NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ruxolitinib

Trial Indication(s)

Myelofibrosis

Protocol Number

CINC424ADE05

Protocol Title

A prospective, two-arm, non interventional study of JAKAVI® (Ruxolitinib) in patients with myelofibrosis

Clinical Trial Phase

Phase IV

Phase of Drug Development

Approval

Study Start/End Dates

Study Start Date: September 20, 2012 (Actual)
Primary Completion Date: September 19, 2022 (Actual)
Study Completion Date: September 19, 2022 (Actual)

Reason for Termination

Not applicable

Study Design/Methodology

The purpose of this non-interventional prospective observational study was to test myelofibrosis therapy with ruxolitinib in the daily clinical practice in a broad patient population whose composition reflected the real world situation without inclusion or exclusion criteria.
This NIS also aimed to investigate the quality of diagnosis and therapy as well as the general health care of myelofibrosis patients in Germany. Of particular interest here was compliance with the DGHO (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie) guidelines for myelofibrosis, but also adherence to the specialist information and the drug application of ruxolitinib.
In this NIS, the validated patient questionnaires MPN-SAF and SF-36 were used to assess changes in constitutional symptoms and changes in quality of life.

During the course of this NIS, ruxolitinib was prescribed and administered according to the SmPC and clinical routine. The current standard dose was 5 to 25 mg twice per day. Patients were treated with trading goods. The treating physician could implement dose adjustments for individual tolerability/safety and effectiveness. Dosage, contraindications, warnings, protective measures and interactions with other medicinal products had to be considered in adherence to the SmPC.

The treatment with ruxolitinib had to be documented over the planned observation period of 36 months.

Centers

Germany (122)

Objectives:

The following specific objectives were of interest:
• Assessment of the drug application of ruxolitinib in daily practice - initial dosage and dosage in the course, potential therapy interruptions and their reasons, characteristics of the patients treated with ruxolitinib, reasons for the therapy decision and side-effect management. Description of the symptoms and treatment reality as well as the diagnostic procedure in patients with myelofibrosis.

• Evaluation of the effectiveness of ruxolitinib treatment in daily practice - change in spleen size (or volume), and constitutional symptoms, as well as overall survival in JAK inhibitor-naive (Arm A) and JAK inhibitor-pretreated (Arm B) patients.

• Analysis of tolerability and safety in daily practice - assessment of the total number of adverse events (AEs) and serious adverse events (SAEs) with and without a causal relationship to ruxolitinib.

• Assessment of QoL under ruxolitinib therapy before and during treatment in JAK inhibitor-naive (Arm A) and JAK inhibitor-pretreated (Arm B) patients.

• Validation of the MPN-SAF patient questionnaire for the assessment of constitutional symptoms and QoL in patients with myelofibrosis in daily clinical practice.

• Comparison of effectiveness, tolerability and safety of ruxolitinib in JAK inhibitor-naïve (Arm A) and JAK inhibitor-pretreated (Arm B) patients.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral ruxolitinib, 5 to 25 mg twice per day

Statistical Methods

The NIS was analyzed using epidemiological methods with primary use of descriptive statistical techniques.
Categorical data were analyzed by presenting frequency tables (absolute and relative adjusted frequencies). For numerical data the sample statistics mean, standard deviation, median, minimum and maximum and quartiles were calculated.
Data measured several times during the study were analyzed by visit presenting absolute and relative differences to baseline for numerical data and shift tables for categorical data.
For the main analysis the visits were adjusted to the inclusion visit. The analysis was performed separately by Arm A and Arm B. Only baseline visit to Month 36 visit were displayed. Baseline and Day 0 was defined as inclusion visit. Post-baseline visits were all visits after the baseline visit.

Generally, missing values still missing after performing quality improvement measures (edit checks, queries), were not replaced.

NOVARTIS

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female patients with Primary Myelofibrosis (PMF), post-Polycythemia Vera-Myelofibrosis (PPV-MF), or post-Essential Thrombocythemia-Myelofibrosis (post-ET-MF), for whom Jakavi® therapy is indicated.
- Patients that were informed about all aspects of this NIS and provided written informed consent.

Participant Flow Table

Table 10-1: Patients enrolled

Diagnosis	Arm A n (%)	Arm B n (%)
Total	513	499
PMF	350 (68.2)	337 (67.5)
PPV-MF	103 (20.1)	105 (21.0)
PET-MF	56 (10.9)	50 (10.0)
Missing	4 (0.8)	7 (1.4)

Abbreviations: PET-MF = Post-Essential Thrombocythemia Myelofibrosis, PMF = Primary Myelofibrosis, PPV-MF = Post-Polycythemia Vera Myelofibrosis

NOVARTIS

Table 10-2: Analysis sets and reasons for exclusion (all patients enrolled)

Analysis Set/Reason	Arm A n (%)	Arm B n (%)
Enrolled	513 (100.0)	499 (100.0)
FAS	479 (93.4)	464 (93.0)
Exclusion from FAS		
No post-baseline visit	25 (4.9)	23 (4.6)
Baseline platelets to low	7 (1.4)	9 (1.8)
No treatment in study	4 (0.8)	6 (1.2)
No indication PMF, PPV-MF or PET-MF	3 (0.6)	6 (1.2)
Baseline neutrophils to low	2 (0.4)	0 (0.0)

Abbreviations: FAS = full analysis set, PET-MF = Post-Essential Thrombocythemia Myelofibrosis, PMF = Primary Myelofibrosis, PPV-MF = Post-Polycythemia Vera Myelofibrosis

NOVARTIS

Table 10-3: Patient disposition - Arm A and Arm B (FAS)

