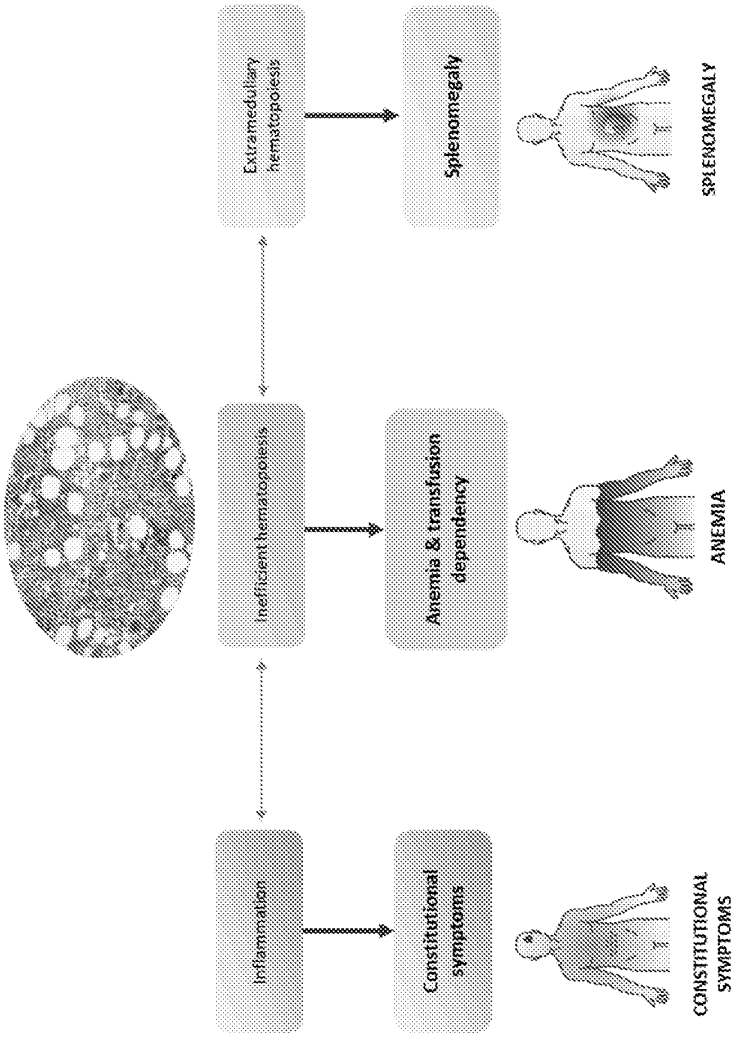

Extramedullary hematopoiesis
Splenomegaly
SPLENOMEGALY
Inefficient hematopoiesis
Anemia & transfusion dependency
ANEMIA
Inflammation
Constitutional symptoms
CONSTITUTIONAL SYMPTOMS

FIG. 1

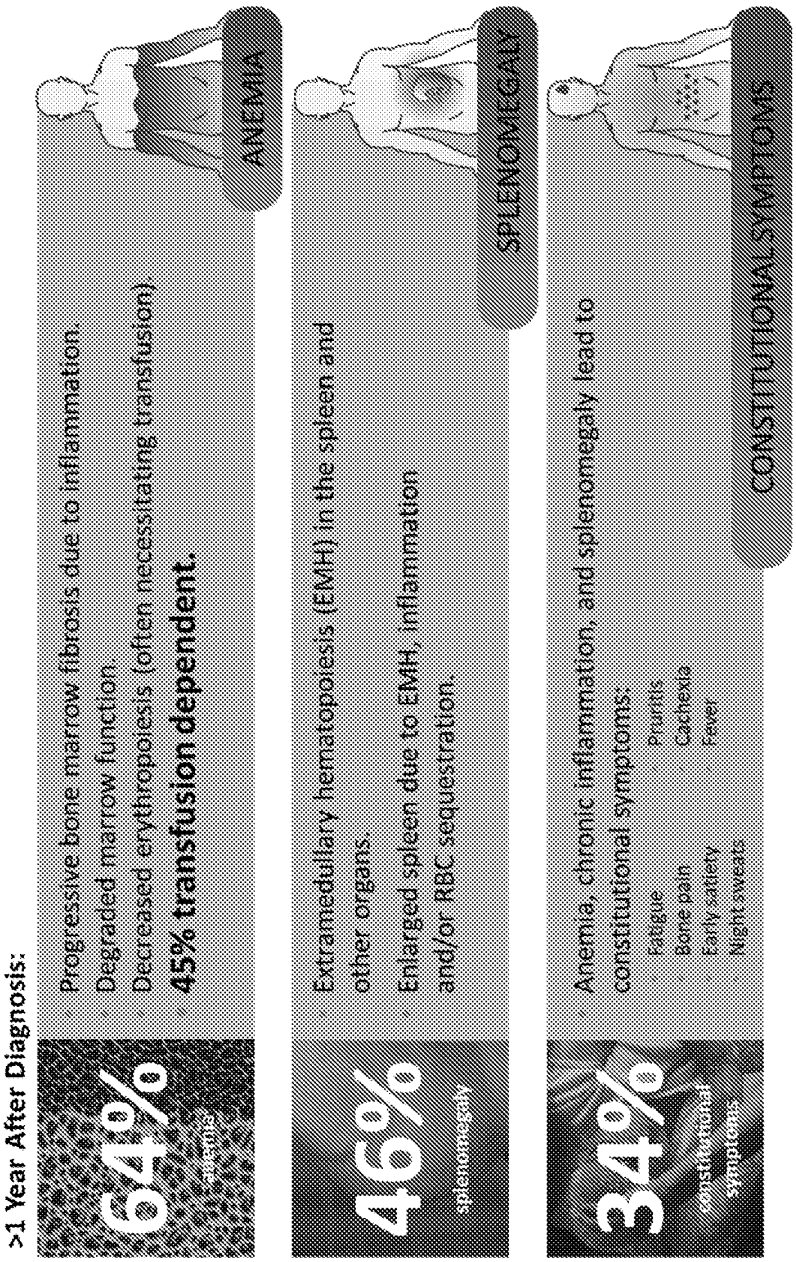

>1 Year After Diagnosis:
64%
anemia
Progressive bone marrow fibrosis due to inflammation.
Degraded marrow function.
Decreased erythropoiesis (often necessitating transfusion).
45% transfusion dependent.
ANEMIA
46%
splenomegaly
Extramedullary hematopoiesis (EMH) in the spleen and other organs.
Enlarged spleen due to EMH, inflammation and/or RBC sequestration.
SPLENOMEGALY
34%
constitutional symptoms
Anemia, chronic inflammation, and splenomegaly lead to constitutional symptoms:
Fatigue
Bone pain
Early satiety
Night sweats
Pruritis
Cachexia
Fever
CONSTITUTIONAL SYMPTOMS

FIG. 2

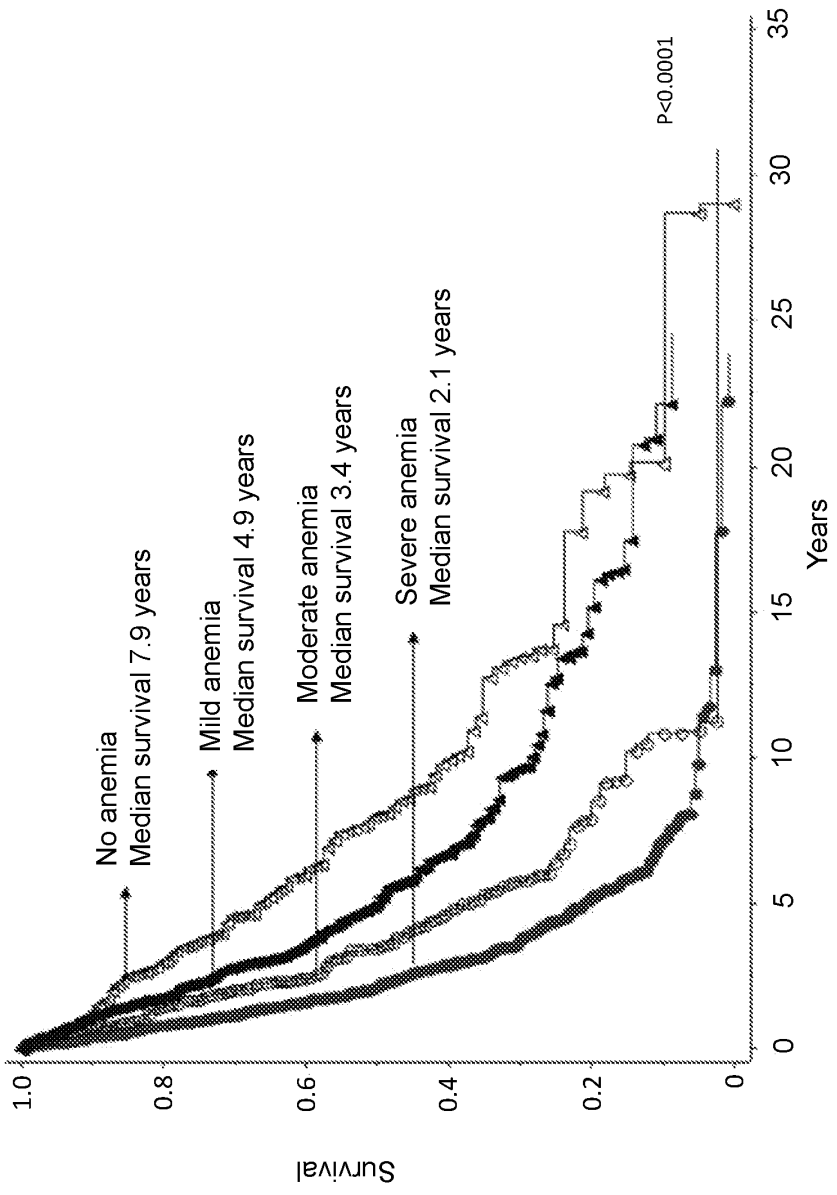

No anemia
Median survival 7.9 years
Mild anemia
Median survival 4.9 years
Moderate anemia
Median survival 3.4 years
Severe anemia
Median survival 2.1 years
P<0.0001
Survival
1.0
0.8
0.6
0.4
0.2
0
0
5
10
15
20
25
30
35
Years

FIG. 3

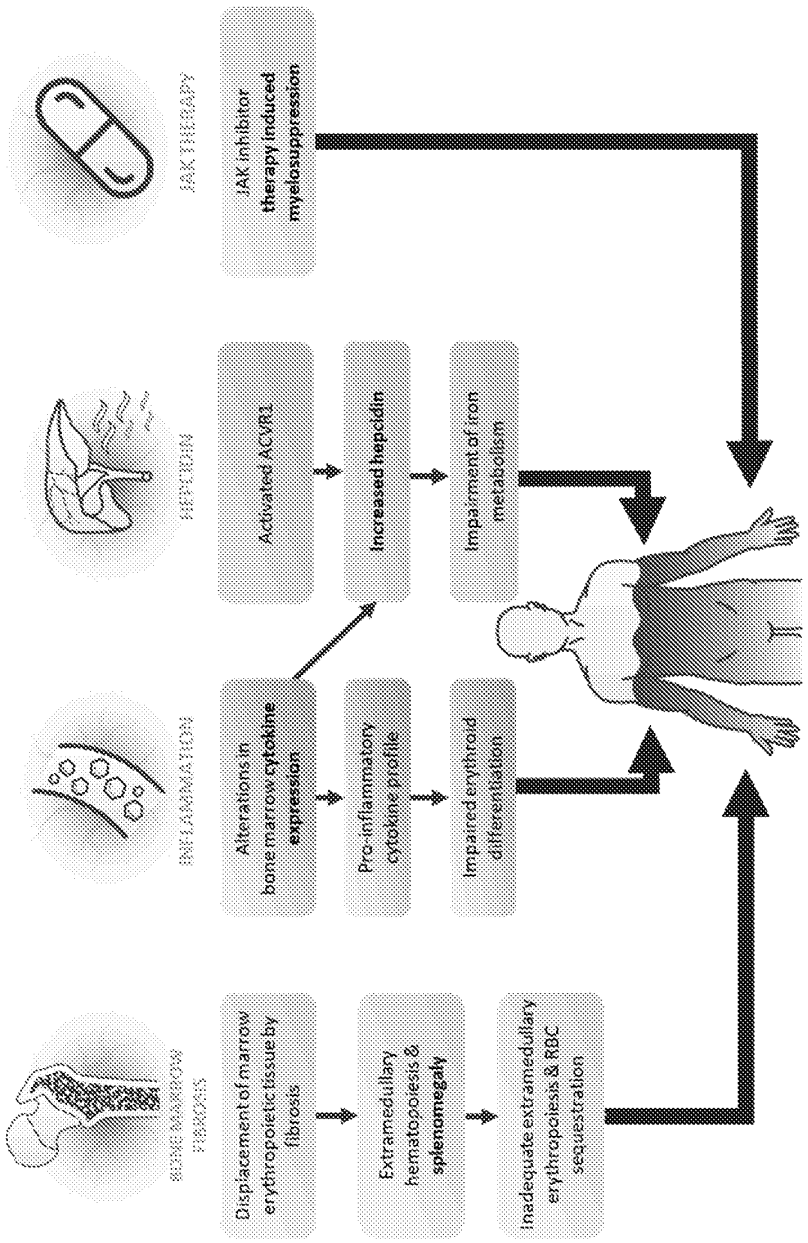

BONE MARROW FIBROSIS
INFLAMMATION
HEPCIDIN
JAK THERAPY
Displacement of marrow erythropoietic tissue by fibrosis
Extramedullary hematopoiesis & splenomegaly
Inadequate extramedullary erythropoiesis & RBC sequestration
Alterations in bone marrow cytokine expression
Pro-inflammatory cytokine profile
Impaired erythroid differentiation
Activated ACVR1
Increased hepcidin
Impairment of iron metabolism
JAK inhibitor therapy induced myelosuppression

FIG. 4

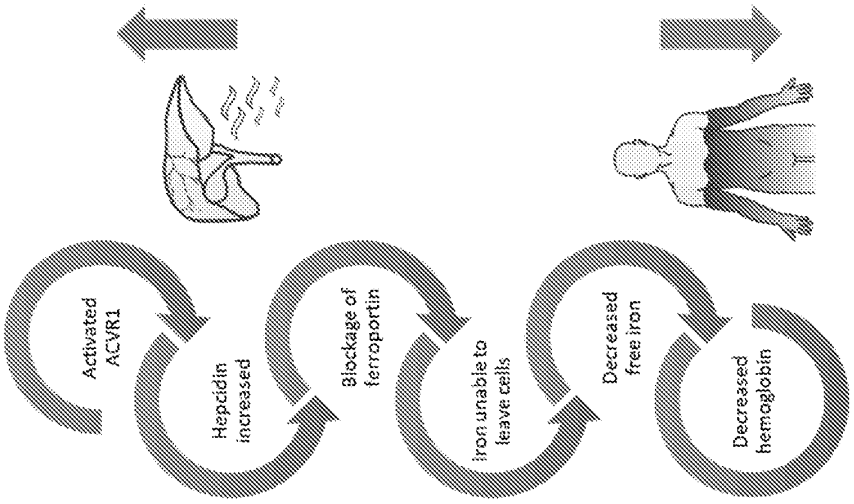

Activated ACVR1
Hepcidin increased
Blockage of ferroportin
Iron unable to leave cells
Decreased free iron
Decreased hemoglobin

