)	0	5 (27.8)	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an adverse event is only counted under the maximum grade. A patient with multiple occurrences of an adverse event under one treatment is counted only once in the adverse event category for that treatment. Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized. AE, adverse event; MSSD, maximum safe starting dose.

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Adverse events regardless of study drug relationship occurring in ≥20% of patients - MSSD cohort (2/2)

	Stratum 1 N=20		Stratum 2 N=18	
n, (%)	All grades	Grade ≥3	All grades	Grade ≥3
Fatigue	4 (20.0)	1 (5.0)	3 (16.7)	0
Back pain	4 (20.0)	0	3 (16.7)	0
Blood bilirubin increased	4 (20.0)	2 (10.0)	1 (5.6)	0
Hemoglobin decreased	4 (20.0)	0	0	0
Asthenia	3 (15.0)	1 (5.0)	5 (27.8)	2 (11.1)
Cough	2 (10.0)	0	6 (33.3)	0
Hypocalcemia	2 (10.0)	0	5 (27.8)	0
Hypertension	1 (5.0)	1 (5.0)	4 (22.2)	0
Headache	1 (5.0)	0	4 (22.2)	0
Nausea	1 (5.0)	0	4 (22.2)	0

Numbers (n) represent counts of subjects. A subject with multiple severity grades for an adverse event is only counted under the maximum grade. A patient with multiple occurrences of an adverse event under one treatment is counted only once in the adverse event category for that treatment. Adverse events occurring more than 30 days after the discontinuation of study treatment are not summarized. MSSD, maximum safe starting dose.

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On-treatment deaths - MSSD cohort

- On-treatment deaths included:
  - S1: Cardiac arrest, acute myeloid leukemia
  - S2: Multiorgan failure, and sepsis
- Only the death due to cardiac arrest was assessed as related to ruxolitinib; the other deaths were assessed as unrelated to study drug

Primary system organ class Primary reason (preferred term), n (%)	Stratum 1 N=20	Stratum 2 N=18
Number of patients who died	2 (10.0)	2 (11.1)
Cardiac disorders	1 (5.0)	0
Cardiac arrest	1 (5.0)	0
General disorders and administration site conditions	0	1 (5.6)
Multiple organ dysfunction syndrome	0	1 (5.6)
Infections and infestations	0	1 (5.6)
Sepsis	0	1 (5.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (5.0)	0
Acute myeloid leukemia	1 (5.0)	0

MSSD, maximum safe starting dose.

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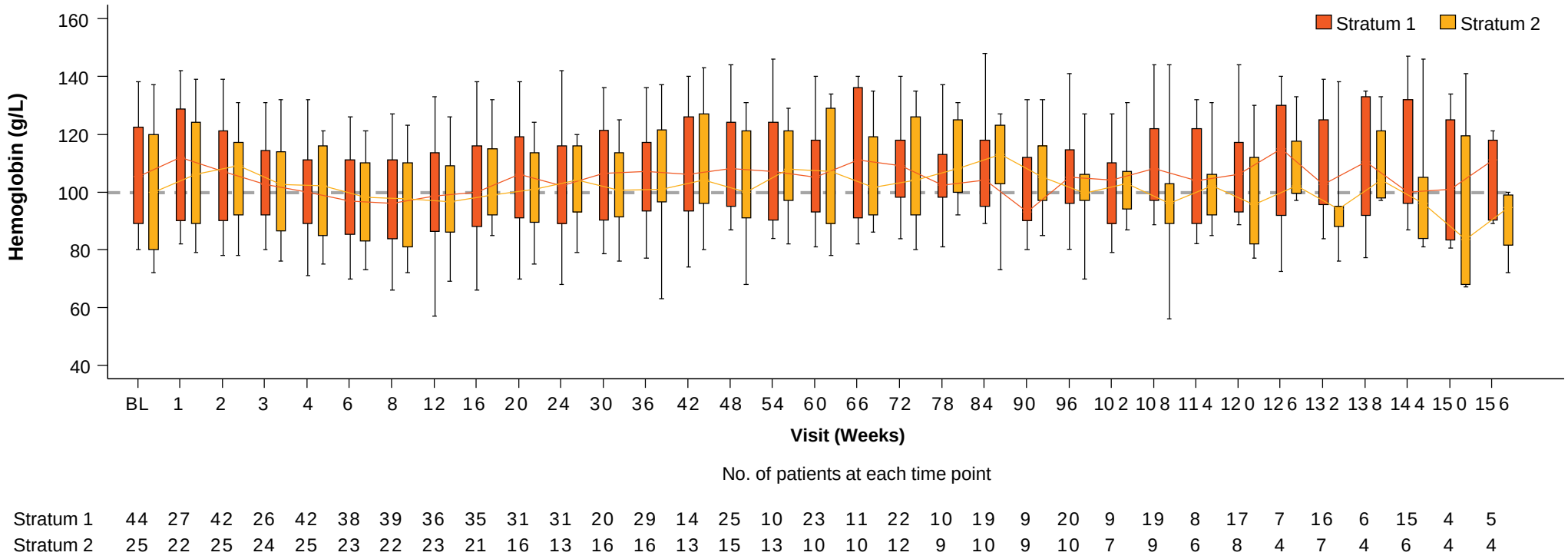
Hemoglobin levels over time – MSSD cohort