		PMF n (%)	PPV-MF n (%)	PET-MF n (%)	Total n (%)
Arm A		**N=325**	**N=99**	**N=55**	**N=479**
Study completed					
Yes (completer)		126 (38.8)	57 (57.6)	25 (45.5)	208 (43.4)
No (premature termination)		199 (61.2)	42 (42.4)	30 (54.5)	271 (56.6)
Arm B		**N=318**	**N=99**	**N=47**	**N=464**
Study completed					
Yes (completer)		151 (47.5)	63 (63.6)	28 (59.6)	242 (52.2)
No (premature termination)		167 (52.5)	36 (36.4)	19 (40.4)	222 (47.8)
Reason for premature termination (*)					
Death	Arm A	64 (19.7)	15 (15.2)	8 (14.5)	87 (18.2)
	Arm B	60 (18.9)	14 (14.1)	4 (8.5)	78 (16.8)
Adverse event	Arm A	42 (12.9)	12 (12.1)	5 (9.1)	59 (12.3)
	Arm B	23 (7.2)	4 (4.0)	3 (6.4)	30 (6.5)
Lost-to-follow-up	Arm A	25 (7.7)	4 (4.0)	3 (5.5)	32 (6.7)
	Arm B	23 (7.2)	8 (8.1)	4 (8.5)	35 (7.5)
Deterioration of general health	Arm A	21 (6.5)	5 (5.1)	5 (9.1)	31 (6.5)
	Arm B	22 (6.9)	2 (2.0)	-	24 (5.2)
Progression of primary disease	Arm A	18 (5.5)	1 (1.0)	5 (9.1)	24 (5.0)
	Arm B	15 (4.7)	2 (2.0)	1 (2.1)	18 (3.9)
Therapy response	Arm A	17 (5.2)	2 (2.0)	4 (7.3)	23 (4.8)
	Arm B	14 (4.4)	2 (2.0)	1 (2.1)	17 (3.7)
Poor compliance	Arm A	4 (1.2)	1 (1.0)	2 (3.6)	7 (1.5)
	Arm B	2 (0.6)	-	3 (6.4)	5 (1.1)
Change to AML	Arm A	7 (2.2)	-	-	7 (1.5)
	Arm B	5 (1.6)	-	-	5 (1.1)
Infection	Arm A	1 (0.3)	-	-	1 (0.2)
	Arm B	2 (0.6)	-	-	2 (0.4)

NOVARTIS

Table 10-3: Patient disposition - Arm A and Arm B (FAS)

		PMF n (%)	PPV-MF n (%)	PET-MF n (%)	Total n (%)
Other	Arm A	45 (13.8)	7 (7.1)	9 (16.4)	61 (12.7)
	Arm B	33 (10.4)	7 (7.1)	4 (8.5)	44 (9.5)
Reason for Death/AML/Progression (disjunct)					
Death (no AML/Progression)	Arm A	63 (19.4)	15 (15.2)	8 (14.5)	86 (18.0)
	Arm B	58 (18.2)	14 (14.1)	4 (8.5)	76 (16.4)
Progression (no Death/AML)	Arm A	16 (4.9)	1 (1.0)	5 (9.1)	22 (4.6)
	Arm B	15 (4.7)	2 (2.0)	1 (2.1)	18 (3.9)
AML (no Death/Progression)	Arm A	1 (0.3)	-	-	1 (0.2)
	Arm B	-	-	-	-
Death & Progression (no AML)	Arm A	1 (0.3)	-	-	1 (0.2)
	Arm B	-	-	-	-
AML & Progression (no Death)	Arm A	1 (0.3)	-	-	1 (0.2)
	Arm B	-	-	-	-
Death & AML (no Progression)	Arm A	-	-	-	-
	Arm B	2 (0.6)	-	-	2 (0.4)
Death & AML & Progression	Arm A	-	-	-	-
	Arm B	-	-	-	-

Abbreviations: AML = acute myeloid leukemia, FAS = full analysis set, PMF = Primary myelofibrosis, PPV-MF = Post-Polycythemia Vera Myelofibrosis, PET-MF = Post-Essential Thrombocythemia Myelofibrosis
(*) Multiple answers possible

NOVARTIS

Baseline Characteristics

		Arm A (N=479)	Arm B (N=464)
Age (years)	n	479	464
	Mean ± SD	70.2 ± 10.7	70.3 ± 11.4
	Median	73.0	73.0
	Minimum	32.0	23.0
	Maximum	95.0	92.0
Sex, n (%)	Male	254 (53.0)	253 (54.5)
	Female	225 (47.0)	211 (45.5)
Weight* (kg)	n	428	383
	Mean ± SD	72.4 ± 14.8	75.0 ± 14.7
	Median	72.0	73.0
	Minimum	40.2	40.0
	Maximum	133.0	130.0
Height* (cm)	n	435	422
	Mean ± SD	169.6 ± 9.1	171.1 ± 8.9
	Median	170.0	170.0
	Minimum	140.0	150.0
	Maximum	193.0	196.0
BMI* (kg/m^2)	n	415	376
	Mean ± SD	25.1 ± 4.3	25.6 ± 4.4
	Median	24.6	24.9
	Minimum	16.0	14.5
	Maximum	45.0	45.5
Smoking status, n (%)	No	349 (76.2)	346 (79.0)
	Yes	40 (8.7)	31 (7.1)
	Ex-smoker	69 (15.1)	61 (13.9)
	Missing	21	26
IPSS score documented by investigator, n (%)	Low	27 (13.3)	34 (18.0)
	Intermediate-1	52 (25.6)	53 (28.0)
	Intermediate-2	78 (38.4)	65 (34.4)
	High	46 (22.7)	37 (19.6)
	Missing	276	275
IPSS score calculated from source data, n (%)	Low	10 (8.5)	5 (8.2)
	Intermediate-1	35 (29.9)	12 (19.7)
	Intermediate-2	40 (34.2)	19 (31.1)
	High	32 (27.4)	25 (41.0)
	Missing	362	403

Abbreviations: BMI = body mass index, FAS = full analysis set, IPSS = International prognostic scoring system, PMF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera Myelofibrosis, PET-MF = Post-essential Thrombocytemia Myelofibrosis, SD = standard deviation

*Data measured at baseline

NOVARTIS

Primary Outcome Result(s)

Ruxolitinib start and end dose

	Full analysis set Arm A			
	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
Start dose [mg/day]				
n	325	99	55	479
Mean	26.7	27.8	26.5	26.9
SD	11.1	10.9	10.6	11.0
Minimum	5.0	5.0	5.0	5.0
1st quartile	15.0	20.0	15.0	20.0
Median	30.0	30.0	30.0	30.0
3rd quartile	40.0	40.0	30.0	40.0
Maximum	40.0	40.0	40.0	40.0
Start dose [mg/day]				
5	3 (0.9)	2 (2.0)	1 (1.8)	6 (1.3)
10	66 (20.3)	16 (16.2)	10 (18.2)	92 (19.2)
15	14 (4.3)	1 (1.0)	3 (5.5)	18 (3.8)
20	34 (10.5)	13 (13.1)	3 (5.5)	50 (10.4)
30	121 (37.2)	37 (37.4)	27 (49.1)	185 (38.6)
40	87 (26.8)	30 (30.3)	11 (20.0)	128 (26.7)
End dose [mg/day]				
n	325	99	55	479