FIG. 5B

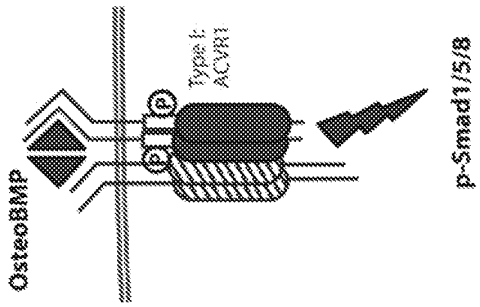

OsteoBMP
Type I ACVR1
p-Smad1/5/8

FIG. 5A

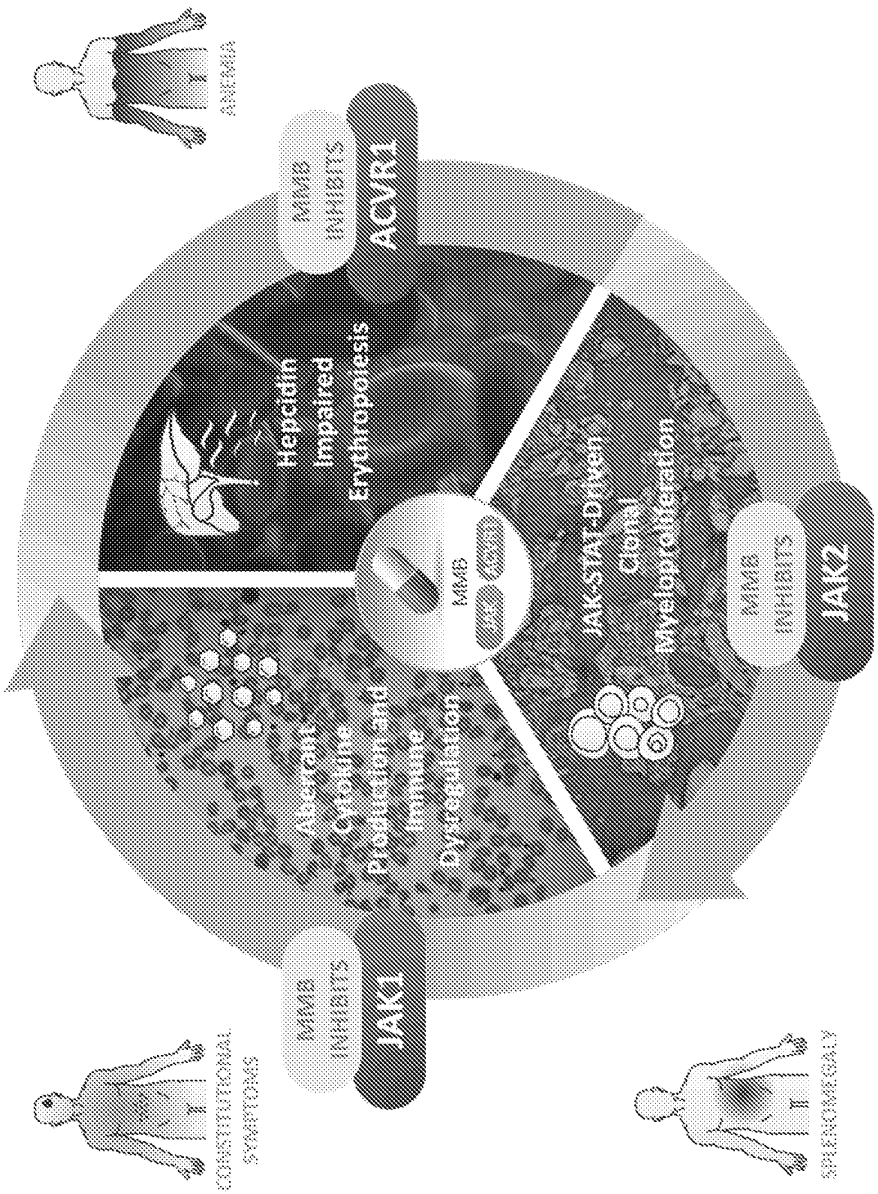

ANEMIA
MMB INHIBITS
ACVR1
Hepcidin Impaired Erythropoiesis
MMB
JAK-STAT Driven Clonal Myeloproliferation
MMB INHIBITS
JAK2
Aberrant Cytokine Production and Immune Dysregulation
MMB INHIBITS
JAK1
CONSTITUTIONAL SYMPTOMS
SPLENOMEGALY

FIG. 6

	Momelotinib (MMB)	Ruxolitinib (RUX)	Fedratinib (FED)	Pacritinib (PAC)
Status in Myelofibrosis	**Phase 3** (2x completed P3s; P2 translational biology)	**Approved** (intermediate / high-risk; platelets ≥50 × 10^3/dL)	**Post-Phase 3** (NDA filing 2018 TBD)	**Phase 2** (P3 trial requested by FDA; EU MAA refiled)
Targets	JAK1, JAK2, ACVR1	JAK1, JAK2	JAK2, FLT3	JAK2, FLT3
Splenic Response	✓	✓	✓	✓
Symptom Benefit	✓	✓	✓	✓
Anemia Benefit	✓	×	×	×
Toxicity: Anemia & Thrombocytopenia	**LOW**	**HIGH**	**HIGH**	**HIGH**

FIG. 7

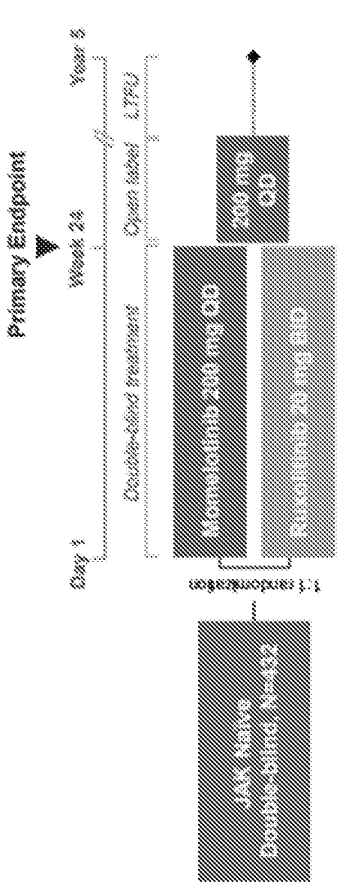

Primary Endpoint
Week 24
Year 5
Day 1
Double-blind treatment
Open label
LTFU
Momelotinib 200 mg QD
Best Available Therapy
QD
200 mg
QD
1:1 randomization
Double-blind, N=432
JAK Naïve
Open label
N=156

FIG. 8A

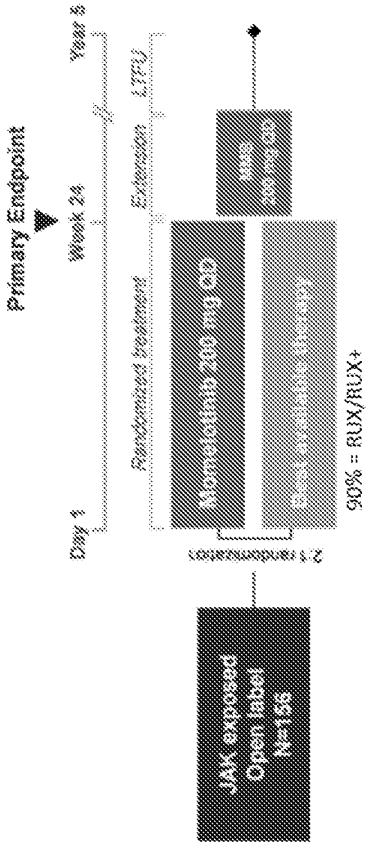

Primary Endpoint
Week 24
Year 5
Day 1
Randomized treatment
Extension
LTFU
Momelotinib 200 mg QD
Best Available Therapy
QD
200 mg
QD
2:1 randomization
90% = RUX/RUX+
JAK exposed
Open label
N=156

FIG. 8B

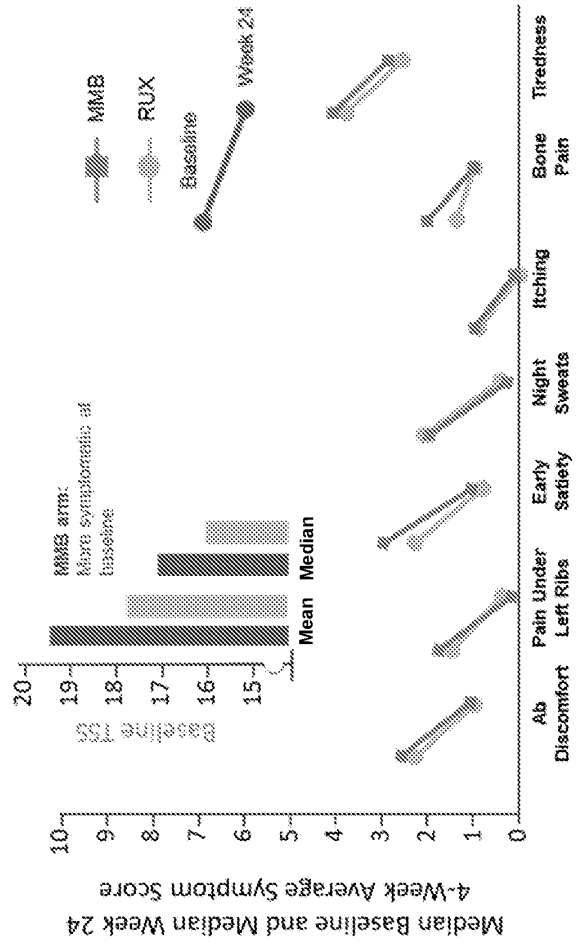

Median Baseline and Median Week 24
4-Week Average Symptom Score
0
1
2
3
4
5
6
7
8
9
10
Baseline TSS
15
16
17
18
19
20
MMB arm:
More symptomatic at
baseline
Mean
Median
MMB
RUX
Baseline
Week 24
Ab
Discomfort
Pain Under
Left Ribs
Early
Satiety
Night
Sweats
Itching
Bone
Pain
Tiredness

FIG. 9

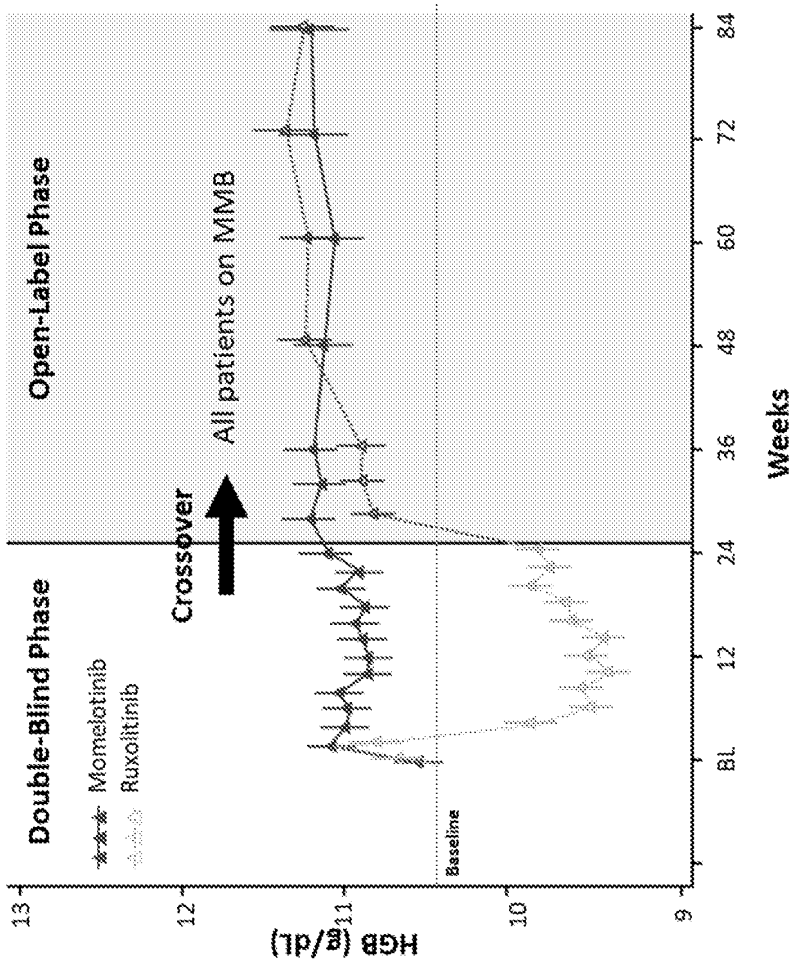

Double-Blind Phase
Open-Label Phase
Momelotinib
Ruxolitinib
Crossover
All patients on MMB
Baseline
HGB (g/dL)
Weeks
13
12
11
10
9
BL
12
24
36
48
60
72
84

FIG. 10

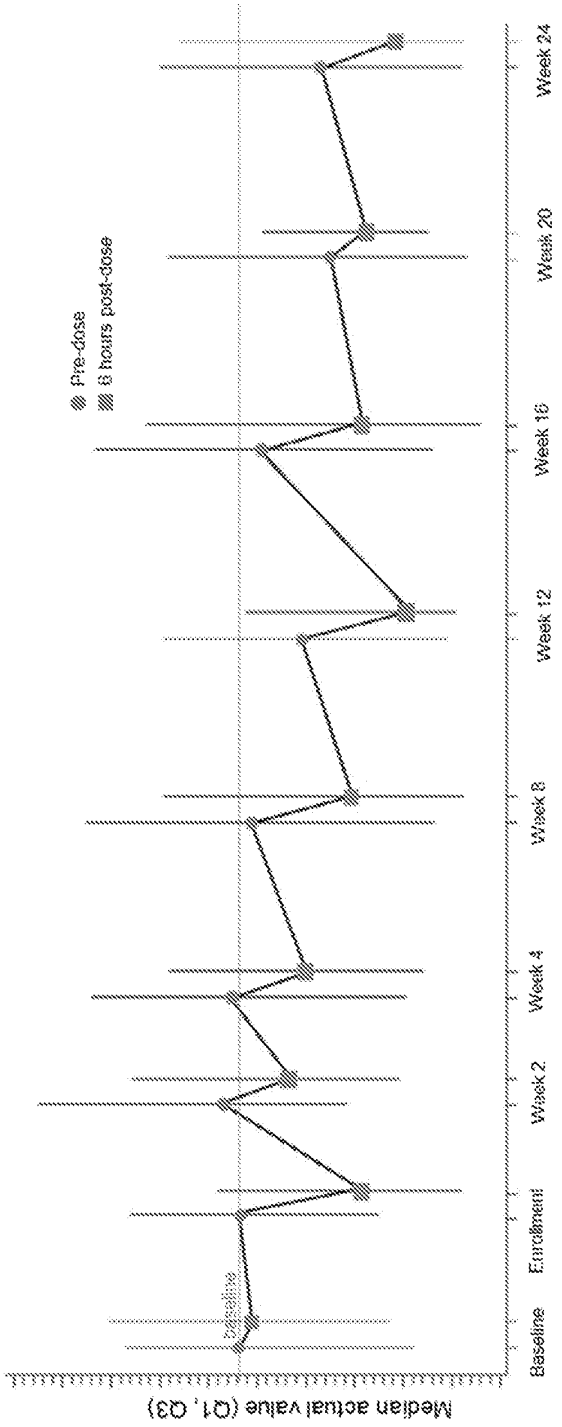
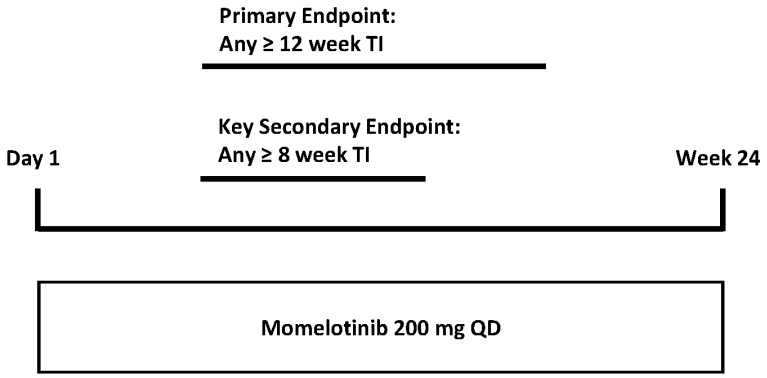

Median actual value (Q1, Q3)
Pre-dose
6 hours post-dose
Baseline
Enrollment
Week 2
Week 4
Week 8
Week 12
Week 16
Week 20
Week 24

FIG. 11

Population:

- Primary MF (PMF), post-polycythemia vera MF (post-PV MF), or post-essential thrombocythemia MF (post-ET MF).
- Requiring MF therapy (in the opinion of the investigator).
- High risk or intermediate-2 (DIPSS).
- Transfusion Dependent (TD) at baseline.
- [defined as ≥4 U red blood cell (RBC) transfusion in the 8 weeks prior to the first dose of MMB].



Serial PD Analyses:
Iron studies (serum iron, ferritin, transferrin, etc.)
Hepcidin
Reticulocytes
CRP
Etc.

Goal: Exploratory translational biology study

MMB: N=41

Objectives:

- Primary objective: determine the transfusion independence response rate (TI; ≥12 week & ≥8 week) for TD subjects with MF treated with momelotinib.
- Secondary objectives:
  - Evaluate baseline levels and changes in markers of iron metabolism.
  - Assess inhibition of JAK1/2.
  - Evaluate momelotinib pharmacokinetics in transfusion-dependent subjects with MF.
  - Evaluate changes in circulating cytokine and inflammatory markers.