No. of patients at each time point

Stratum 1	44	27	42	26	42	38	39	36	35	31	31	20	29	14	25	10	23	11	22	10	19	9	20	9	19	8	17	7	16	6	15	4	5
Stratum 2	25	22	25	24	25	23	22	23	21	16	13	16	16	13	15	13	10	10	12	9	10	9	10	7	9	6	8	4	7	4	6	4	4

Hemoglobin levels over time were similar across strata

After week 24, various lab visits existed according to different versions of protocols. In this boxplot, only time points of every 6 weeks are displayed as per the lab schedules in the latest protocol amendment. For each patient, the closest visit within the ± 3 week time window of each time point displayed after week 24 was chosen. Boxes represent median and interquartile range, whiskers (lines) represent 5th and 95th percentiles. MSSD, maximum safe starting dose.

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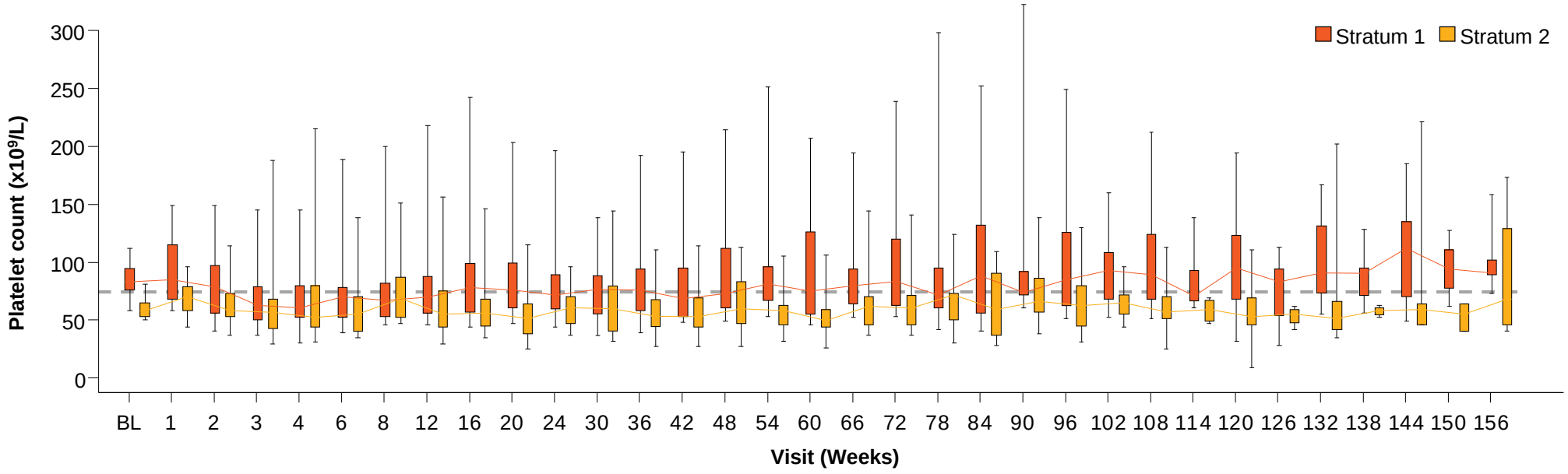
Platelet counts over time – MSSD cohort