NOVARTIS

	Full analysis set Arm A			
	P-MF (N=325)	**PPV-MF (N=99)**	**PET-MF (N=55)**	**Total (N=479)**
Mean	23.1	23.6	22.5	23.1
SD	11.5	12.1	11.5	11.6
Minimum	5.0	5.0	5.0	5.0
1st quartile	10.0	10.0	10.0	10.0
Median	20.0	20.0	20.0	20.0
3rd quartile	30.0	30.0	30.0	30.0
Maximum	50.0	50.0	40.0	50.0
End dose [mg/day]				
5	20 (6.2)	9 (9.1)	5 (9.1)	34 (7.1)
10	66 (20.3)	16 (16.2)	10 (18.2)	92 (19.2)
15	22 (6.8)	6 (6.1)	6 (10.9)	34 (7.1)
20	72 (22.2)	23 (23.2)	9 (16.4)	104 (21.7)
30	78 (24.0)	24 (24.2)	16 (29.1)	118 (24.6)
40	57 (17.5)	19 (19.2)	9 (16.4)	85 (17.7)
50	3 (0.9)	2 (2.0)	0	5 (1.0)

NOVARTIS

	Full analysis set Arm B			
	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
Start dose [mg/day]				
n	317	99	47	463
Mean	24.7	23.4	24.3	24.4
SD	10.8	9.7	9.9	10.4
Minimum	5.0	5.0	5.0	5.0
1st quartile	15.0	20.0	20.0	20.0
Median	30.0	20.0	25.0	25.0
3rd quartile	30.0	30.0	30.0	30.0
Maximum	50.0	40.0	50.0	50.0
Start dose [mg/day]				
5	10 (3.2)	2 (2.0)	1 (2.1)	13 (2.8)
10	53 (16.7)	18 (18.2)	7 (14.9)	78 (16.8)
15	17 (5.4)	4 (4.0)	3 (6.4)	24 (5.2)
20	72 (22.7)	30 (30.3)	11 (23.4)	113 (24.4)
30	95 (30.0)	33 (33.3)	18 (38.3)	146 (31.5)
40	58 (18.3)	11 (11.1)	4 (8.5)	73 (15.8)
50	2 (0.6)	0	1 (2.1)	3 (0.6)
-missing	0	0	0	0
End dose [mg/day]				
n	317	99	47	463

	Full analysis set Arm B			
	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
Mean	23.7	23.8	21.9	23.5
SD	11.9	11.0	11.8	11.7
Minimum	5.0	5.0	5.0	5.0
1st quartile	10.0	15.0	10.0	15.0
Median	20.0	20.0	20.0	20.0
3rd quartile	30.0	30.0	30.0	30.0
Maximum	60.0	50.0	60.0	60.0
End dose [mg/day]				
5	14 (4.4)	2 (2.0)	3 (6.4)	19 (4.1)
10	67 (21.1)	18 (18.2)	10 (21.3)	95 (20.5)
15	23 (7.3)	7 (7.1)	5 (10.6)	35 (7.6)
20	67 (21.1)	30 (30.3)	11 (23.4)	108 (23.3)
30	80 (25.2)	19 (19.2)	12 (25.5)	111 (24.0)
40	50 (15.8)	15 (15.2)	5 (10.6)	70 (15.1)
50	7 (2.2)	2 (2.0)	0	9 (1.9)
-missing	0	0	0	0

Abbreviations: P-MF = Primary myelofibrosis, PPV-MF= Post-Polycy-themia Vera Myelofibrosis , PET_MF = Post-Essential Thrombocythemia Myelofibrosis

NOVARTIS

Therapy discontinuation and dose adjustments

Table 10-9: Therapy discontinuations and dose adjustments Arm A and Arm B (FAS)

	Arm A N=479 n (%)	Arm B N=464 n (%)
Therapy discontinuations per patient		
0	311 (64.9)	373 (80.4)
1	116 (24.2)	69 (14.9)
2	37 (7.7)	14 (3.0)
3	8 (1.7)	8 (1.7)
≥4	7 (1.4)	0
Reason for discontinuation *		
Adverse event	109 (22.8)	57 (12.3)
Thrombocytopenia	45 (9.4)	16 (3.4)
Lack of efficacy	7 (1.5)	5 (1.1)
Kidney dysfunction	2 (0.4)	1 (0.2)
Liver dysfunction	0	1 (0.2)
Other	45 (9.4)	38 (8.2)
Dose adjustments per patient		
0	123 (25.7)	183 (39.4)
1	98 (20.5)	109 (23.5)
2	97 (20.3)	71 (15.3)
3	55 (11.5)	46 (9.9)
≥4	106 (22.1)	55 (11.7)
Reason for dose adjustments *		
Adverse event	85 (17.7)	75 (16.2)
Thrombocytopenia	48 (10.0)	25 (5.4)
Lack of efficacy	20 (4.2)	27 (5.8)
Concomitant medication	1 (0.02)	1 (0.2)
Kidney dysfunction	1 (0.2)	2 (0.4)
Liver dysfunction	2 (0.4)	1 (0.2)
Other	139 (29.0)	118 (25.4)

Abbreviations: FAS = full analysis set
* multiple answers possible

NOVARTIS

Number of patients with co-morbidities

Table 10-12:Concomitant diseases by MedDRA system organ class and preferred term, if present in at least 10 patients in any Arm (FAS)