FIG. 12

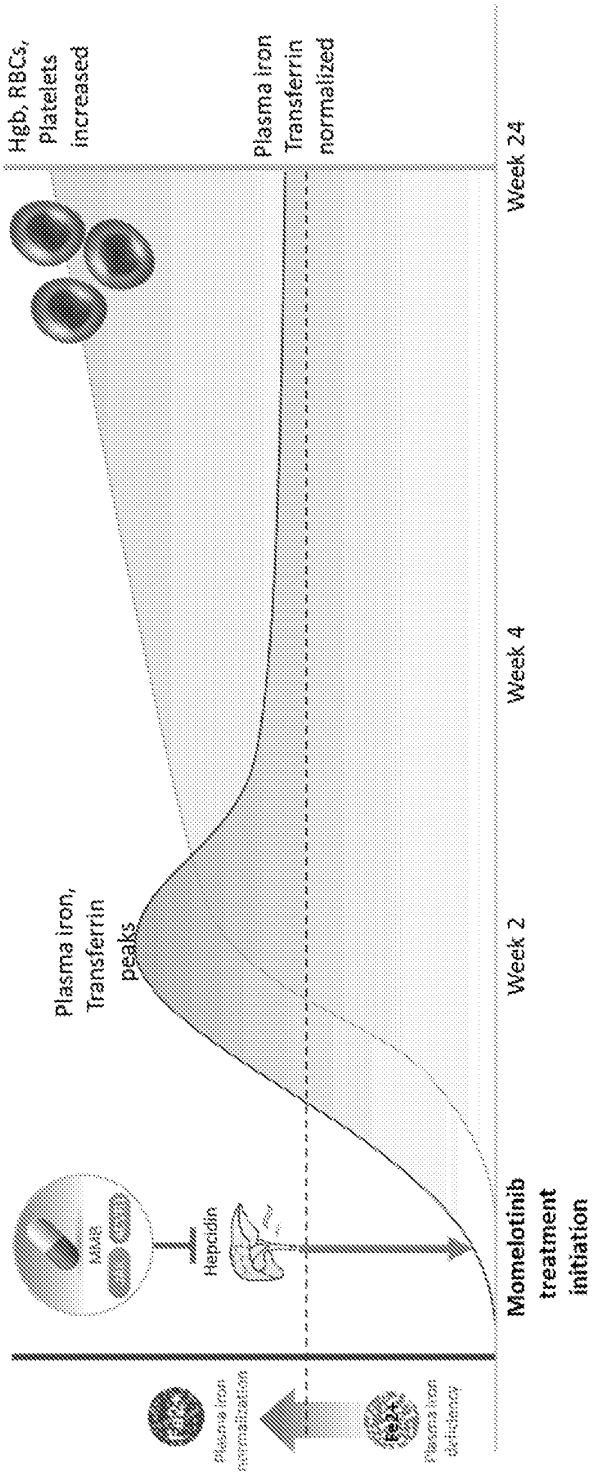

Hgb, RBCs, Platelets increased
Plasma iron Transferrin normalized
Week 24
Week 4
Week 2
Plasma iron, Transferrin peaks
Momelotinib treatment initiation
Hepcidin
Plasma iron normalization
Plasma iron deficiency

FIG. 13

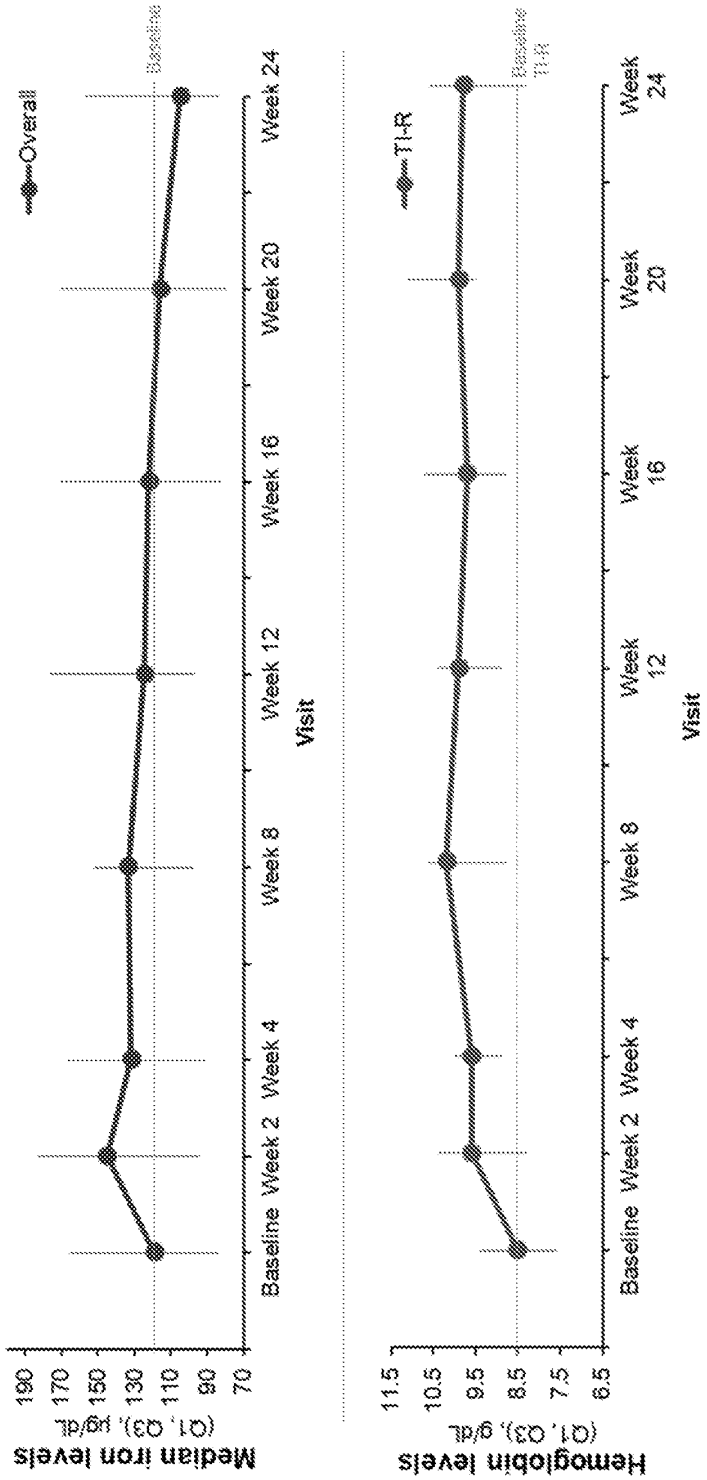

Median iron levels
(Q1, Q3), µg/dL
190
170
150
130
110
90
70
Overall
Baseline
Baseline Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
Visit
Hemoglobin levels
(Q1, Q3), g/dL
11.5
10.5
9.5
8.5
7.5
6.5
TI-R
Baseline
TI-R
Baseline Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
Visit

FIG. 14

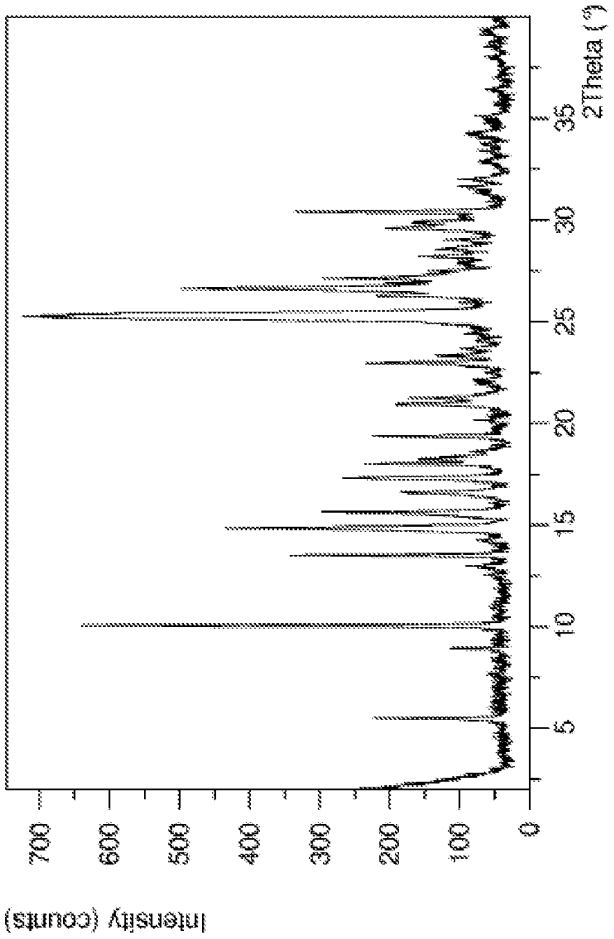

Intensity (counts)
700
600
500
400
300
200
100
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 15

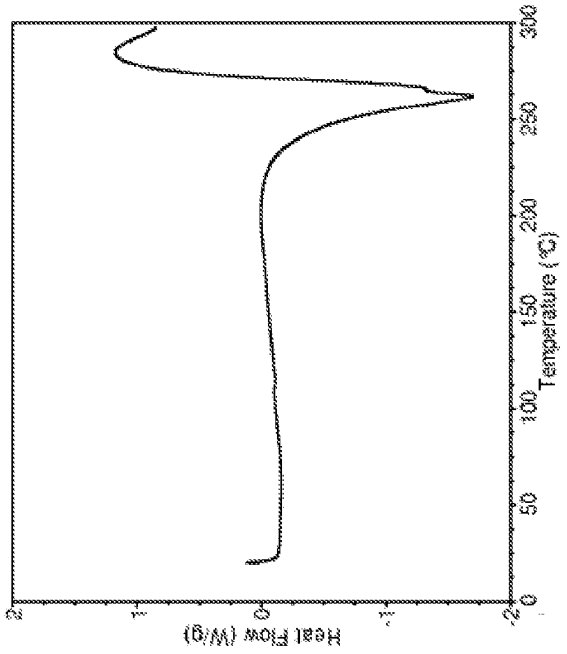


FIG. 16

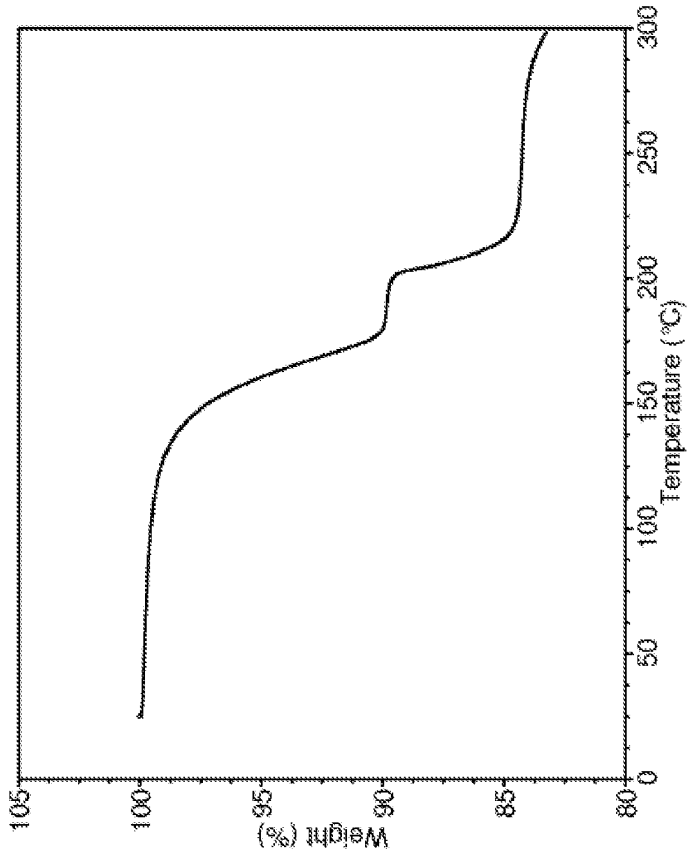

Weight (%)
105
100
95
90
85
80
0
50
100
150
200
250
300
Temperature (°C)

FIG. 17

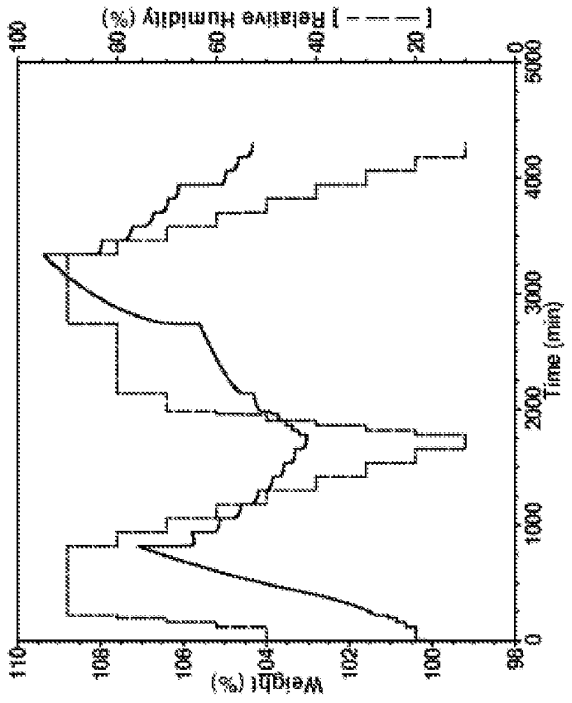


FIG. 18

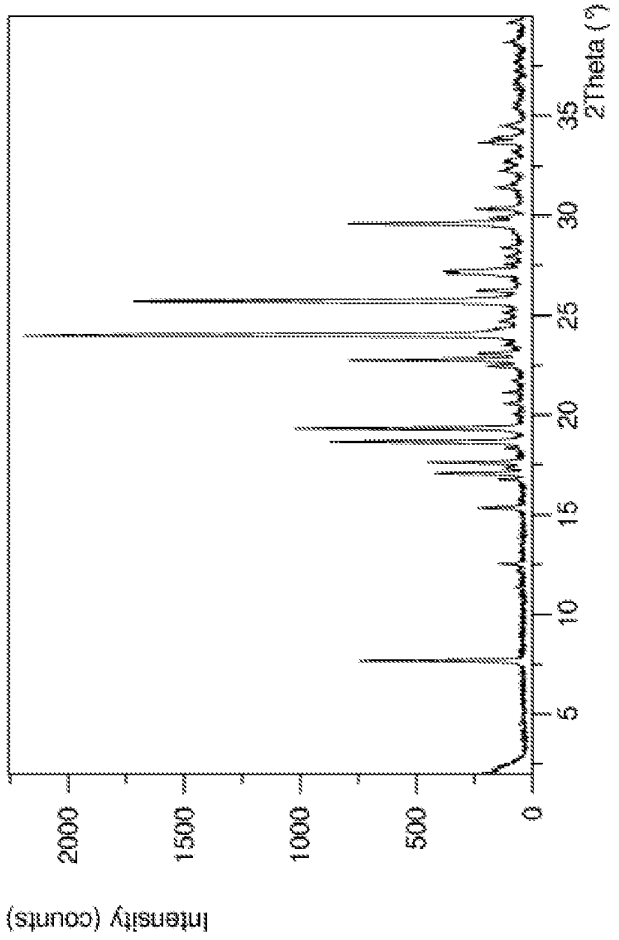

Intensity (counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 19

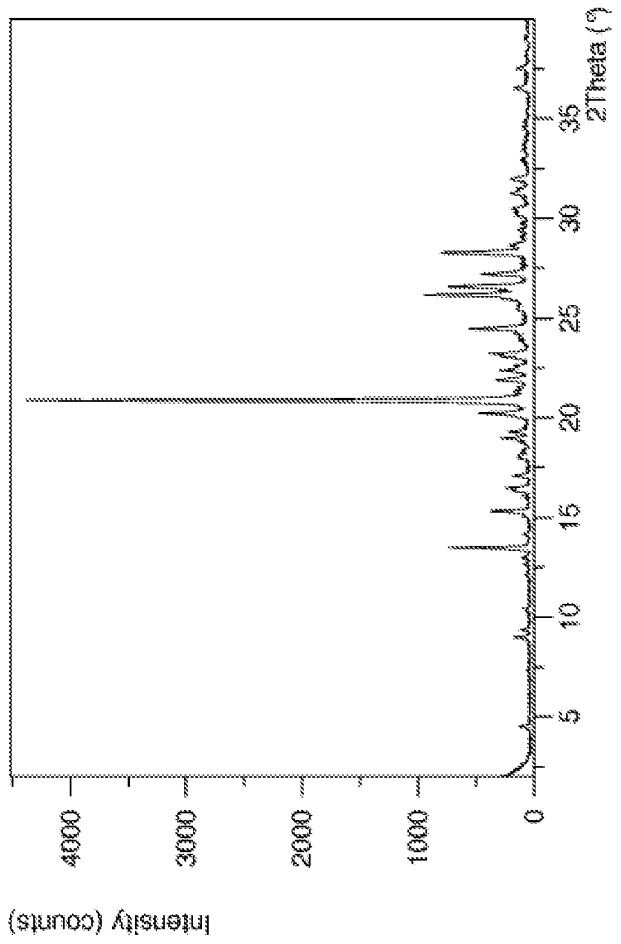

Intensity (counts)
4000
3000
2000
1000
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 20

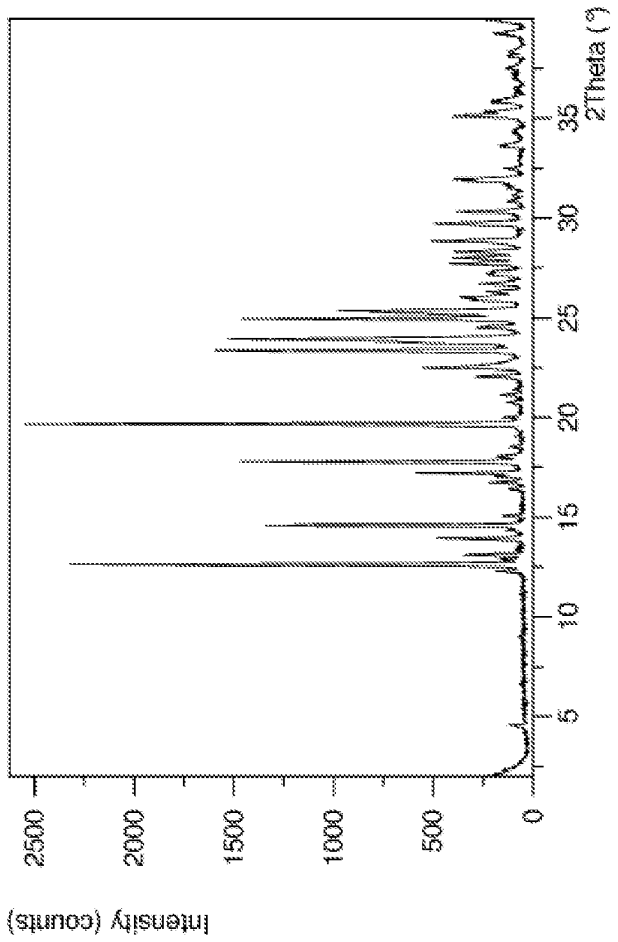

Intensity (counts)
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
2Theta (°)