Number of patients at each time point

Stratum 1	44	27	42	26	42	38	39	36	35	32	31	20	29	14	25	10	23	11	22	10	19	9	20	9	19	8	17	7	16	6	15	4	5
Stratum 2	25	22	25	24	25	23	22	23	21	16	13	16	16	13	15	13	10	10	12	9	10	9	10	7	9	6	8	4	7	4	6	3	4

Decreases in platelet counts were observed in both strata over the first 4 weeks, stabilizing after that period

After week 24, various lab visits existed according to different versions of protocols. In this boxplot, only time points of every 6 weeks are displayed as per the lab schedules in the latest protocol amendment. For each patient, the closest visit within the ± 3 week time window of each time point displayed after week 24 was chosen. Boxes represent median and interquartile range, whiskers (lines) represent 5th and 95th percentiles. MSSD, maximum safe starting dose.

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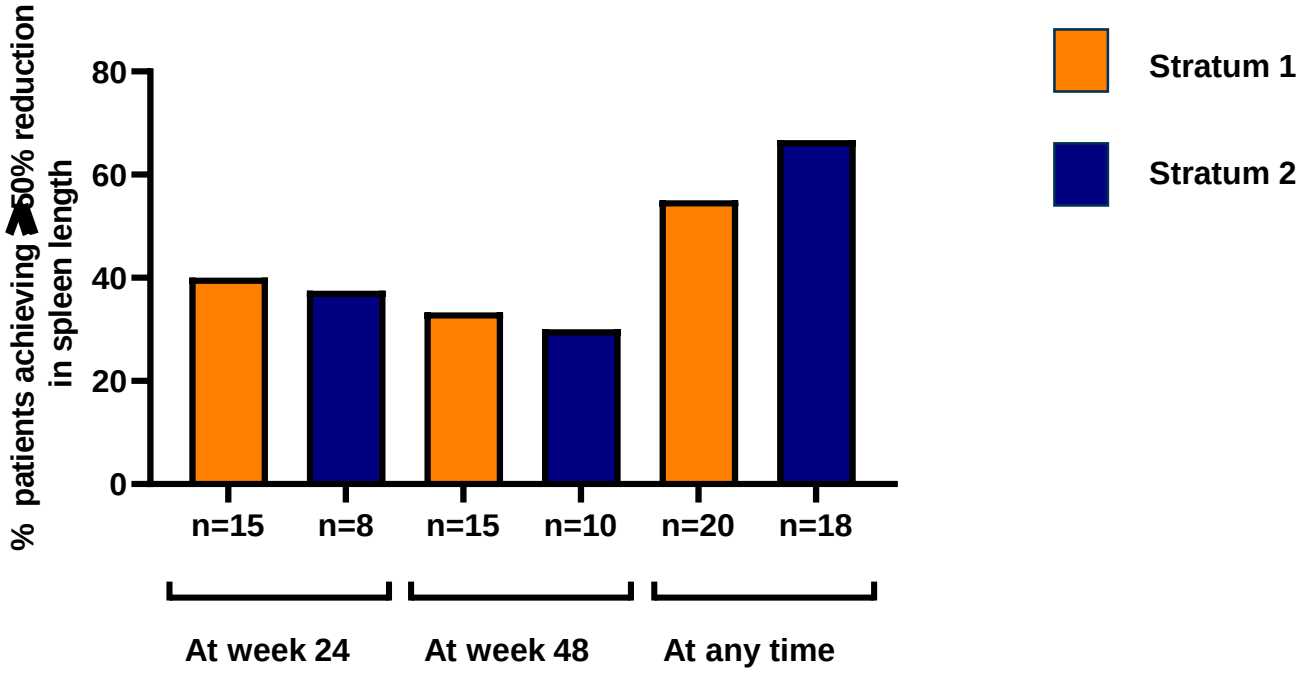
Spleen length over time by stratum – MSSD cohort

