SUPPLEMENTARY APPENDIX

EXPAND, a dose-finding study of ruxolitinib in patients with myelofibrosis and low platelet counts: 48-week follow-up analysis

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Supplementary Appendix

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Dose-Determining Set

The dose-determining set (DDS) consisted of all patients from the safety set who met the minimum exposure criterion and had sufficient safety evaluations or experienced a dose-limiting toxicity (DLT). The DDS included all patients who experienced a DLT regardless of whether they permanently discontinued treatment. The patients in the DDS enrolled in the dose-finding part of the study were studied for determination of the maximum safe starting dose (MSSD). A patient was considered to have met the minimum exposure criterion and to have had sufficient safety evaluations if they had not missed >20% of the planned doses and no more than 6 consecutive doses in the first 28 days, and had completed all required safety evaluations through study day 28.

Planned Enrollment

Cohorts of at least 3 patients per dose level and stratum were enrolled from the DDS, including at least 9 patients at the MSSD level within each stratum from the DDS. Due to the potential for dropouts during the first treatment cycle (eg, early disease progression), a cohort could be expanded to include additional patient(s). Cohorts could be expanded at any dose level below the MSSD for further elaboration of safety and pharmacokinetic parameters if deemed appropriate per the clinical trial team (per protocol). Approximately, 21 patients were planned within each stratum in the dose-finding portion of the study, assuming 3 patients were treated at each of the 5 dose levels tested. Once the MSSD was determined, additional patients were planned to be enrolled per stratum in the safety-expansion phase in order to further evaluate the end points in patients starting at the MSSD. Patients from both strata were enrolled

simultaneously during the safety-expansion phase and were allocated to a dose equal to the respective MSSD for their stratum. If the MSSD was the same in both strata, all patients in the safety-expansion phase were treated with the same dose, regardless of the baseline platelet counts.

Based on a review of the interim analysis data, a decision was made to expand the 10 mg twice daily (bid) starting dose for stratum 1. Following protocol amendment, new patients enrolled in stratum 1 in the safety-expansion phase were assigned a ruxolitinib dose of 10 mg bid. In line with the original sample size specification for the MSSD cohorts (ie, >9 patients for the dose-escalation phase and 10 patients for the safety-expansion phase), approximately 20 patients in total were planned to be enrolled, including those already enrolled at the 10 mg bid dose level in stratum 1. Patients already receiving the 15 mg bid dose in stratum 1 in the safety-expansion phase continued to take their assigned dose. Stratum 2 maintained its original enrollment requirement of 10 patients at the MSSD.

The approximate number of patients planned to be enrolled in the DDS for this study was 72.

Bayesian Logistic Regression Model

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control principle was used to guide the dose escalation to determine the MSSD of ruxolitinib. During the course of the study, patients were dose escalated to the next higher dose level only once every 2 cycles (each cycle was 28 days). The model used accumulated data on observed DLTs at each dose level and stratum. Bayesian inference was used to assess the risks of overdose at each dose level. The use of

Bayesian response adaptive models for phase 1 studies has been advocated by the European Medicines Agency guidelines for clinical trials in small populations (2006) and is one of the key elements of the Critical Path Initiative by the Food and Drug Administration. A 3-parameter BLRM was used to establish the safety of ruxolitinib treatment in patients with MF with platelet counts between 50×10^9/L and 100×10^9/L. A prior distribution for the model parameters was derived based on the experience with ruxolitinib in adult patients in study 251, which was the dose-finding study in patients with MF that preceded the pivotal phase 3 studies. This prior distribution was then updated with the accumulated DLT data from the current study after each cohort of patients in each stratum completed at least 28 days of treatment.

Statistical Methods and Data Analysis

The statistical analyses in this study were performed using SAS® software version 9.3. The data were summarized with respect to demographic and baseline characteristics, occurrence of DLTs, efficacy observations/measurements, and safety observations/measurements. The categorical data were presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum were presented. Unless otherwise specified, the safety and efficacy outputs were summarized by stratum, and for each stratum, the patients were grouped according to the first dose level they received: Group 1 (stratum 1 and stratum 2): patients with starting dose of 5 mg ante meridiem (AM) + 5 mg post meridiem (PM) (cohort 1) or 5 mg AM + 10 mg PM (cohort 2); Group 2 (stratum 1 and stratum 2): patients with starting dose of 10 mg AM + 10 mg PM (cohort 3) or 10 mg AM + 15 mg PM (cohort 4); Group 3 (stratum 1 only): patients with starting dose of 15 mg

AM + 15 mg PM (cohort 5). DLT outcomes were summarized separately by dose level and stratum.