FIG. 21

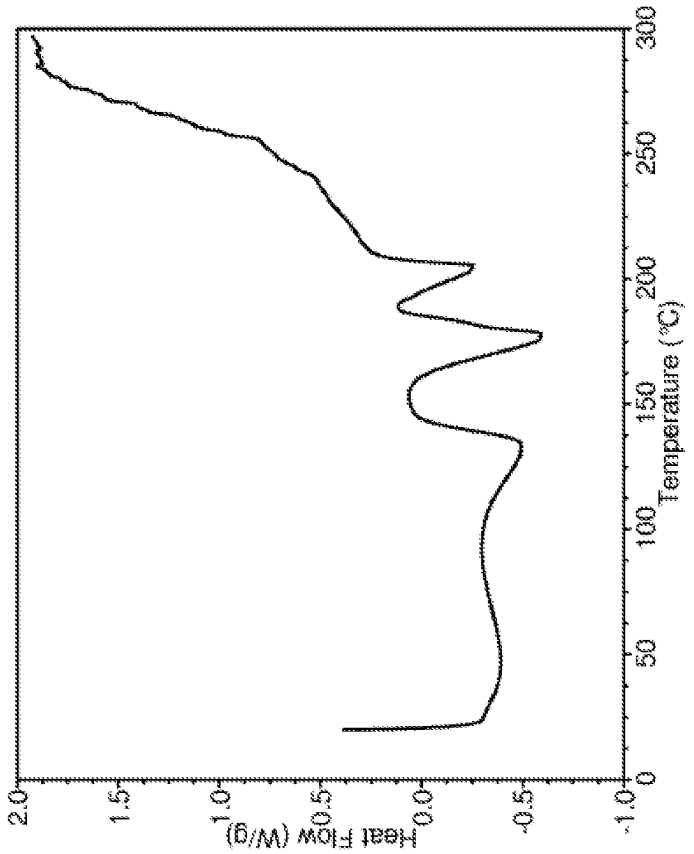

Heat Flow (W/g)
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
300
Temperature (°C)

FIG. 22

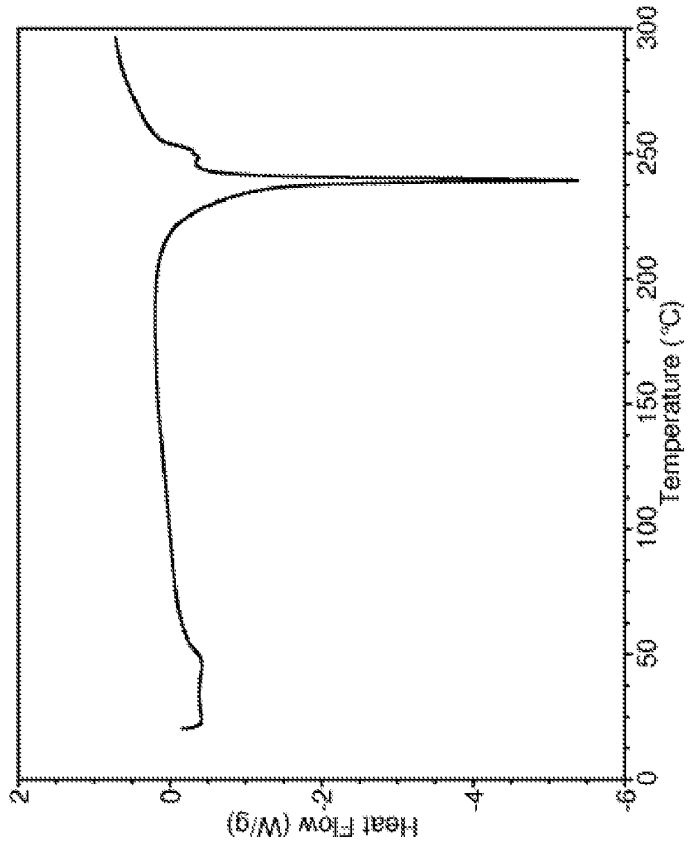


FIG. 23

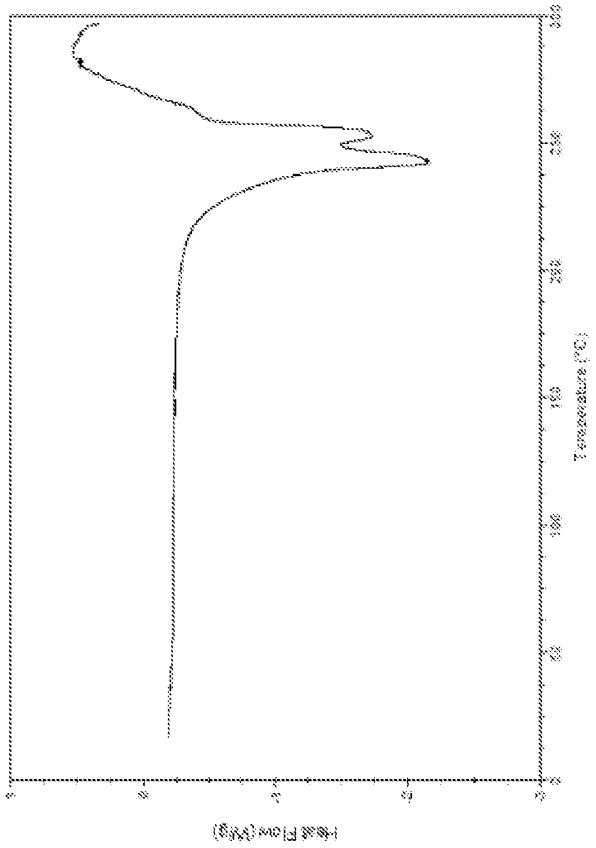


FIG. 24

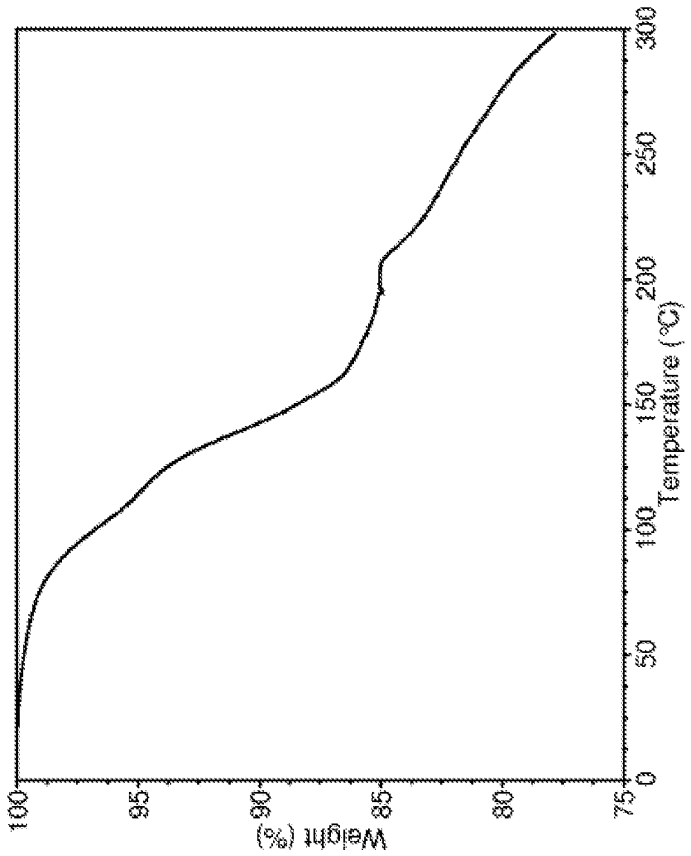


FIG. 25

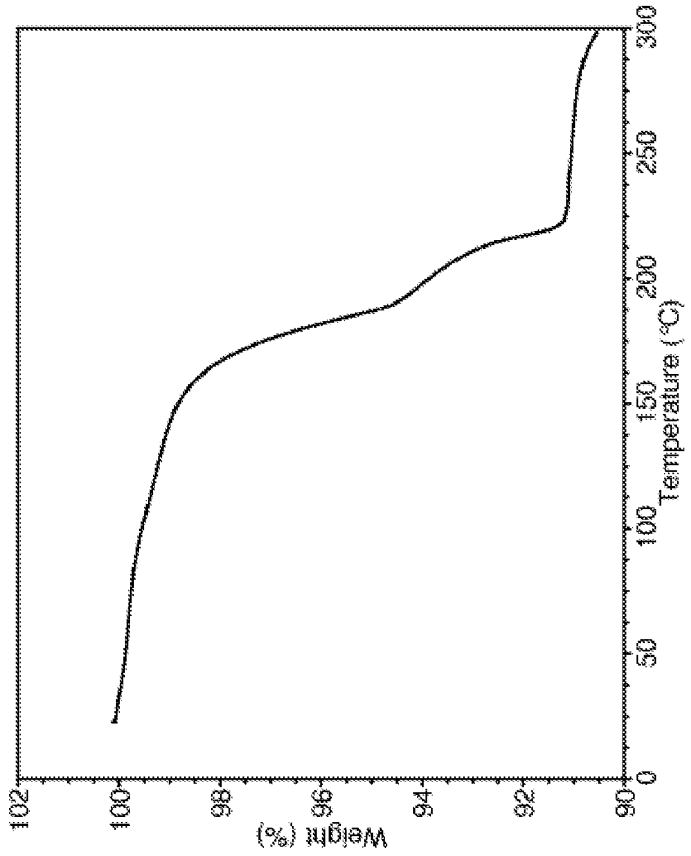

Weight (%)
102
100
98
96
94
92
90
Temperature (°C)
0
50
100
150
200
250
300

FIG. 26

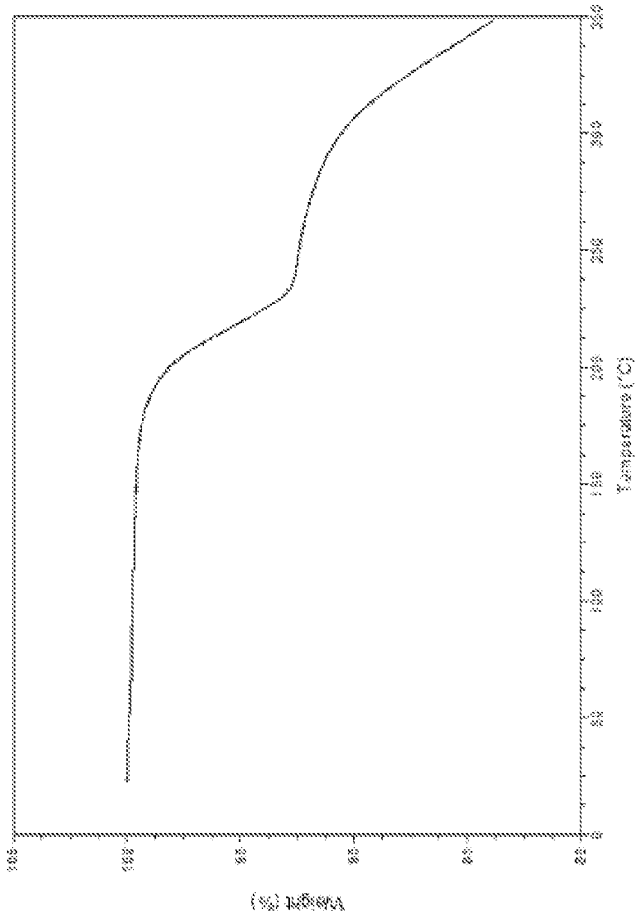


FIG. 27

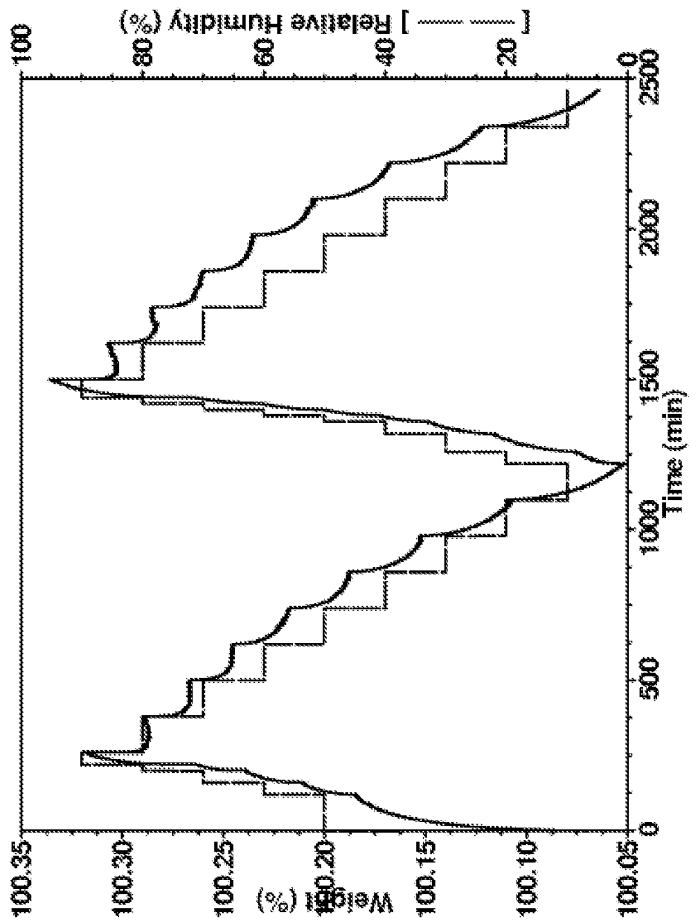

Relative Humidity (%)
100
80
60
40
20
0
2500
2000
1500
1000
500
0
Time (min)
100.35
100.30
100.25
100.20
100.15
100.10
100.05
Weight (%)

FIG. 28

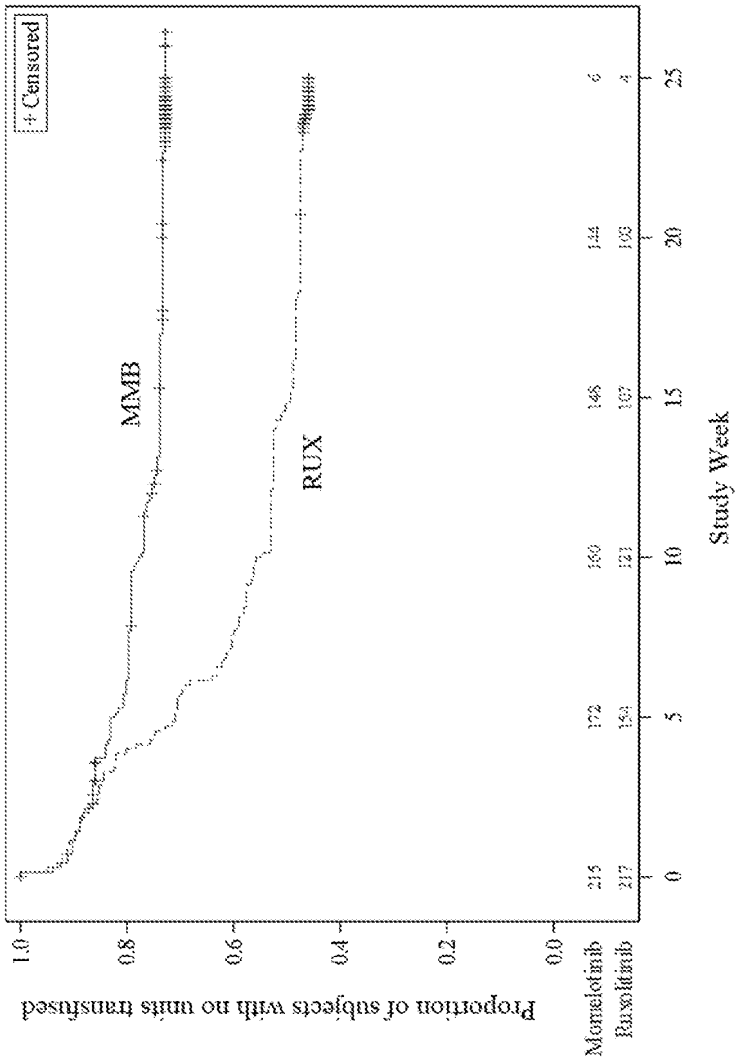

+ Censored
MMB
RUX
Proportion of subjects with no units transfused
1.0
0.8
0.6
0.4
0.2
0.0
Momelotinib 215 172 160 146 144 6
Ruxolitinib 217 150 123 107 103 4
0 5 10 15 20 25
Study Week