A large proportion of patients achieved clinically meaningful reductions in spleen length



CI, confidence interval; MSSD, maximum safe starting dose.

Study period: March 2011 to February 2020.

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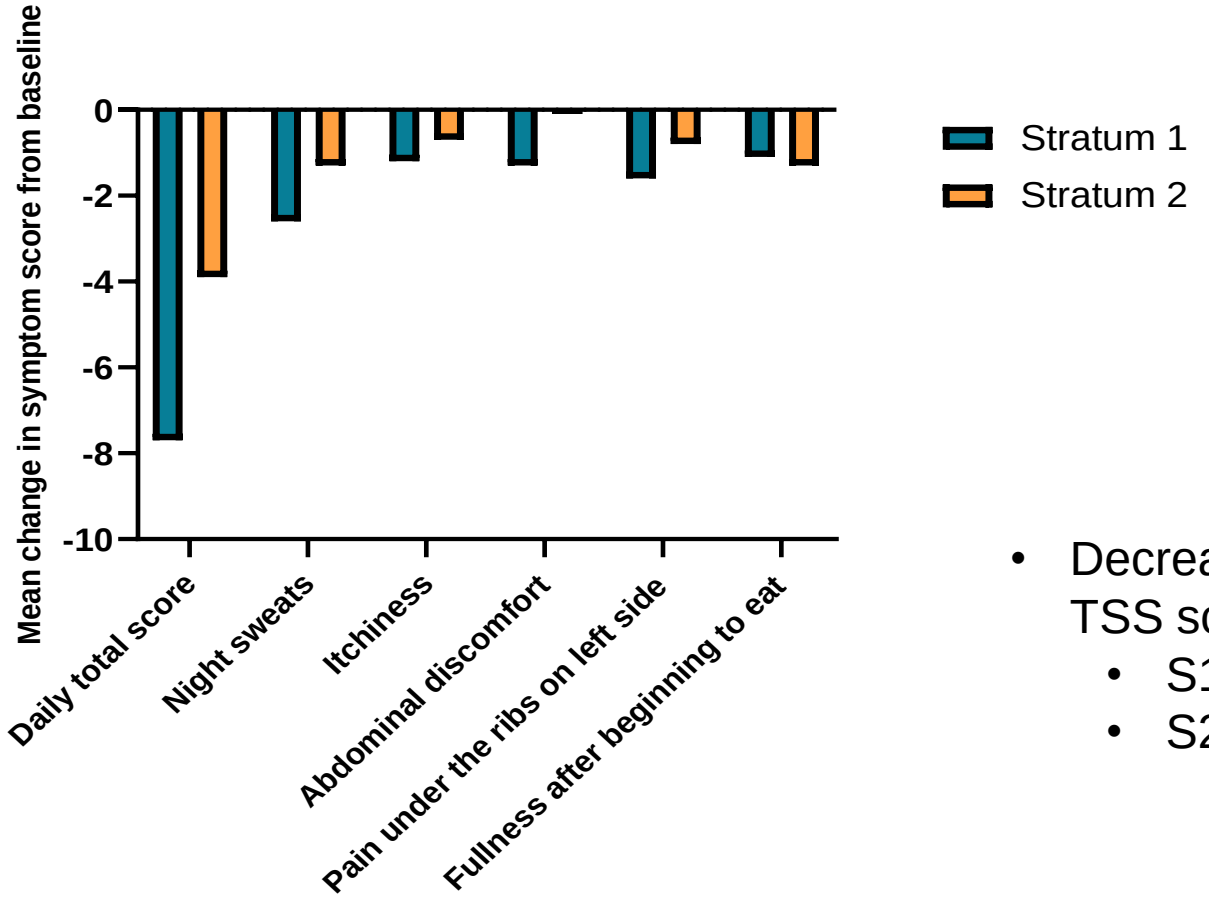
Symptom response - MSSD cohort