	Arm A (N=479) n (%)	Arm B (N=464) n (%)
Any patients	**395 (82.5)**	**364 (78.4)**
Vascular disorders	**231 (48.2)**	**230 (49.6)**
Hypertension	210 (43.8)	198 (42.7)
Peripheral arterial occlusive disease	12 (2.5)	17 (3.7)
Deep vein thrombosis	5 (1.0)	15 (3.2)
Metabolism and nutrition disorders	**160 (33.4)**	**141 (30.4)**
Hyperuricemia	47 (9.8)	45 (9.7)
Diabetes mellitus	33 (6.9)	21 (4.5)
Type 2 diabetes mellitus	31 (6.5)	31 (6.7)
Hyperlipidemia	20 (4.2)	9 (1.9)
Hypercholesterolemia	19 (4.0)	20 (4.3)
Obesity	13 (2.7)	6 (1.3)
Gout	10 (2.1)	12 (2.6)
Iron overload	7 (1.5)	14 (3.0)
Cardiac disorders	**114 (23.8)**	**122 (26.3)**
Coronary artery disease	42 (8.8)	42 (9.1)
Atrial fibrillation	34 (7.1)	38 (8.2)
Cardiac failure	19 (4.0)	15 (3.2)
Myocardial infarction	12 (2.5)	6 (1.3)
Mitral valve incompetence	9 (1.9)	13 (2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**74 (15.4)**	**70 (15.1)**
Prostate cancer	14 (2.9)	8 (1.7)
Nervous system disorders	**71 (14.8)**	**70 (15.1)**
Cerebrovascular accident	15 (3.1)	9 (1.9)
Blood and lymphatic disorders	**69 (14.4)**	**96 (20.7)**
Anemia	34 (7.1)	48 (10.3)
Splenomegaly	18 (3.8)	22 (4.7)
Thrombocytosis	6 (1.3)	10 (2.2)
Musculoskeletal and connective tissue disorders	**69 (14.4)**	**77 (16.6)**
Osteoarthritis	20 (4.2)	23 (5.0)
Osteoporosis	12 (2.5)	12 (2.6)
Surgical and medical procedures	**61 (12.7)**	**64 (13.8)**
Cholecystectomy	5 (1.0)	10 (2.2)
Respiratory, thoracic and mediastinal disorders	**58 (12.1)**	**63 (13.6)**
Chronic obstructive pulmonary disease	21 (4.4)	16 (3.4)
Asthma	14 (2.9)	7 (1.5)

NOVARTIS

Table 10-12:Concomitant diseases by MedDRA system organ class and preferred term, if present in at least 10 patients in any Arm (FAS)

	Arm A (N=479) n (%)	Arm B (N=464) n (%)
Renal and urinary disorders	**55 (11.5)**	**59 (12.7)**
Chronic kidney disease	17 (3.5)	27 (5.8)
Renal failure	14 (2.9)	16 (3.4)
Gastrointestinal disorders	**54 (11.3)**	**59 (12.7)**
Endocrine disorders	**53 (11.1)**	**53 (11.4)**
Hypothyroidism	34 (7.1)	33 (7.1)
Psychiatric disorders	**35 (7.3)**	**26 (5.6)**
Depression	15 (3.1)	13 (2.8)
Hepatobiliary disorders	**31 (6.5)**	**33 (7.1)**
Cholelithiasis	13 (2.7)	16 (3.4)
Infections and infestations	**31 (6.5)**	**25 (5.4)**
Reproductive system and breast disorders	**26 (5.4)**	**36 (7.8)**
Benign prostatic hyperplasia	22 (4.6)	32 (6.9)
Skin and subcutaneous disorders	**25 (5.2)**	**26 (5.6)**
General disorders and administration site condtions	**22 (4.6)**	**24 (5.2)**
Eye disorders	**14 (2.9)**	**9 (1.9)**
Investigations	**13 (2.7)**	**18 (3.9)**
Congenital, familial and genetic disorders	**11 (2.3)**	**17 (3.7)**
Injury, poisoning and procedural complications	**10 (2.1)**	**13 (2.8)**

Abbreviations: FAS = full analysis set, MedDRA = Medical dictionary of regulatory affairs

NOVARTIS

Blood transfusion dependency

Blood transfusions at baseline:

Full analysis set Arm A				
	P-MF (N=325) n (%)	**PPV-MF (N=99) n (%)**	**PET-MF (N=55) n (%)**	**Total (N=479) n (%)**
Need for transfusion, n (%)				
strong need for transfusion (> 4 EKs/month)	9 (2.8)	0 (0.0)	2 (3.8)	11 (2.4)
moderate need for transfusion (2-4 EKs/month)	41 (12.9)	3 (3.1)	5 (9.4)	49 (10.5)
low need for transfusion (< 2 EKs/month)	121 (38.2)	34 (35.1)	19 (35.8)	174 (37.3)
no need for transfusion	146 (46.1)	60 (61.9)	27 (50.9)	233 (49.9)
Time since start transfusion to baseline [month]				
n	94	14	19	127
Mean	23.8	9.5	30.0	23.2
SD	31.8	15.5	40.0	32.1
Minimum	-2.3	-1.2	-0.3	-2.3
q1	1.4	0.2	1.7	1.3
Median	7.2	2.0	10.6	7.0
q3	37.1	14.8	50.7	36.2
Maximum	131.7	51.3	136.4	136.4

NOVARTIS

Full analysis set Arm A				
	P-MF (N=325) n (%)	**PPV-MF (N=99) n (%)**	**PET-MF (N=55) n (%)**	**Total (N=479) n (%)**
Number of EKs since diagnosis to start Jakavi$treatment, n (%)				
< 20	102 (80.3)	24 (92.3)	15 (71.4)	141 (81.0)
20 - 39	10 (7.9)	2 (7.7)	2 (9.5)	14 (8.0)
40 - 59	6 (4.7)	0 (0.0)	2 (9.5)	8 (4.6)
60 - 79	5 (3.9)	0 (0.0)	0 (0.0)	5 (2.9)
>= 80	4 (3.1)	0 (0.0)	2 (9.5)	6 (3.4)
-missing	44	11	5	60
Actual EK per/month				
n	149	35	25	209
Mean	1.5	0.6	1.3	1.3
SD	2.0	1.0	1.5	1.8
Minimum	0.0	0.0	0.0	0.0
q1	0.0	0.0	0.0	0.0
Median	1.0	0.0	2.0	0.0
q3	2.0	2.0	2.0	2.0
Maximum	10.0	4.0	6.0	10.0
Time since last transfusion to baseline [month]				
n	75	12	15	102
Mean	3.4	7.9	2.5	3.8
SD	8.5	16.5	4.8	9.4