Treatment Dose Levels

The following cohorts/dose levels were used in the study (for both strata):

- Cohort/dose level 1: ruxolitinib 10 mg (5 mg bid)
- Cohort/dose level 2: ruxolitinib 15 mg (5 mg AM/10 mg PM)
- Cohort/dose level 3: ruxolitinib 20 mg (10 mg bid)
- Cohort/dose level 4: ruxolitinib 25 mg (10 mg AM/15 mg PM) (for stratum 1 only)
- Cohort/dose level 5: ruxolitinib 30 mg (15 mg bid) (for stratum 1 only)

Following protocol amendment, new patients enrolled in stratum 1 in the safety-expansion phase were assigned a ruxolitinib dose of 10 mg bid. Patients already taking the 15 mg bid dose in stratum 1 in the safety-expansion phase continued to take their assigned dose.

End of Treatment

The end of treatment was defined as the time at which the administration of study treatment was permanently discontinued due to any reason (eg, planned completion, disease progression, adverse event, withdrawn consent, or until switch to commercially available ruxolitinib treatment [if applicable by local regulations] in each participating country).

Supplementary Tables

Supplementary Table 1. Criteria for defining DLTs.

Toxicity	**Any of the following treatment-related criteria (occurring through study day 28)**
Hematology	Platelet counts $<25\times10^9$/L[a]
	Grade 4 neutropenia (absolute neutrophil count $<0.5\times10^9$/L)[a]
	Grade ≥3 febrile neutropenia[a]
Other AEs	Any grade thrombocytopenia requiring platelet transfusion
	Any grade ≥2 hemorrhagic event
	Grade ≥2 serum bilirubin with coincident direct bilirubin ≥0.5 mg/dL
	Grade 3 nonhematologic toxicity for ≥7 consecutive days
	Grade 4 nonhematologic toxicity

[a]At the discretion of the investigator, laboratory values could be confirmed with a second assessment. In this case, only the result of the second assessment would be considered valid and final. AE: adverse event; DLT: dose-limiting toxicity.

Supplementary Table 2. Baseline patient characteristics (overall study cohort).

Demographic variable/disease characteristic	Stratum 1 (platelet count 75-99×10^9/L) N=44, N (%)	Stratum 2 (platelet count 50-74×10^9/L) N=25, N (%)	Total N=69, N (%)
Age, median (range), years	69.0 (27-81)	67.0 (46-86)	69.0 (27-86)
Age ≥65 years	27 (61.4)	16 (64.0)	43 (62.3)
Sex			
Male	20 (45.5)	13 (52.0)	33 (47.8)
Female	24 (54.5)	12 (48.0)	36 (52.2)
ECOG performance status			
0	19 (43.2)	5 (20.0)	24 (34.8)
1	18 (40.9)	14 (56.0)	32 (46.4)
2	7 (15.9)	6 (24.0)	13 (18.8)
MF subtype			
PMF	34 (77.3)	17 (68.0)	51 (73.9)
PPV-MF	7 (15.9)	5 (20.0)	12 (17.4)
PET-MF	3 (6.8)	3 (12.0)	6 (8.7)
Spleen length, median (range), cm	13.0 (5-30)	11.0 (4-33)	12.0 (4-33)
JAK2 mutation			
Positive	36 (81.8)	19 (76.0)	55 (79.7)
Negative	6 (13.6)	5 (20.0)	11 (15.9)
Not assessed	2 (4.5)	1 (4.0)	3 (4.3)
IWG risk level at screening			
Intermediate risk level 1	13 (29.5)	3 (12.0)	16 (23.2)
Intermediate risk level 2	16 (36.4)	9 (36.0)	25 (36.2)
High risk	15 (34.1)	13 (52.0)	28 (40.6)
Time since initial diagnosis, median (range), months	22.768 (0.23-234.32)	25.068 (1.35-335.54)	23.359 (0.23-335.54)
Hemoglobin, median (range), (g/L)	105.325 (51.00-155.00)	100.000 (58.00-150.00)	103.000 (51.00-155.00)
Baseline platelet count, median (range), (×10^9/L)	83.0 (40-132)	58.0 (47-100)	76.0 (40-132)