FIG. 29

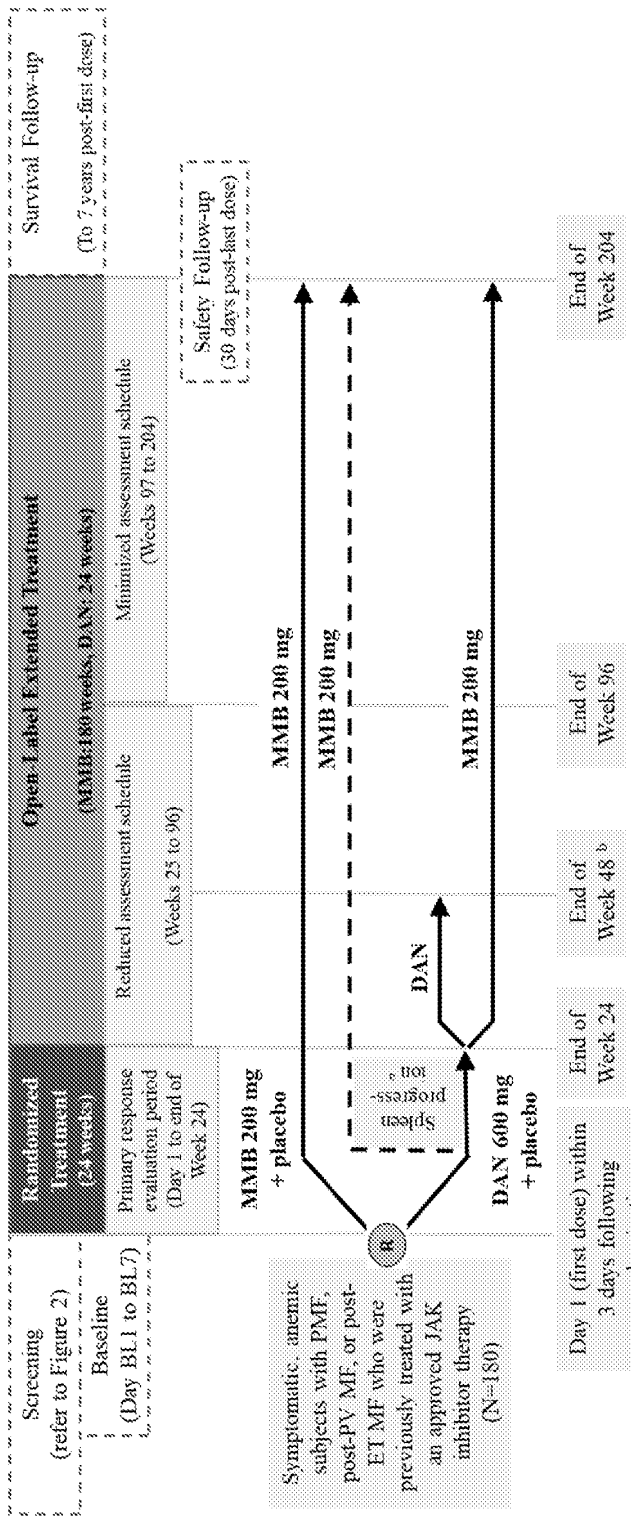

Screening
(refer to Figure 2)
Baseline
(Day BL1 to BL7)
Randomized Treatment (24 weeks)
Open-Label Extended Treatment
(MMB: 180 weeks, DAN: 24 weeks)
Survival Follow-up
(To 7 years post-first dose)
Primary response evaluation period
(Day 1 to end of Week 24)
Reduced assessment schedule
(Weeks 25 to 96)
Minimized assessment schedule
(Weeks 97 to 204)
Safety Follow-up
(30 days post-last dose)
MMB 200 mg + placebo
DAN 600 mg + placebo
MMB 200 mg
MMB 200 mg
MMB 200 mg
DAN
Spleen progression a
Symptomatic, anemic subjects with PMF, post-PV MF, or post-ET MF who were previously treated with an approved JAK inhibitor therapy (N=180)
R
Day 1 (first dose) within 3 days following randomization
End of Week 24
End of Week 48 b
End of Week 96
End of Week 204

FIG. 30

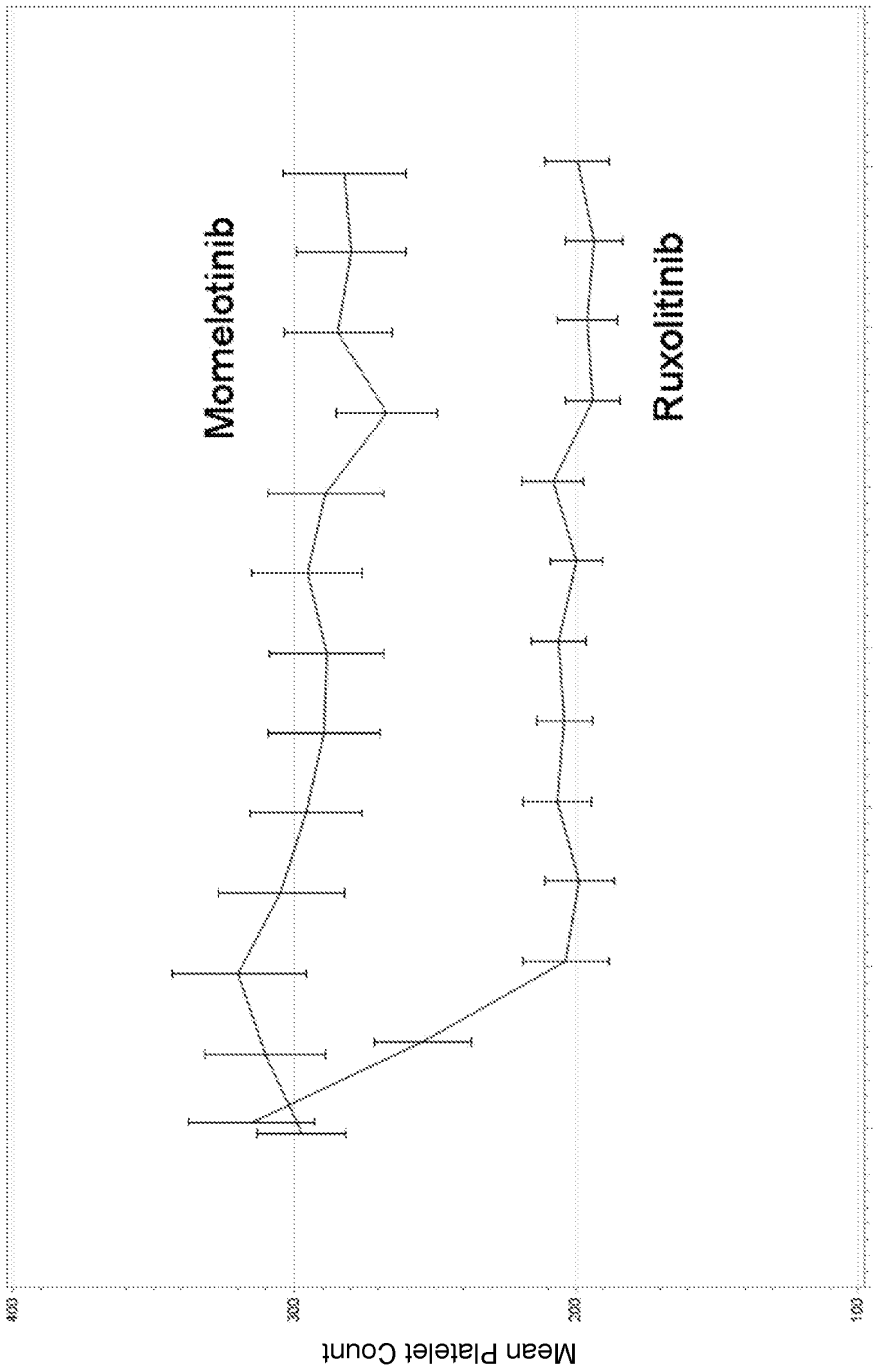

Momelotinib
Ruxolitinib
Mean Platelet Count
Weeks
400
300
200
100
0
4
8
12
16
20
24

FIG. 31

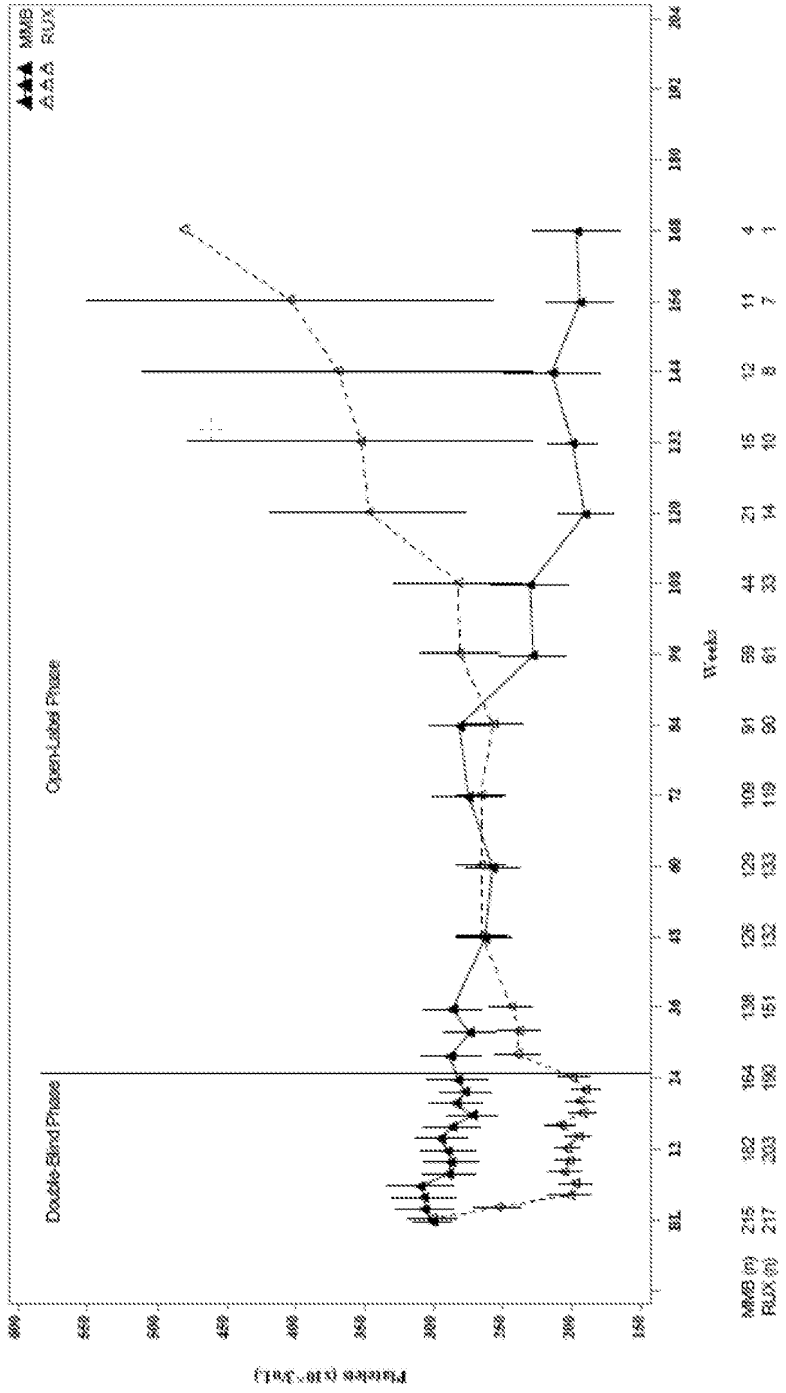

MMB
RUX
Open-Label Phase
Double-Blind Phase
Weeks
MMB (n) 215 182 164 138 126 109 91 59 44 21 15 12 11 4
RUX (n) 217 203 180 151 132 119 80 61 33 14 10 8 7 1

FIG. 32

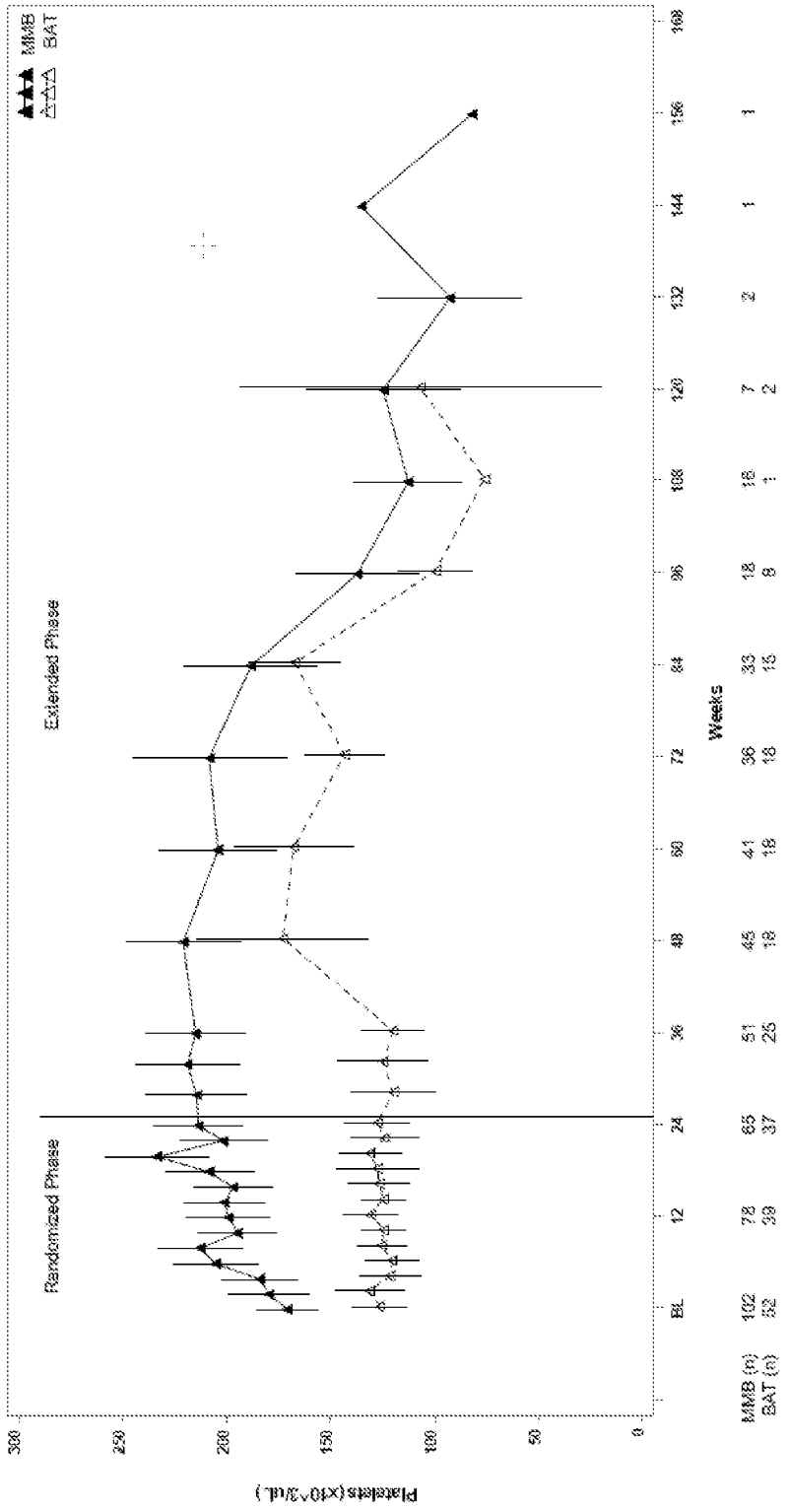
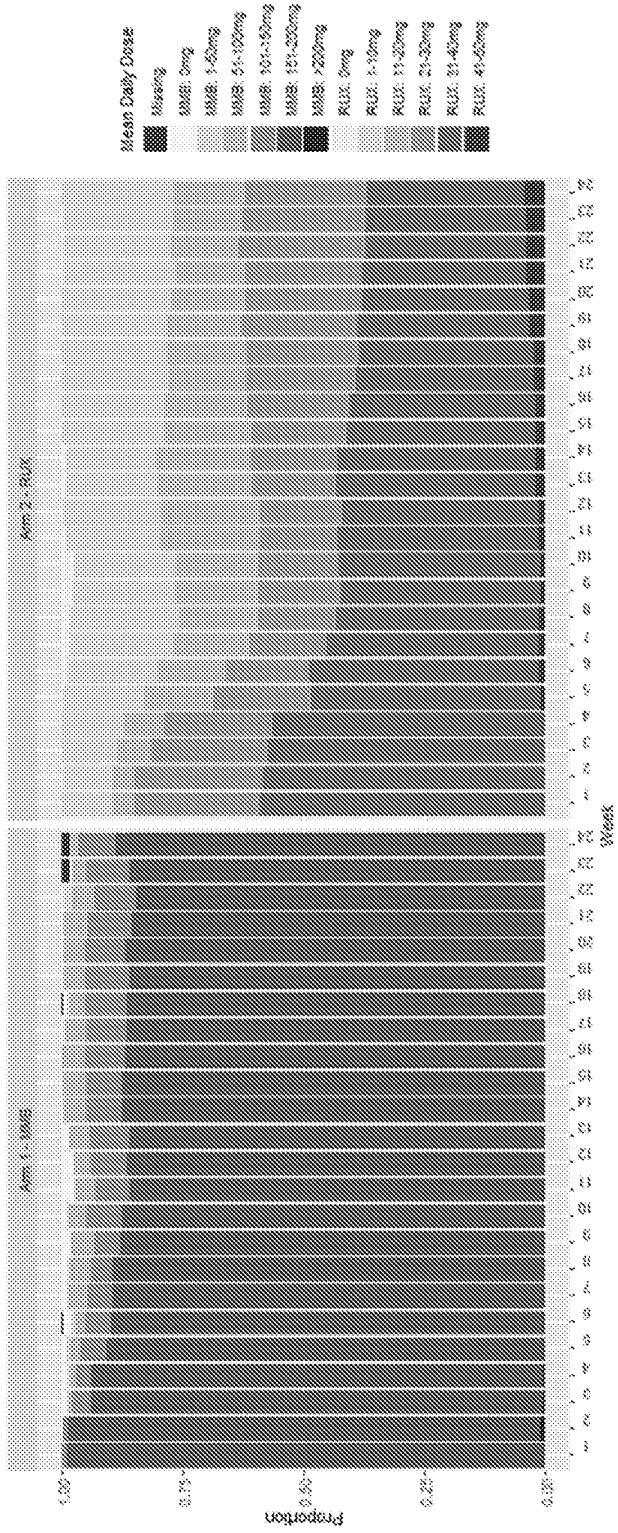
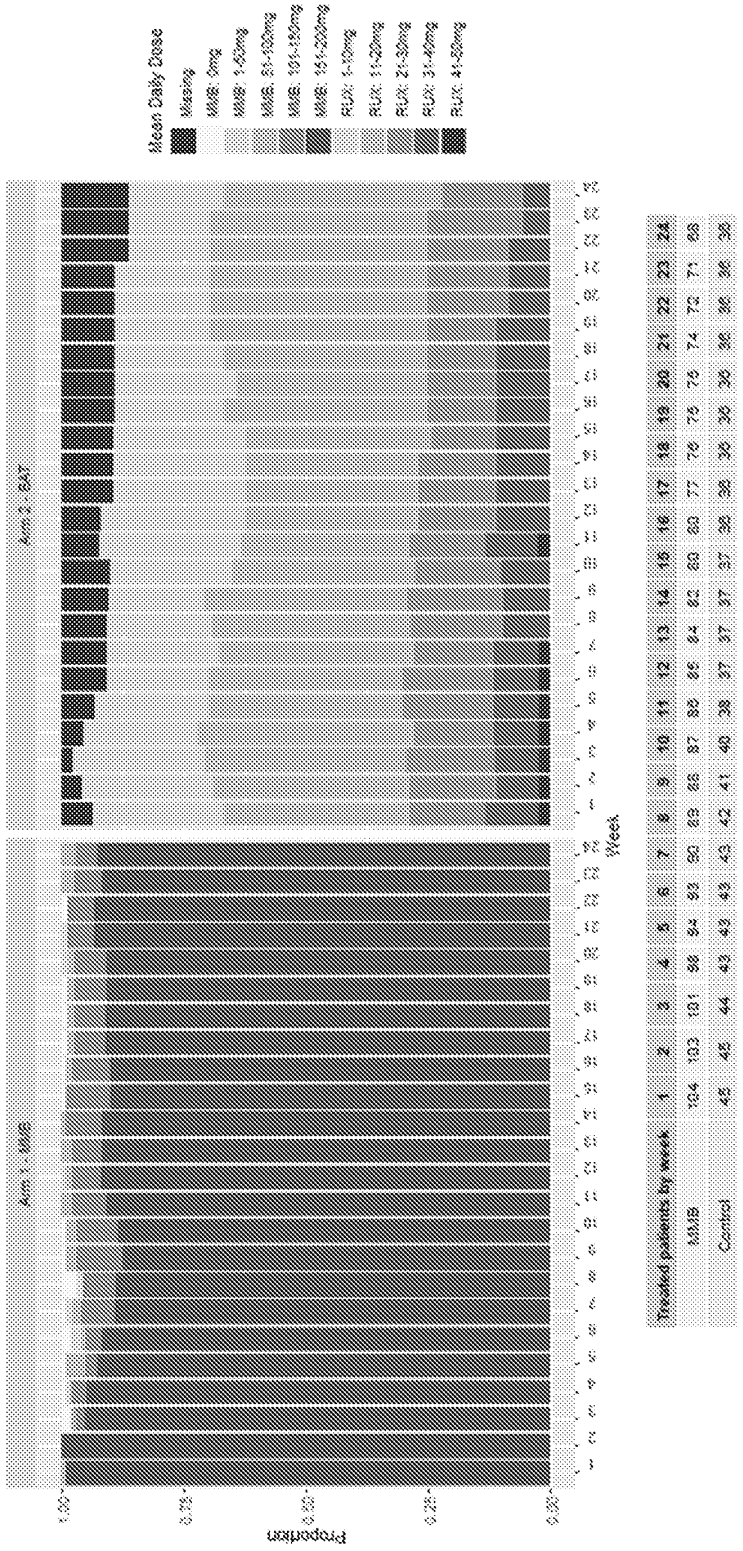