NOVARTIS

Full analysis set Arm A

	P-MF (N=325) n (%)	PPV-MF (N=99) n (%)	PET-MF (N=55) n (%)	Total (N=479) n (%)
Minimum	0.0	0.0	0.0	0.0
q1	0.0	0.2	0.0	0.0
Median	0.5	0.6	0.5	0.5
q3	1.4	3.8	2.7	1.8
Maximum	43.2	49.8	17.8	49.8
Erythropoetin treatment, n (%)				
no	159 (93.0)	34 (91.9)	20 (76.9)	213 (91.0)
yes	12 (7.0)	3 (8.1)	6 (23.1)	21 (9.0)
Iron overload, n (%)				
no	116 (77.3)	30 (93.8)	19 (76.0)	165 (79.7)
yes	34 (22.7)	2 (6.3)	6 (24.0)	42 (20.3)
-missing	21	5	1	27

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis.

NOVARTIS

Full analysis set Arm B				
	P-MF (N=318) n (%)	**PPV-MF (N=99) n (%)**	**PET-MF (N=47) n (%)**	**Total (N=464) n (%)**
Need for transfusion, n (%)				
strong need for transfusion (> 4 EKs/month)	3 (1.0)	0 (0.0)	1 (2.1)	4 (0.9)
moderate need for transfusion (2-4 EKs/month)	47 (15.3)	3 (3.2)	4 (8.5)	54 (12.0)
low need for transfusion (< 2 EKs/month)	189 (61.6)	74 (77.9)	36 (76.6)	299 (66.6)
no need for transfusion	68 (22.1)	18 (18.9)	6 (12.8)	92 (20.5)
Time since start transfusion to baseline [month]				
n	124	19	19	162
Mean	17.9	14.2	18.5	17.5
SD	24.2	17.1	19.6	22.9
Minimum	-7.1	-6.5	0.9	-7.1
q1	2.2	1.5	4.8	2.2
Median	7.0	7.3	10.7	8.2
q3	28.1	26.6	21.6	27.3
Maximum	126.0	56.2	68.0	126.0

NOVARTIS

Full analysis set Arm B

	P-MF (N=318) n (%)	PPV-MF (N=99) n (%)	PET-MF (N=47) n (%)	Total (N=464) n (%)
Number of EKs since diagnosis to start Jakavi$treatment, n (%)				
< 20	150 (87.7)	46 (95.8)	24 (88.9)	220 (89.4)
20 - 39	9 (5.3)	1 (2.1)	1 (3.7)	11 (4.5)
40 - 59	5 (2.9)	0 (0.0)	0 (0.0)	5 (2.0)
60 - 79	2 (1.2)	1 (2.1)	1 (3.7)	4 (1.6)
>= 80	5 (2.9)	0 (0.0)	1 (3.7)	6 (2.4)
-missing	68	29	14	111
Actual EK per/month				
n	207	70	37	314
Mean	1.0	0.2	0.9	0.8
SD	1.3	0.6	1.1	1.2
Minimum	0.0	0.0	0.0	0.0
q1	0.0	0.0	0.0	0.0
Median	0.0	0.0	0.0	0.0
q3	2.0	0.0	2.0	2.0
Maximum	8.0	3.0	4.0	8.0
Time since last transfusion to baseline [month]				
n	104	15	18	137
Mean	5.2	11.1	5.1	5.8
SD	14.7	13.3	10.1	14.1

NOVARTIS

Full analysis set Arm B				
	P-MF (N=318) n (%)	**PPV-MF (N=99) n (%)**	**PET-MF (N=47) n (%)**	**Total (N=464) n (%)**
Minimum	0.0	0.1	0.0	0.0
q1	0.5	1.7	0.8	0.6
Median	0.9	6.7	1.2	1.1
q3	2.3	14.5	2.0	3.3
Maximum	126.0	46.8	41.7	126.0
Erythropoetin treatment, n (%)				
no	219 (91.6)	75 (97.4)	35 (85.4)	329 (92.2)
yes	20 (8.4)	2 (2.6)	6 (14.6)	28 (7.8)
Iron overload, n (%)				
no	186 (78.8)	72 (94.7)	35 (85.4)	293 (83.0)
yes	50 (21.2)	4 (5.3)	6 (14.6)	60 (17.0)
-missing	3	1	0	4

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis.

NOVARTIS

Blood transfusions – Post baseline, analysis based per patient

Full analysis set Arm A

Transfusions	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
Transfusions, n (%)				
1	184 (56.6)	73 (73.7)	30 (54.5)	287 (59.9)
2	26 (8.0)	8 (8.1)	2 (3.6)	36 (7.5)
3	21 (6.5)	3 (3.0)	5 (9.1)	29 (6.1)
4	16 (4.9)	5 (5.1)	2 (3.6)	23 (4.8)
5	16 (4.9)	3 (3.0)	0	19 (4.0)
6	12 (3.7)	3 (3.0)	5 (9.1)	20 (4.2)
7	13 (4.0)	1 (1.0)	3 (5.5)	17 (3.5)
8	9 (2.8)	1 (1.0)	3 (5.5)	13 (2.7)
9	9 (2.8)	1 (1.0)	2 (3.6)	12 (2.5)
10	2 (0.6)	0	1 (1.8)	3 (0.6)
11	4 (1.2)	0	1 (1.8)	5 (1.0)
12	1 (0.3)	0	0	1 (0.2)
13	3 (0.9)	0	1 (1.8)	4 (0.8)
14	3 (0.9)	0	0	3 (0.6)
17	1 (0.3)	0	0	1 (0.2)
19	1 (0.3)	0	0	1 (0.2)
21	1 (0.3)	0	0	1 (0.2)
23	1 (0.3)	0	0	1 (0.2)
26	1 (0.3)	0	0	1 (0.2)
52	1 (0.3)	0	0	1 (0.2)
53	0	1 (1.0)	0	1 (0.2)