ECOG: Eastern Cooperative Oncology Group; IWG: International Working Group; JAK: Janus kinase; MF: myelofibrosis; PET-MF: post–essential thrombocythemia MF; PMF: primary MF; PPV-MF: post–polycythemia vera MF.

Supplementary Table 3. Patient disposition (overall study cohort).

Patient disposition	Stratum 1 (N=44) N (%)	Stratum 2 (N=25) N (%)	Total (N=69) N (%)
Patients treated			
End of treatment	30 (68.2)	22 (88.0)	52 (75.4)
Treatment ongoing[a]	14 (31.8)	3 (12.0)	17 (24.6)
Primary reason for end of treatment			
AE	11 (25.0)	7 (28.0)	18 (26.1)
Completed	7 (15.9)	6 (24.0)	13 (18.8)
Death	0	3 (12.0)	3 (4.3)
Other	3 (6.8)	0	3 (4.3)
Physician decision	4 (9.1)	3 (12.0)	7 (10.1)
Progressive disease	4 (9.1)	1 (4.0)	5 (7.2)
Withdrawal by patient	1 (2.3)	2 (8.0)	3 (4.3)

[a]Patients ongoing treatment at the time of data cutoff (December 7, 2017). AE: adverse event.

Supplementary Table 4. All-grade AEs, in ≥20% of patients in either stratum in the overall study cohort (regardless of study drug relationship).

Preferred term	Stratum 1 (N=44)		Stratum 2 (N=25)	
	All grades N (%)	Grade 3 or 4 N (%)	All grades N (%)	Grade 3 or 4 N (%)
Thrombocytopenia	28 (63.6)	22 (50.0)	19 (76.0)	19 (76.0)
Anemia	23 (52.3)	14 (31.8)	12 (48.0)	6 (24.0)
Diarrhea	13 (29.5)	2 (4.5)	8 (32.0)	0
Pyrexia	9 (20.5)	0	7 (28.0)	2 (8.0)
Asthenia	8 (18.2)	3 (6.8)	7 (28.0)	2 (8.0)
Cough	4 (9.1)	0	10 (40.0)	0
Abdominal pain	8 (18.2)	0	5 (20.0)	0
Headache	6 (13.6)	0	6 (24.0)	0
Back pain	6 (13.6)	1 (2.3)	5 (20.0)	1 (4.0)
Epistaxis	10 (22.7)	1 (2.3)	1 (4.0)	0
Nasopharyngitis	5 (11.4)	0	6 (24.0)	0
Nausea	5 (11.4)	0	5 (20.0)	0
Edema peripheral	5 (11.4)	3 (6.8)	5 (20.0)	0
Pain in extremity	4 (9.1)	0	6 (24.0)	0
Hypocalcemia	3 (6.8)	0	6 (24.0)	0
Hypertension	2 (4.5)	2 (4.5)	5 (20.0)	0

AE: adverse event.

Supplementary Table 5. Deaths.

Stratum	Treatment	On-treatment[a]	Principal cause reported
Stratum 1	10 mg AM/10 mg PM[c]	Yes	Acute myeloid leukemia
		Yes	Cardiac arrest
	10 mg AM/15 mg PM	Yes	Unknown
Stratum 2[b]	5 mg AM/5 mg PM	Yes	Unspecified complications after gastric ulcer[d]
	10 mg AM/10 mg PM[c]	No	Transformation to acute myeloid leukemia
		No	Laryngeal cancer
		Yes	Multiple organ failure

[a]Not all on-treatment deaths were the primary reason for treatment discontinuation. [b]Only 2 of 4 deaths in stratum 2 were considered to be on-treatment. [c]In the MSSD cohort. [d]Platelet count measured at the last visit (May 31, 2013; study day 390 [relative to first day of treatment, study day 1]) before the patient's death (June 9, 2013; study day 399) was 61×10^9/L (common toxicity criteria, grade 2). MSSD: maximum safe starting dose.