MMB
BAT
Randomized Phase
Extended Phase
Platelets (x10^3/uL)
Weeks
MMB (n)
BAT (n)

FIG. 33



Treated patients by week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
MJB	214	209	208	208	202	202	193	184	183	181	181	191	188	188	183	187	188	185	182	181	179	176	176	167
Control	216	216	215	215	215	214	213	213	213	213	212	212	210	209	208	208	207	206	205	205	205	202	202	195

FIG. 34



Treated patients by week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
MMB	124	103	101	98	94	93	92	89	88	87	80	66	64	62	60	60	77	76	75	75	74	73	71	68
Control	45	45	44	43	43	43	43	42	41	40	38	37	37	37	37	36	36	36	36	35	35	35	35	35

FIG. 35

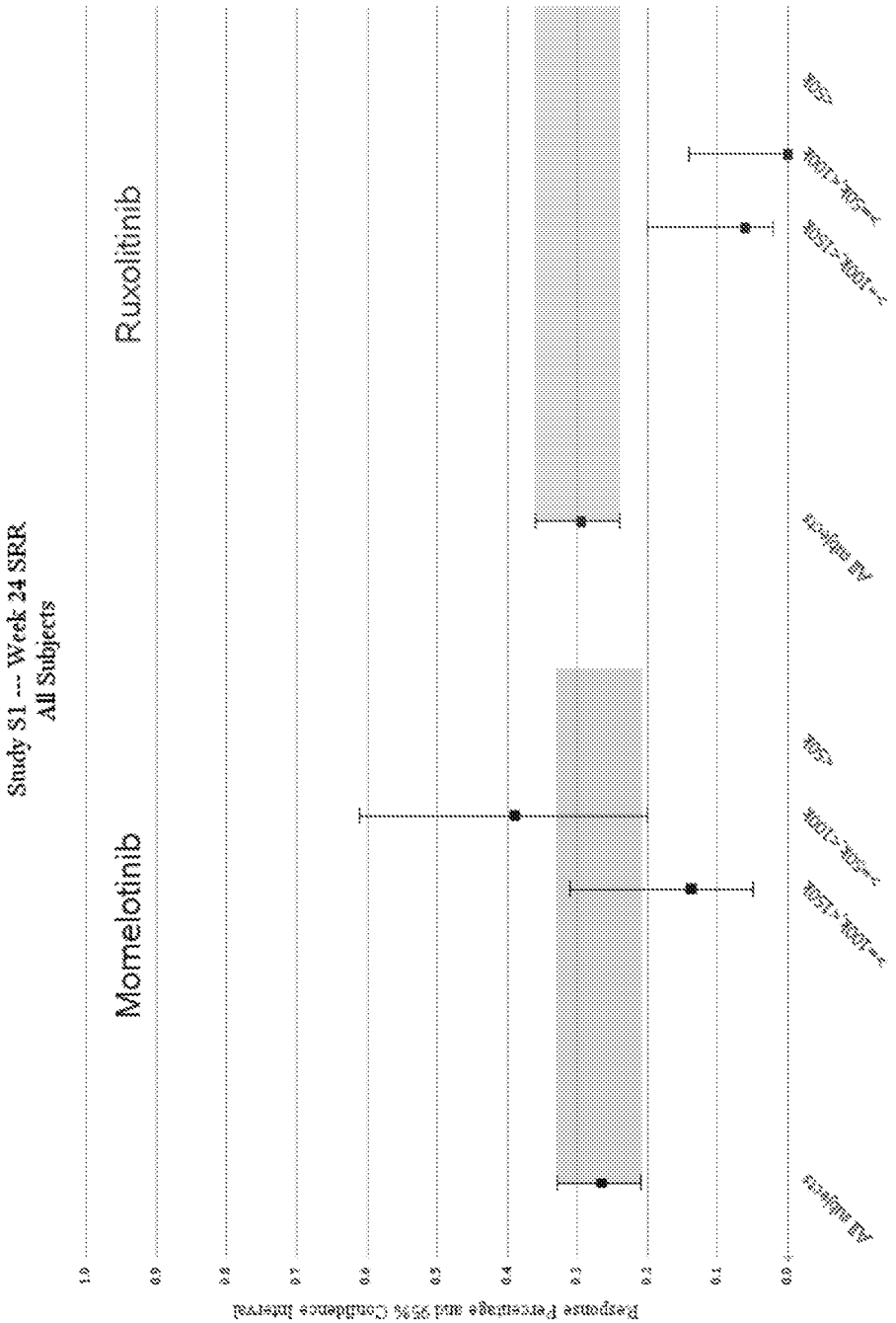

Study S1 --- Week 24 SRR
All Subjects
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All subjects
JAK2
JAK1>JAK2**
JAK1>JAK1**
Baseline Platelet Category

FIG. 36

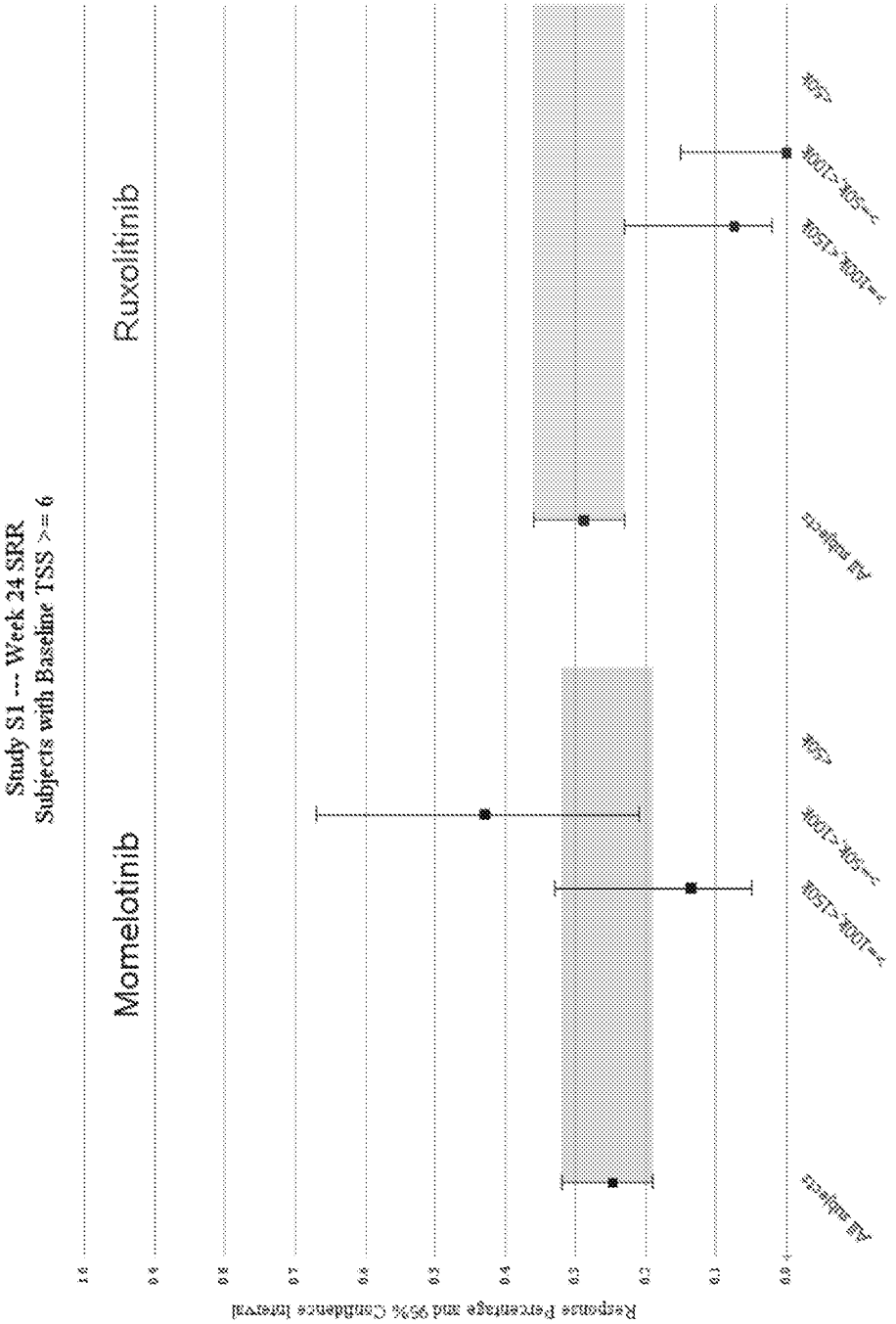

Study S1 --- Week 24 SRR
Subjects with Baseline TSS >= 6
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
<100
100 - <150
150 - <200
>= 200
All Subjects
<100
100 - <150
150 - <200
>= 200
Baseline Platelet Category

FIG. 37

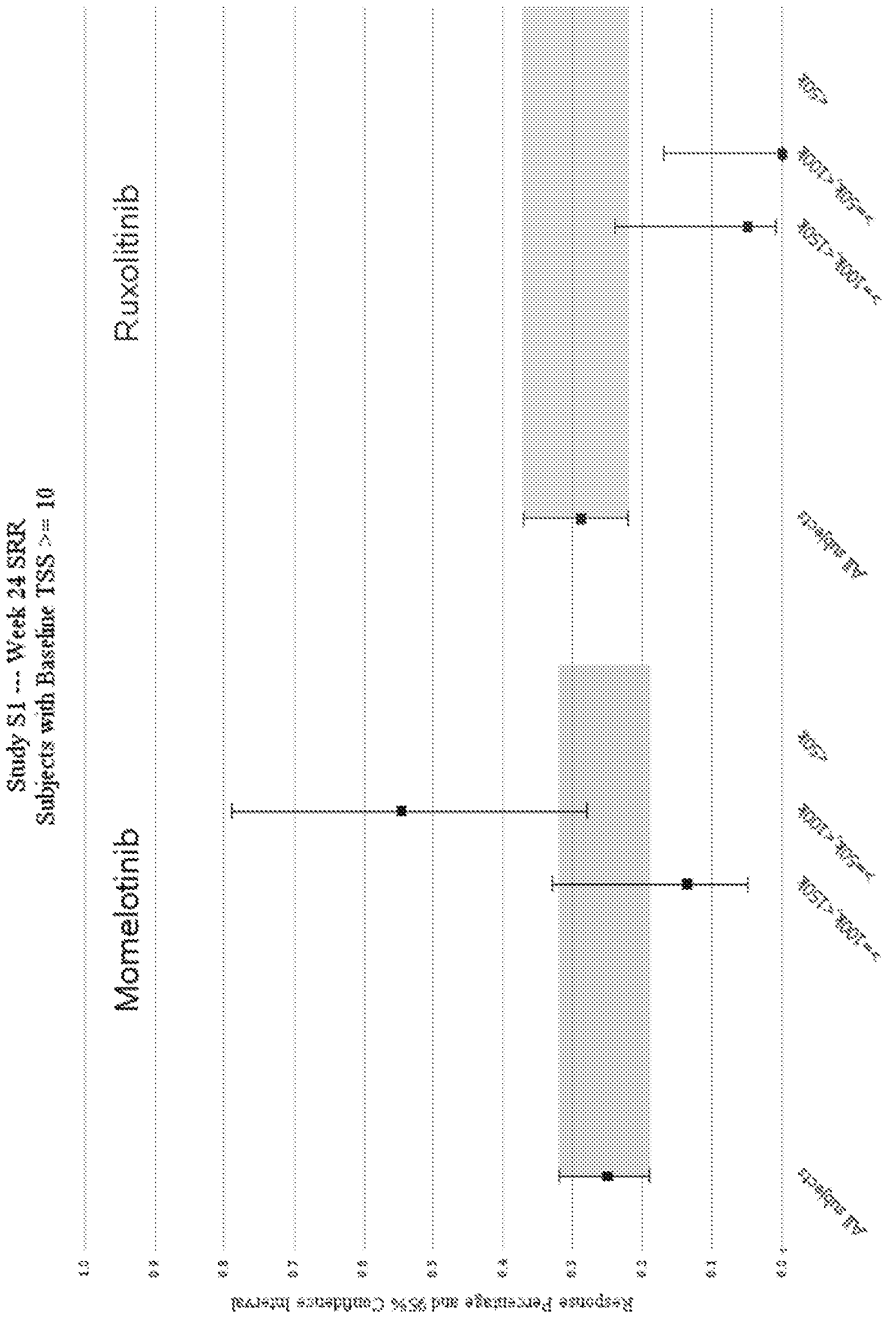

Study S1 --- Week 24 SRR
Subjects with Baseline TSS >= 10
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
<50
50 to <100
100 to <200
≥200
All Subjects
<50
50 to <100
100 to <200
≥200
Baseline Platelet Category