Improvement in total score individual symptom scores of MF-SAF TSS diary from baseline to week 24



- Decrease (improvement) in total daily MF-SAF TSS score from baseline to week 24, mean (SD):
  - S1: 7.7 (9.7)
  - S2: 3.9 (11.4)

n is the number of patients with both baseline and post-baseline scores at the time point.
MF-SAF TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score; MSSD, maximum safe starting dose; SD, standard deviation.

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Symptom response – MSSD cohort

Proportion of patients achieving at least 50% reduction from baseline in total symptom scores of MF-SAF TSS diary at week 24

	Stratum 1 N=20	Stratum 2 N=18
n	16	16
n at week 24	13	10
Patients achieving ≥50% reduction in total symptom score at week 24, n (%)	4 (30.8)	4 (40.0)
95% CI of the response rate	(9.1, 61.4)	(12.2, 73.8)

n is the number of patients with both baseline and post-baseline scores at the time point.
CI, confidence interval; MF-SAF TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score; MSSD, maximum safe starting dose.

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PK/PD results

- A population PK model for ruxolitinib was developed using pooled data from one phase 1/2 study and one phase 3 study and validated using a different phase 3 study in subjects diagnosed with PMF, PPV-MF, or PET-MF
  - No significant difference was found in the PK of ruxolitinib between MF subjects with baseline platelet count of ≥ 100 × 10^9/L and those with baseline platelet count of ≥ 50 × 10^9/L to < 100 × 10^9/L
- A PopPKPD model for spleen volume versus average PK concentration was fitted using derived spleen volumes based on scaling observed spleen length
  - The results showed similar trends for all dosing regimens and PK quartiles, suggesting that spleen length was not detrimentally affected in the different dose groups
- The existing PopPKPD model for platelet count versus average concentration was fitted, to assess whether the observed relationship in the original MF indication (platelet count: ≥ 100 x 10^9/L) was validated in the low-platelet population (platelet count: ≥ 50 x 10^9/L and < 100 x 10^9/L)
  - The fit of the model showed that the observed platelet counts in this study were predicted well by the use of the previous model, suggesting the existing relationship between platelet count and concentration is consistent in this population

MF, myelofibrosis; PD, pharmacodynamics; PET, post-essential thrombocythemia; PK, pharmacokinetics; PMF, primary myelofibrosis; PPV, post-polycythemia vera.

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Conclusions

- Our results show that a starting dose of ruxolitinib 10 mg bid was well tolerated in MF patient populations with low baseline platelet counts (50 to < 75 × 10^9/L and 75 to < 100 × 10^9/L), which were previously unstudied
- The observed AEs were consistent with the known safety profile of ruxolitinib, and no new or unexpected safety signals were reported
- Ruxolitinib treatment at a starting dose of 10 mg bid provided clinically meaningful reductions in spleen length and improvement in clinical symptoms
- Tolerability and safety of ruxolitinib in this patient population was supported by the PK/PD results
- EXPAND final results confirm that a starting dose of ruxolitinib 10 mg bid is suitable for patients with MF who have low platelet counts at baseline, even those in advanced stages of disease

AE, adverse event; bid, twice daily; MF, myelofibrosis; PD, pharmacodynamics; PK, pharmacokinetics.

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