Supplementary Table 6. Baseline patient characteristics (MSSD cohort).

Demographic variable/disease characteristic	Stratum 1 (platelet count 75-99×10^9/L) N=20, N (%)	Stratum 2 (platelet count 50-74×10^9/L) N=18, N (%)
Age, median (range), years	64.5 (27-81)	66.5 (46-86)
Age ≥65 years	10 (50.0)	11 (61.1)
Sex		
Male	8 (40.0)	11 (61.1)
Female	12 (60.0)	7 (38.9)
ECOG performance status		
0	9 (45.0)	4 (22.2)
1	9 (45.0)	10 (55.6)
2	2 (10.0)	4 (22.2)
MF subtype		
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)
JAK2 mutation		
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		
Intermediate risk level 1	10 (50.0)	2 (11.1)
Intermediate risk level 2	8 (40.0)	8 (44.4)
High risk	2 (10.0)	8 (44.4)
Time since initial diagnosis, median (range), months	19.138 (1.71-190.03)	39.507 (1.35-335.54)
Hemoglobin, median (range), (g/L)	107.500 (51.00-155.00)	104.000 (58.00-150.00)
Baseline platelet count, median (range), (×10^9/L)	83.0 (40-132)	57.5 (50-81)

ECOG: Eastern Cooperative Oncology Group; IWG: International Working Group; JAK: Janus kinase; MF: myelofibrosis; MSSD: maximum safe starting dose; PET-MF: post–essential thrombocythemia MF; PMF: primary MF; PPV-MF: post–polycythemia vera MF.

Supplementary Table 7. Number of patients with study drug dose reductions/interruptions[a] by stratum at MSSD.

Parameter	Stratum 1 N=20, N (%)	Stratum 2 N=18, N (%)
Dose reductions/interruptions		
Number of patients		
Without dose reduction/interruption	11 (55.0)	2 (11.1)
With at least 1 dose reduction/interruption	9 (45.0)	16 (88.9)
With only 1 dose reduction/interruption	2 (10.0)	5 (27.8)
With more than 1 dose reduction/interruption	7 (35.0)	11 (61.1)
Dose reductions		
Number of patients		
Without dose reduction/interruption	11 (55.0)	2 (11.1)
With at least 1 dose reduction/interruption	9 (45.0)	16 (88.9)
With only 1 dose reduction/interruption	2 (10.0)	7 (38.9)
With more than 1 dose reduction/interruption	7 (35.0)	9 (50.0)
Dose interruptions		
Number of patients		
Without dose reduction/interruption	16 (80.0)	13 (72.2)
With at least 1 dose reduction/interruption	4 (20.0)	5 (27.8)
With only 1 dose reduction/interruption	3 (15.0)	3 (16.7)
With more than 1 dose reduction/interruption	1 (5.0)	2 (11.1)

[a]A patient with multiple occurrences of a reason for dose reduction or interruption is only counted once in that category. A dose reduction is defined as a reduction of the total daily dose to a nonzero dose of 1 day or greater. A dose interruption is defined as a total daily dose of 0 mg for a duration of 1 day or greater.

MSSD: maximum safe starting dose.

Supplementary Table 8. Number of patients with study drug dose reductions/interruptions[a] (within first 12 weeks) by subgroup and stratum at MSSD.

Parameter	Stratum 1 N=20, N (%)	Stratum 2 N=18, N (%)
Dose reductions/interruptions within first 12 weeks		
Number of patients		
Without dose reduction/interruption	0 (0.0)	0 (0.0)
With at least 1 dose reduction/interruption	6 (30.0)	11 (61.1)
With only 1 dose reduction/interruption	2 (10.0)	2 (11.1)
With more than 1 dose reduction/interruption	4 (20.0)	9 (50.0)
Dose reductions within first 12 weeks		
Number of patients		
Without dose reduction/interruption	0 (0.0)	0 (0.0)
With at least 1 dose reduction/interruption	6 (30.0)	9 (50.0)
With only 1 dose reduction/interruption	2 (10.0)	3 (16.7)
With more than 1 dose reduction/interruption	4 (20.0)	6 (33.3)
Dose interruptions within first 12 weeks		
Number of patients		
Without dose reduction/interruption	0 (0.0)	0 (0.0)
With at least 1 dose reduction/interruption	1 (5.0)	3 (16.7)
With only 1 dose reduction/interruption	0 (0.0)	2 (11.1)
With more than 1 dose reduction/interruption	1 (5.0)	1 (5.6)