NOVARTIS

Full analysis set Arm A				
Transfusions	**P-MF (N=325)**	**PPV-MF (N=99)**	**PET-MF (N=55)**	**Total (N=479)**
Transfusions per year				
n	325	99	55	479
Mean	1.10	0.77	1.12	1.03
SD	1.5361	1.8048	1.0834	1.5551
Minimum	0.33	0.33	0.33	0.33
1st quartile	0.333	0.333	0.333	0.333
Median	0.333	0.333	0.333	0.333
3rd quartile	1.333	0.667	2.000	1.333
Maximum	17.33	17.67	4.33	17.67
P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis				

NOVARTIS

Full analysis set Arm B

Transfusions	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
Transfusions, n (%)				
1	193 (60.7)	86 (86.9)	33 (70.2)	312 (67.2)
2	23 (7.2)	6 (6.1)	2 (4.3)	31 (6.7)
3	16 (5.0)	2 (2.0)	3 (6.4)	21 (4.5)
4	12 (3.8)	0	2 (4.3)	14 (3.0)
5	17 (5.3)	1 (1.0)	0	18 (3.9)
6	7 (2.2)	0	1 (2.1)	8 (1.7)
7	5 (1.6)	1 (1.0)	0	6 (1.3)
8	12 (3.8)	1 (1.0)	2 (4.3)	15 (3.2)
9	8 (2.5)	0	1 (2.1)	9 (1.9)
10	3 (0.9)	0	2 (4.3)	5 (1.1)
11	4 (1.3)	1 (1.0)	0	5 (1.1)
12	1 (0.3)	0	0	1 (0.2)
13	2 (0.6)	0	0	2 (0.4)
14	1 (0.3)	0	0	1 (0.2)
15	1 (0.3)	1 (1.0)	0	2 (0.4)
16	1 (0.3)	0	0	1 (0.2)
17	1 (0.3)	0	1 (2.1)	2 (0.4)
21	1 (0.3)	0	0	1 (0.2)
22	2 (0.6)	0	0	2 (0.4)
23	1 (0.3)	0	0	1 (0.2)
26	2 (0.6)	0	0	2 (0.4)
31	1 (0.3)	0	0	1 (0.2)
38	2 (0.6)	0	0	2 (0.4)

NOVARTIS

Full analysis set Arm B				
Transfusions	**P-MF (N=318)**	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
42	1 (0.3)	0	0	1 (0.2)
49	1 (0.3)	0	0	1 (0.2)
Transfusions per year				
n	318	99	47	464
Mean	1.23	0.51	0.87	1.04
SD	2.0627	0.6605	1.1178	1.7943
Minimum	0.33	0.33	0.33	0.33
1st quartile	0.333	0.333	0.333	0.333
Median	0.333	0.333	0.333	0.333
3rd quartile	1.333	0.333	1.000	1.000
Maximum	16.33	5.00	5.67	16.33
P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis				

NOVARTIS

Blood transfusions - Postbaseline, analysis based per transfusion

Full analysis set Arm A				
	P-MF (N=325)	**PPV-MF (N=99)**	**PET-MF (N=55)**	**Total (N=479)**
caused by myelofibrosis, n (%)				
No	452 (42.1)	164 (71.9)	79 (42.9)	695 (46.8)
Yes	622 (57.9)	64 (28.1)	105 (57.1)	791 (53.2)
caused by Jakavi therapy, n (%)				
No	1021 (95.1)	208 (91.2)	168 (91.3)	1397 (94.0)
Yes	53 (4.9)	20 (8.8)	16 (8.7)	89 (6.0)
iron overload, n (%)				
No	623 (68.9)	108 (65.9)	117 (73.1)	848 (69.1)
Yes	281 (31.1)	56 (34.1)	43 (26.9)	380 (30.9)
missing	170	64	24	258

NOVARTIS

Full analysis set Arm A

	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
number Eks since last examination				
n	812	152	143	1107
Mean	8	3	6	7
SD	15.12	2.52	7.78	13.38
Minimum	0	0	0	0
1st quartile	2.0	2.0	2.0	2.0
Median	2.0	2.0	2.0	2.0
3rd quartile	6.0	2.0	8.0	6.0
Maximum	104	18	56	104
actual EK/month				
n	711	126	145	982
Mean	3	3	2	3
SD	2.07	1.53	1.40	1.93
Minimum	0	0	0	0
1st quartile	2.0	2.0	2.0	2.0
Median	2.0	2.0	2.0	2.0
3rd quartile	3.0	4.0	2.0	3.0
Maximum	20	8	8	20

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis

NOVARTIS

Full analysis set Arm B				
	P-MF (N=318)	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
caused by myelofibrosis, n (%)				
No	501 (42.6)	92 (61.3)	66 (54.1)	659 (45.5)
Yes	676 (57.4)	58 (38.7)	56 (45.9)	790 (54.5)
caused by Jakavi therapy, n (%)				
No	1139 (96.8)	146 (97.3)	120 (98.4)	1405 (97.0)
Yes	38 (3.2)	4 (2.7)	2 (1.6)	44 (3.0)
iron overload, n (%)				
No	501 (49.9)	61 (80.3)	59 (64.8)	621 (53.0)
Yes	503 (50.1)	15 (19.7)	32 (35.2)	550 (47.0)
missing	173	74	31	278

Full analysis set Arm B				
	P-MF (N=318)	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
number Eks since last examination				
n	853	72	82	1007
Mean	4	3	4	4
SD	4.88	2.52	3.54	4.66
Minimum	0	0	1	0
1st quartile	2.0	2.0	2.0	2.0
Median	2.0	2.0	2.0	2.0
3rd quartile	4.0	2.0	4.0	4.0
Maximum	57	14	20	57
actual EK/month				
n	838	49	67	954
Mean	2	2	2	2
SD	1.47	1.01	0.83	1.42
Minimum	0	0	0	0
1st quartile	2.0	2.0	2.0	2.0
Median	2.0	2.0	2.0	2.0
3rd quartile	2.0	2.0	2.0	2.0
Maximum	12	4	4	12
P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis, PET-MF = Post essential thrombocytemia myelofibrosis				

NOVARTIS

Number of patients with concomitant medications

Table 10-11: Concomitant medication after start of ruxolitinib (≥10 patients in any arm) (FAS)