FIG. 38

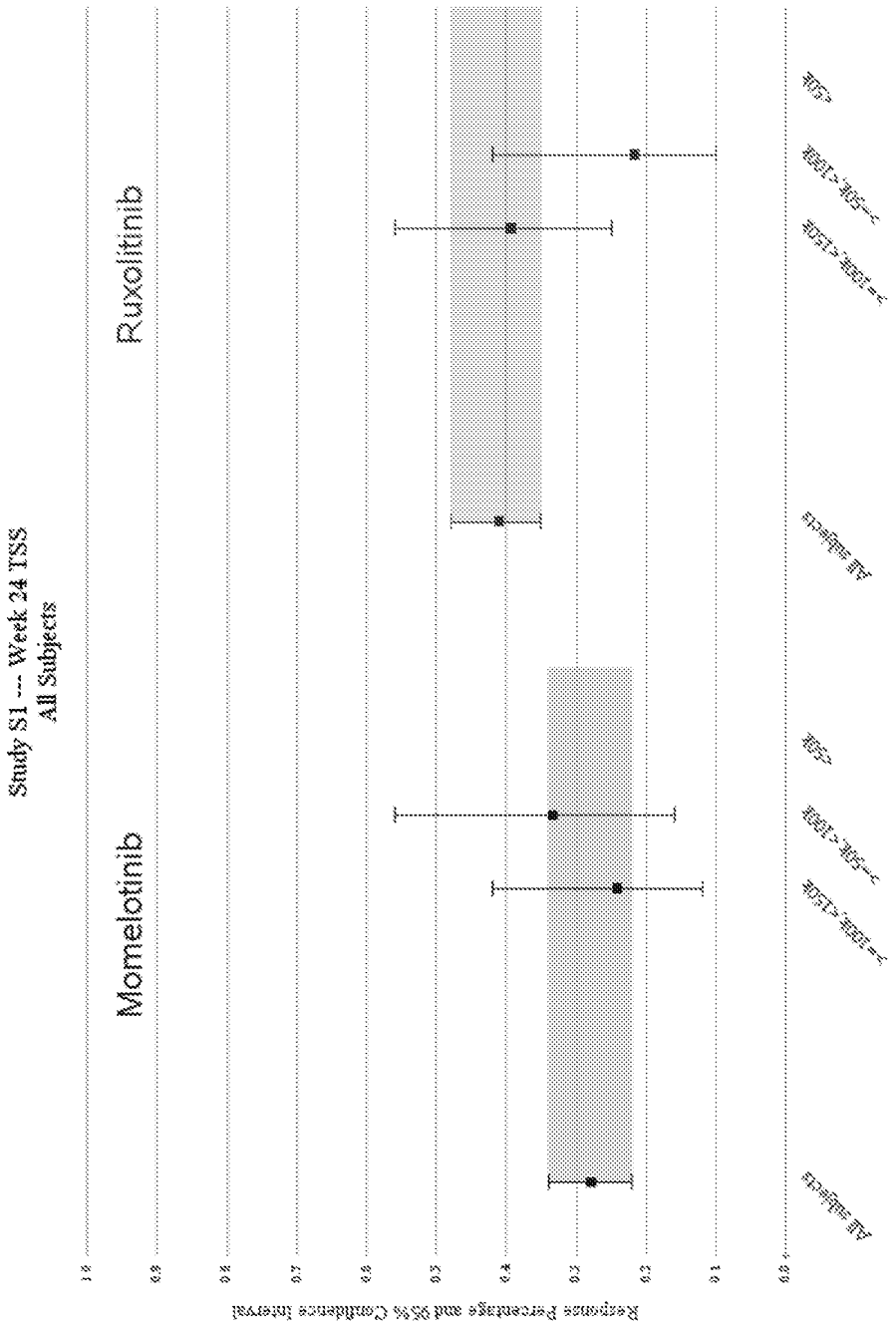

Study S1 --- Week 24 TSS
All Subjects
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
<100
100 to <200
≥200
All Subjects
<100
100 to <200
≥200
Baseline Platelet Category

FIG. 39

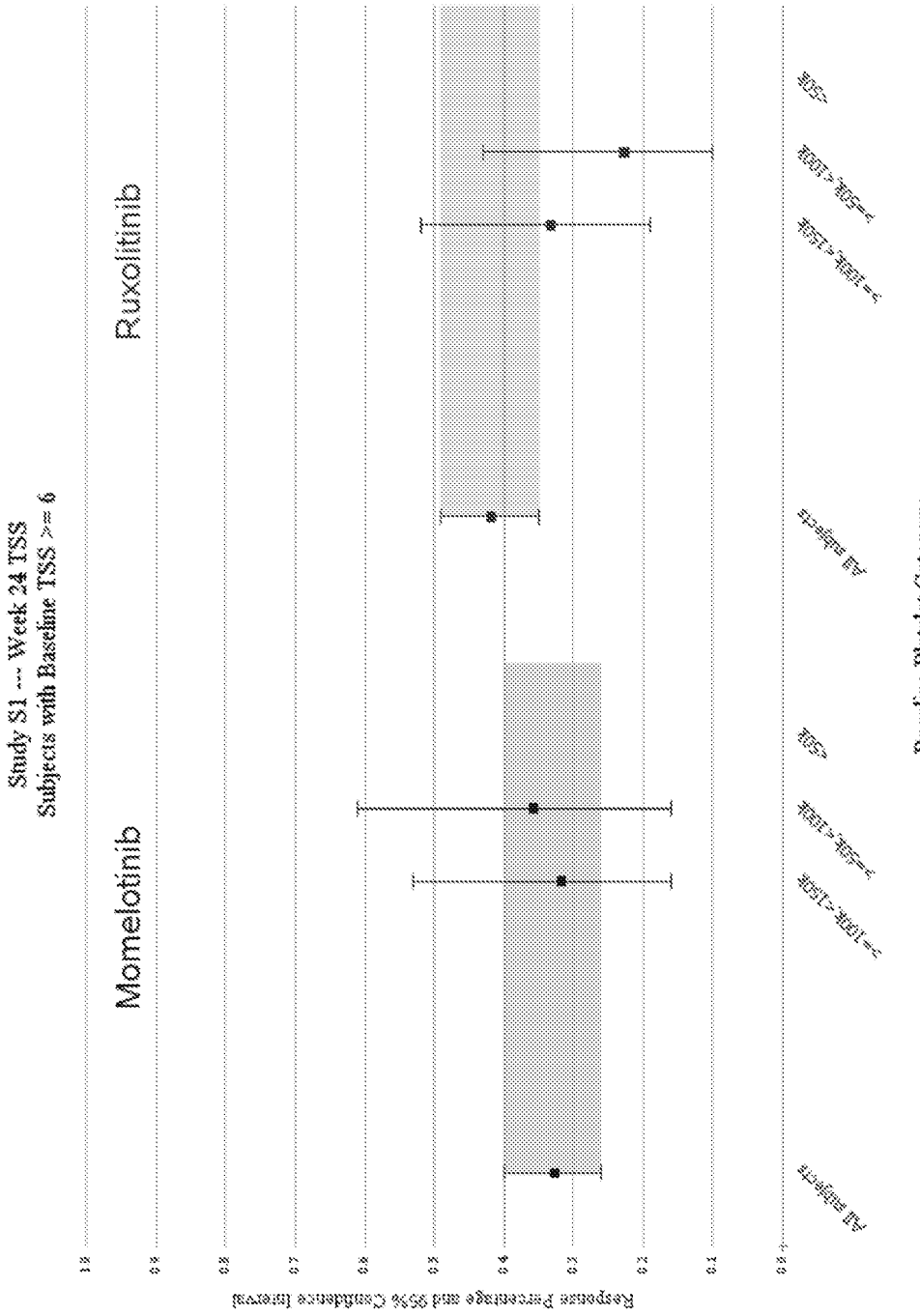

Study S1 --- Week 24 TSS
Subjects with Baseline TSS >= 6
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence (error)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
TSS>
TSS1>=100 and TSS<
TSS1<100
All Subjects
TSS>
TSS1>=100 and TSS<
TSS1<100
Baseline Platelet Category

FIG. 40

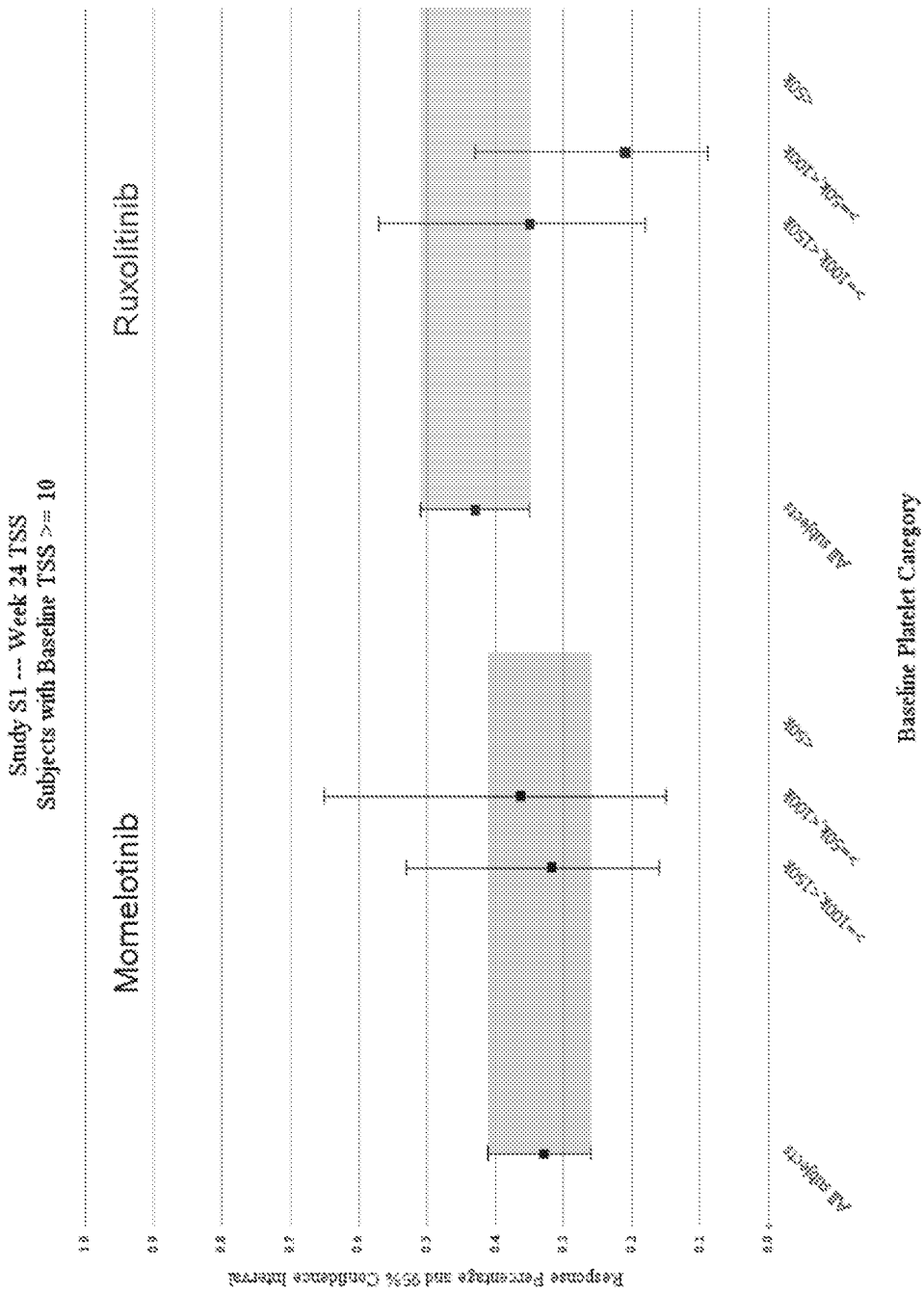

Study S1 -- Week 24 TSS
Subjects with Baseline TSS >= 10
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All subjects
>=100
150 > 100
< 150
Baseline Platelet Category

FIG. 41

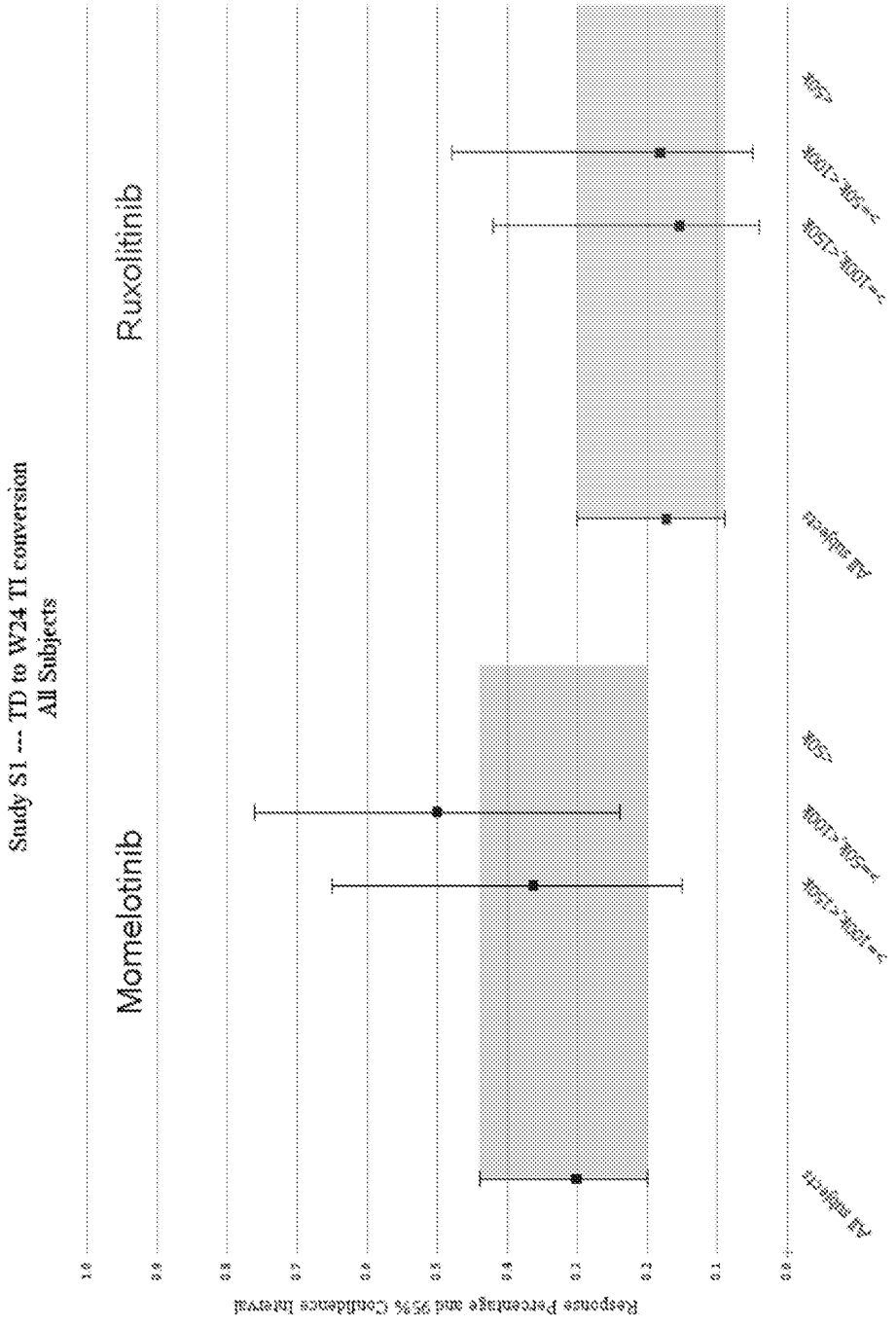

Study S1 --- TD to W24 TI conversion
All Subjects
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
≥150 x 10^9/L
≥100 x 10^9/L and <150 x 10^9/L
≥50 x 10^9/L and <100 x 10^9/L
<50 x 10^9/L
All Subjects
≥150 x 10^9/L
≥100 x 10^9/L and <150 x 10^9/L
≥50 x 10^9/L and <100 x 10^9/L
<50 x 10^9/L
Baseline Platelet Category

FIG. 42

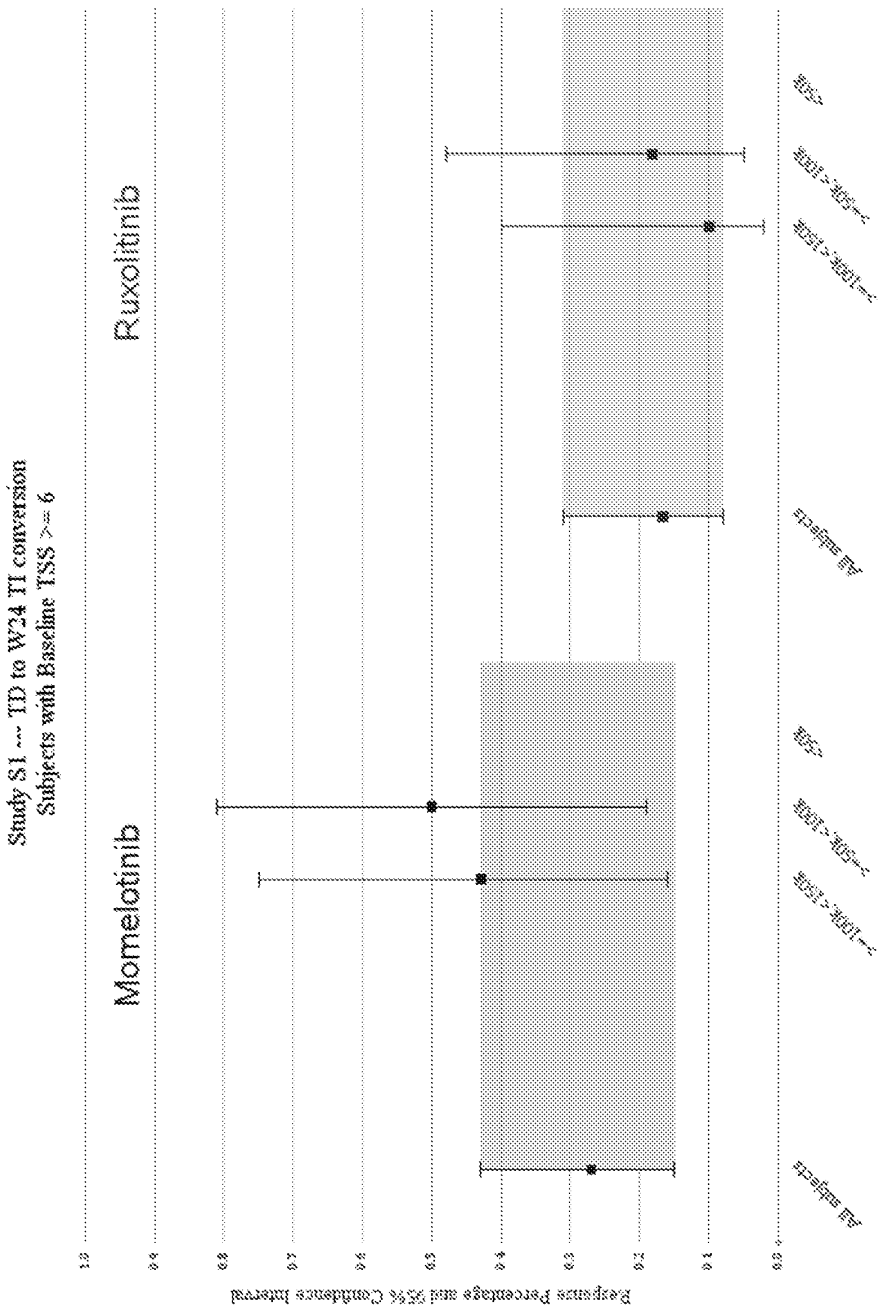

Study S1 --- TD to W24 TI conversion
Subjects with Baseline TSS >= 6
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All subjects
<50
50 - <100
>=100
All subjects
<50
50 - <100
>=100
Baseline Platelet Category