[a]A patient with multiple occurrences of a reason for dose reduction or interruption is only counted once in that category. A dose reduction is defined as a reduction of the total daily dose to a nonzero dose of 1 day or greater. A dose interruption is defined as a total daily dose of 0 mg for a duration of 1 day or greater.

MSSD: maximum safe starting dose.

Supplementary Table 9. Proportion of patients achieving at least 50% of reduction from baseline in total symptom score of MFSAF diary at week 24, by stratum and subgroup at MSSD.

Parameter	Stratum 1 N=20, N (%)	Stratum 2 N=18, N (%)
Patients with dose down-titration[a] in first 12 weeks		
Number of patients[b]	3	10
Number of patients at week 24[c]	3	6
Number of patients achieving ≥50% of reduction in total symptom scores at week 24	2 (66.7)	2 (33.3)
95% CI of the response rate	(9.4, 99.2)	(4.3, 77.7)
Patients without dose down-titration in first 12 weeks		
Number of patients[b]	13	6
Number of patients at week 24[c]	10	4
Number of patients achieving ≥50% of reduction in total symptom scores at week 24	2 (20.0)	2 (50.0)
95% CI of the response rate	(2.5, 55.6)	(6.8, 93.2)

[a]Patients with dose down-titration in the first 12 weeks are defined as all patients who received at least 1 dose of study medication at MSSD and have dose reduction/interruption during the first 12 weeks and continue with the dose below MSSD. [b]Number of patients only includes patients that had a valid baseline assessment. [c]Number of patients at week 24 includes patients that had daily total scores at week 24. CI: confidence interval; MFSAF: Myelofibrosis Symptom Assessment Form; MSSD: maximum safe starting dose.

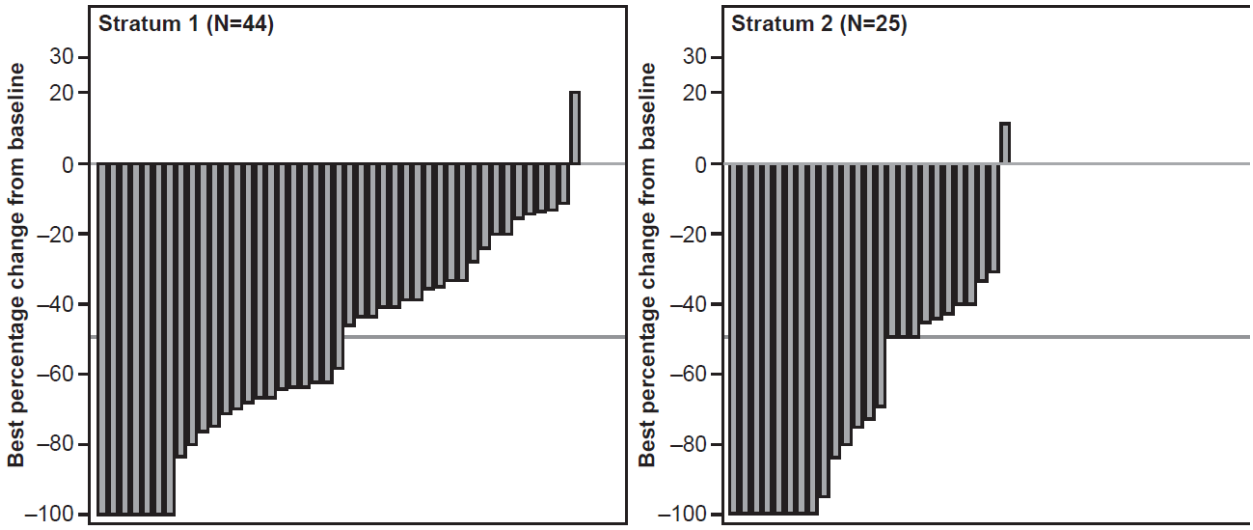
Supplementary Figures

Supplementary Figure 1. Waterfall plot of best response in spleen length by stratum (overall study population).