ATC class (level 1) Name	Arm A (N=479) n (%)	Arm B (N= 464) n (%)
Patients with at least one specification	**217 (45.3)**	**213 (45.9)**
Alimentary tract and metabolism	**76 (15.9)**	**57 (12.3)**
Pantoprazole	17 (3.6)	10 (2.2)
Pantoprazole sodium sesquihydrate	15 (3.1)	9 (1.9)
Colecalciferol	7 (1.5)	12 (2.6)
Blood and blood forming organs	**75 (15.7)**	**84 (18.1)**
Acetylsalicylic acid	21 (4.4)	12 (2.6)
Epoetin alfa	9 (1.9)	12 (2.6)
Nervous system	**68 (14.2)**	**54 (11.6)**
Metamizole Sodium	26 (5.4)	16 (3.5)
Cardiovascular system	**63 (13.2)**	**66 (14.2)**
Torasemide	23 (4.8)	26 (5.6)
Ramipril	14 (2.9)	12 (2.6)
Metoprolol	10 (2.1)	3 (0.7)
Bisoprolol	9 (1.9)	10 (2.2)
Antiinfectives for systemic use	**61 (12.7)**	**33 (7.1)**
Cefuroxime	10 (2.1)	2 (0.4)
Ciprofolixacin	10 (2.1)	8 (1.7)
Musculo-Skeletal system	**46 (9.6)**	**30 (6.5)**
Allopurinol	23 (4.8)	12 (2.6)
Ibuprofen	17 (3.6)	9 (1.9)
Antineoplastic and immunomodulating agents	**41 (8.6)**	**34 (7.3)**
Hydroxycarbamide	30 (6.3)	20 (4.3)
Various	**36 (7.5)**	**51 (11.0)**
Deferasirox	32 (6.7)	42 (9.1)
Systemic hormonal preparations, excl. Sex hormones and insulins	**23 (4.8)**	**15 (3.2)**
Prednisolone	10 (2.1)	8 (1.7)
Respiratory system	**10 (2.1)**	**11 (2.4)**

Abbreviations: ATC = Anatomical Therapeutic Chemical, FAS = full analysis set
Data are sorted by descending order in Arm A

NOVARTIS

Eastern Cooperative Oncology Group (ECOG) performance status

Full analysis set Arm A					
Visit	**Value**	**P-MF (N=325)**	**PPV-MF (N=99)**	**PET-MF (N=55)**	**Total (N=479)**
Baseline visit	ECOG, n (%)				
	0	97 (31.7)	24 (25.5)	16 (29.1)	137 (30.1)
	1	167 (54.6)	47 (50.0)	29 (52.7)	243 (53.4)
	2	37 (12.1)	22 (23.4)	9 (16.4)	68 (14.9)
	3	5 (1.6)	1 (1.1)	1 (1.8)	7 (1.5)
	4	0	0	0	0
	5	0	0	0	0
	-missing	19	5	0	24
FU Month 1	0	85 (34.4)	21 (28.4)	11 (22.9)	117 (31.7)
	1	130 (52.6)	36 (48.6)	30 (62.5)	196 (53.1)
	2	29 (11.7)	15 (20.3)	6 (12.5)	50 (13.6)
	3	3 (1.2)	2 (2.7)	1 (2.1)	6 (1.6)
	4	0	0	0	0
	5	0	0	0	0
	-missing	38	8	1	47
FU Month 2	0	78 (34.8)	21 (29.6)	12 (29.3)	111 (33.0)
	1	114 (50.9)	36 (50.7)	21 (51.2)	171 (50.9)

NOVARTIS

Full analysis set Arm A

Visit	Value	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
	2	29 (12.9)	13 (18.3)	8 (19.5)	50 (14.9)
	3	3 (1.3)	1 (1.4)	0	4 (1.2)
	4	0	0	0	0
	5	0	0	0	0
	-missing	37	7	3	47
FU Month 3	0	81 (31.5)	33 (40.7)	15 (34.9)	129 (33.9)
	1	141 (54.9)	35 (43.2)	21 (48.8)	197 (51.7)
	2	33 (12.8)	12 (14.8)	6 (14.0)	51 (13.4)
	3	2 (0.8)	1 (1.2)	1 (2.3)	4 (1.0)
	4	0	0	0	0
	5	0	0	0	0
	-missing	31	7	2	40
FU Month 6	0	97 (39.9)	30 (42.3)	12 (28.6)	139 (39.0)
	1	111 (45.7)	35 (49.3)	25 (59.5)	171 (48.0)
	2	28 (11.5)	6 (8.5)	5 (11.9)	39 (11.0)
	3	6 (2.5)	0	0	6 (1.7)
	4	1 (0.4)	0	0	1 (0.3)
	5	0	0	0	0
	-missing	21	5	2	28

Full analysis set Arm A

Visit	Value	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
FU Month 9	0	77 (36.8)	27 (40.9)	9 (24.3)	113 (36.2)
	1	95 (45.5)	34 (51.5)	24 (64.9)	153 (49.0)
	2	32 (15.3)	5 (7.6)	4 (10.8)	41 (13.1)
	3	4 (1.9)	0	0	4 (1.3)
	4	1 (0.5)	0	0	1 (0.3)
	5	0	0	0	0
	-missing	20	10	1	31
FU Month 12	0	75 (37.5)	30 (47.6)	10 (32.3)	115 (39.1)
	1	96 (48.0)	25 (39.7)	14 (45.2)	135 (45.9)
	2	26 (13.0)	8 (12.7)	7 (22.6)	41 (13.9)
	3	3 (1.5)	0	0	3 (1.0)
	4	0	0	0	0
	5	0	0	0	0
	-missing	18	8	4	30
FU Month 18	0	67 (39.6)	29 (48.3)	8 (25.0)	104 (39.8)
	1	84 (49.7)	27 (45.0)	18 (56.3)	129 (49.4)
	2	16 (9.5)	4 (6.7)	6 (18.8)	26 (10.0)
	3	2 (1.2)	0	0	2 (0.8)
	4	0	0	0	0