FIG. 43

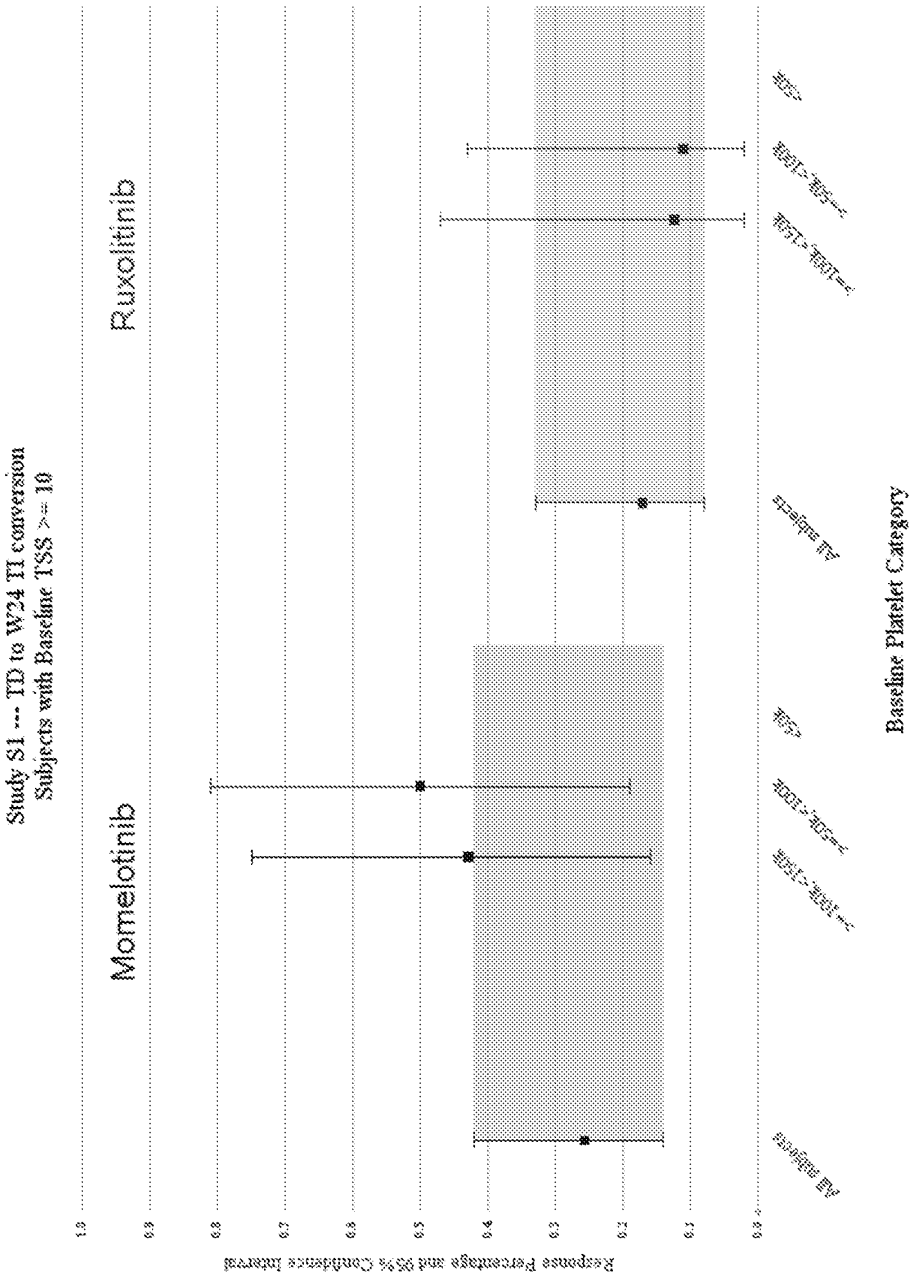

Study S1 --- TD to W24 TI conversion
Subjects with Baseline TSS >= 10
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Baseline Platelet Category
All Subjects
TSS>
TSS<
All Subjects
TSS>
TSS<

FIG. 44

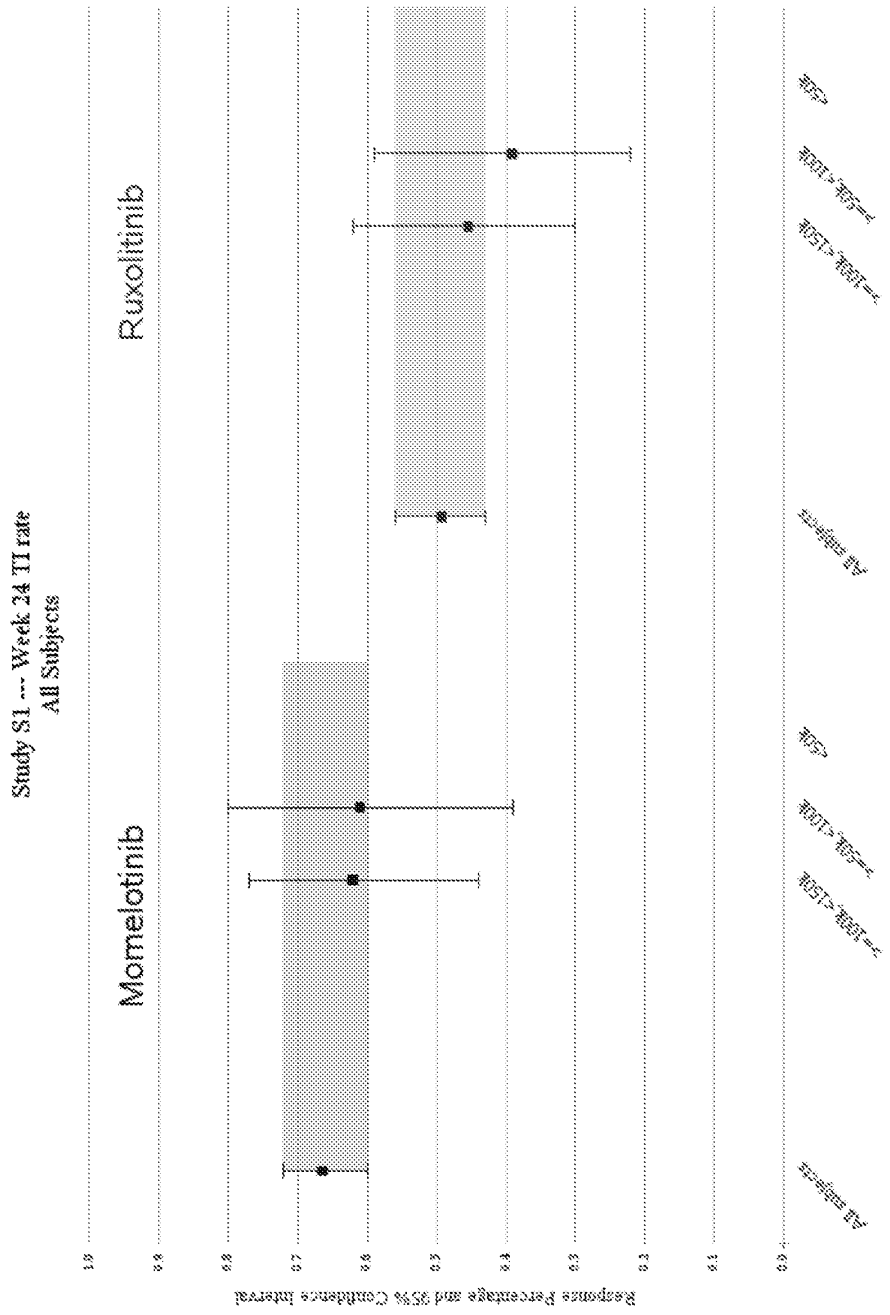

Study S1 --- Week 24 TI rate
All Subjects
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All subjects
≥50
≥35 to <50
≥25 to <35
All subjects
≥50
≥35 to <50
≥25 to <35
Baseline Platelet Category

FIG. 45

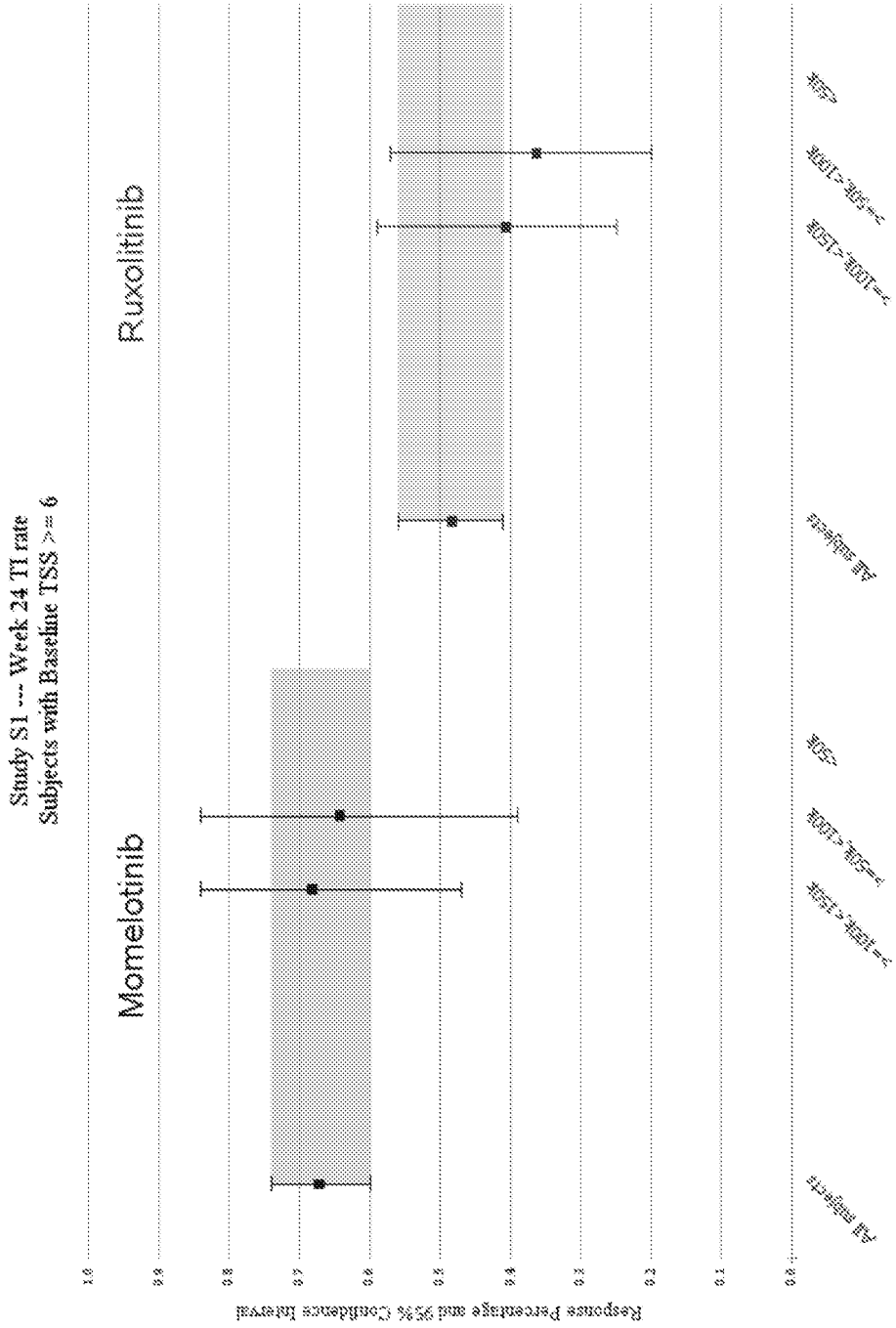

Study S1 --- Week 24 TI rate
Subjects with Baseline TSS >= 6
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
All Subjects
<105
105-<152
>=152-<208
>=208
All Subjects
<105
105-<152
>=152-<208
>=208
Baseline Platelet Category

FIG. 46

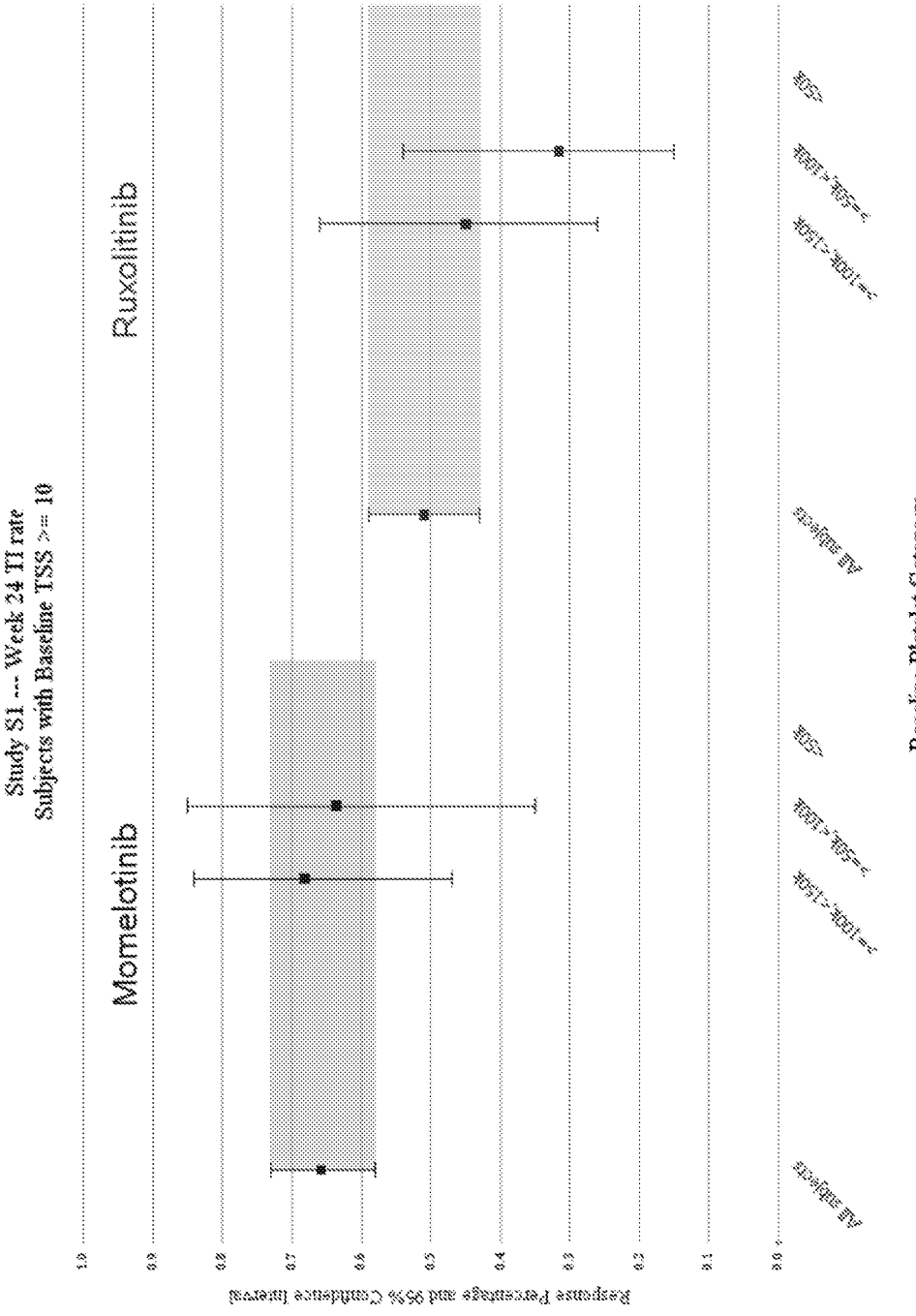

Study S1 --- Week 24 TI rate
Subjects with Baseline TSS >= 10
Momelotinib
Ruxolitinib
Response Percentage and 95% Confidence Interval
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
<100
100 - <150
150 - <200
>=200
Baseline Platelet Category

FIG. 47