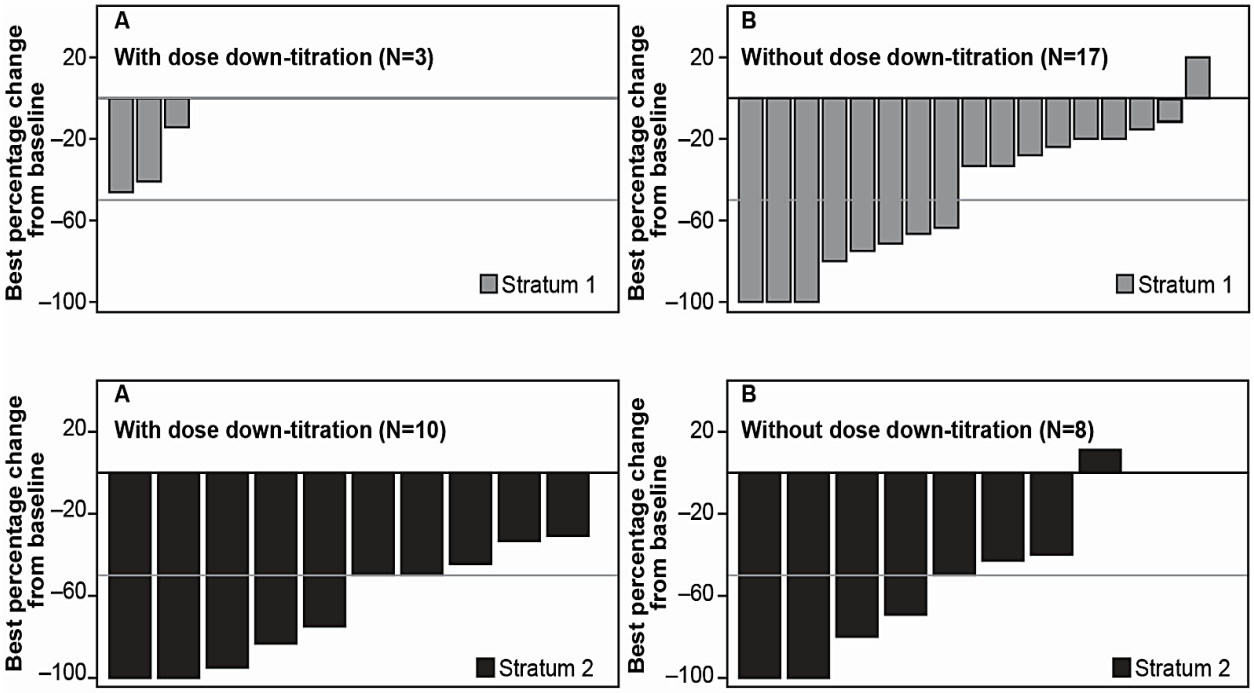
Supplementary Figure 2. Waterfall plot of best response in spleen length by stratum and by subgroup (with or without early dose titration) at MSSD. **(A)** Patients with dose down-titration in the first 12 weeks and **(B)** patients without dose down-titration in the first 12 weeks. Patients with dose down-titration in first 12 weeks are defined as all patients who received at least 1 dose of study medication at MSSD and have dose reduction/interruption during the first 12 weeks and continue with the dose below MSSD. MSSD: maximum safe starting dose.

Supplementary Figure 3. Change in total score and individual symptom scores of MFSAF diary from baseline to week 24 by stratum and subgroup at MSSD. **(A)** Patients with dose down-titration in the first 12 weeks and **(B)** patients without dose down-titration in the first 12 weeks. Patients with dose down-titration in the first 12 weeks are defined as all patients who received at least 1 dose of study medication at MSSD and have dose reduction/interruption during the first 12 weeks and continue with the dose below MSSD. MFSAF: Myelofibrosis Symptom Assessment Form; MSSD: maximum safe starting dose.

Supplementary Figure 1.



Supplementary Figure 2.



Supplementary Figure 3.