NOVARTIS

Full analysis set Arm A

Visit	Value	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
	5	0	0	0	0
	-missing	18	8	1	27
FU Month 24	0	67 (45.6)	29 (56.9)	9 (36.0)	105 (47.1)
	1	65 (44.2)	19 (37.3)	12 (48.0)	96 (43.0)
	2	15 (10.2)	3 (5.9)	4 (16.0)	22 (9.9)
	3	0	0	0	0
	4	0	0	0	0
	5	0	0	0	0
	-missing	13	7	2	22
FU Month 30	0	57 (43.8)	19 (38.0)	11 (44.0)	87 (42.4)
	1	59 (45.4)	25 (50.0)	11 (44.0)	95 (46.3)
	2	12 (9.2)	4 (8.0)	2 (8.0)	18 (8.8)
	3	2 (1.5)	2 (4.0)	1 (4.0)	5 (2.4)
	4	0	0	0	0
	5	0	0	0	0
	-missing	7	7	1	15
FU Month 36	0	52 (45.2)	15 (34.1)	9 (37.5)	76 (41.5)
	1	51 (44.3)	24 (54.5)	10 (41.7)	85 (46.4)

Full analysis set Arm A

Visit	Value	P-MF (N=325)	PPV-MF (N=99)	PET-MF (N=55)	Total (N=479)
	2	10 (8.7)	4 (9.1)	5 (20.8)	19 (10.4)
	3	2 (1.7)	1 (2.3)	0	3 (1.6)
	4	0	0	0	0
	5	0	0	0	0
	-missing	13	8	1	22

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis
PET-MF = Post essential thrombocytemia myelofibrosis

NOVARTIS

Full analysis set Arm B					
Visit	**Value**	**P-MF (N=318)**	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
Baseline visit	ECOG, n (%)				
	0	125 (42.8)	48 (49.5)	18 (40.9)	191 (44.1)
	1	147 (50.3)	42 (43.3)	21 (47.7)	210 (48.5)
	2	19 (6.5)	6 (6.2)	4 (9.1)	29 (6.7)
	3	1 (0.3)	1 (1.0)	1 (2.3)	3 (0.7)
	4	0	0	0	0
	5	0	0	0	0
	-missing	26	2	3	31
FU Month 1	0	88 (39.3)	34 (53.1)	8 (27.6)	130 (41.0)
	1	112 (50.0)	23 (35.9)	17 (58.6)	152 (47.9)
	2	22 (9.8)	7 (10.9)	4 (13.8)	33 (10.4)
	3	2 (0.9)	0	0	2 (0.6)
	4	0	0	0	0
	5	0	0	0	0
	-missing	24	6	8	38
FU Month 2	0	76 (39.0)	30 (49.2)	9 (34.6)	115 (40.8)
	1	102 (52.3)	27 (44.3)	15 (57.7)	144 (51.1)

Full analysis set Arm B

Visit	Value	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
	2	16 (8.2)	4 (6.6)	2 (7.7)	22 (7.8)
	3	1 (0.5)	0	0	1 (0.4)
	4	0	0	0	0
	5	0	0	0	0
	-missing	34	11	7	52
FU Month 3	0	109 (44.7)	37 (49.3)	14 (43.8)	160 (45.6)
	1	117 (48.0)	33 (44.0)	15 (46.9)	165 (47.0)
	2	15 (6.1)	4 (5.3)	3 (9.4)	22 (6.3)
	3	3 (1.2)	1 (1.3)	0	4 (1.1)
	4	0	0	0	0
	5	0	0	0	0
	-missing	28	5	6	39
FU Month 6	0	105 (44.1)	41 (50.6)	14 (42.4)	160 (45.5)
	1	110 (46.2)	34 (42.0)	17 (51.5)	161 (45.7)
	2	21 (8.8)	5 (6.2)	2 (6.1)	28 (8.0)
	3	2 (0.8)	1 (1.2)	0	3 (0.9)
	4	0	0	0	0
	5	0	0	0	0
	-missing	23	9	4	36

NOVARTIS

Full analysis set Arm B					
Visit	**Value**	**P-MF (N=318)**	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
FU Month 9	0	101 (45.5)	36 (45.6)	11 (37.9)	148 (44.8)
	1	104 (46.8)	36 (45.6)	16 (55.2)	156 (47.3)
	2	15 (6.8)	6 (7.6)	1 (3.4)	22 (6.7)
	3	2 (0.9)	1 (1.3)	1 (3.4)	4 (1.2)
	4	0	0	0	0
	5	0	0	0	0
	-missing	21	5	6	32
FU Month 12	0	92 (42.4)	39 (51.3)	11 (37.9)	142 (44.1)
	1	105 (48.4)	29 (38.2)	15 (51.7)	149 (46.3)
	2	16 (7.4)	6 (7.9)	2 (6.9)	24 (7.5)
	3	4 (1.8)	2 (2.6)	1 (3.4)	7 (2.2)
	4	0	0	0	0
	5	0	0	0	0
	-missing	25	6	6	37
FU Month 18	0	83 (41.7)	37 (51.4)	11 (39.3)	131 (43.8)
	1	99 (49.7)	29 (40.3)	15 (53.6)	143 (47.8)
	2	13 (6.5)	5 (6.9)	2 (7.1)	20 (6.7)
	3	4 (2.0)	1 (1.4)	0	5 (1.7)
	4	0	0	0	0

Full analysis set Arm B

Visit	Value	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
	5	0	0	0	0
	-missing	15	7	5	27
FU Month 24	0	67 (38.5)	31 (49.2)	12 (48.0)	110 (42.0)
	1	88 (50.6)	29 (46.0)	13 (52.0)	130 (49.6)
	2	17 (9.8)	2 (3.2)	0	19 (7.3)
	3	1 (0.6)	1 (1.6)	0	2 (0.8)
	4	1 (0.6)	0	0	1 (0.4)
	5	0	0	0	0
	-missing	19	9	5	33
FU Month 30	0	68 (47.6)	30 (48.4)	10 (47.6)	108 (47.8)
	1	58 (40.6)	27 (43.5)	9 (42.9)	94 (41.6)
	2	17 (11.9)	4 (6.5)	2 (9.5)	23 (10.2)
	3	0	1 (1.6)	0	1 (0.4)
	4	0	0	0	0
	5	0	0	0	0
	-missing	24	6	8	38
FU Month 36	0	51 (41.5)	30 (54.5)	9 (45.0)	90 (45.5)
	1	55 (44.7)	20 (36.4)	9 (45.0)	84 (42.4)

Full analysis set Arm B

Visit	Value	P-MF (N=318)	PPV-MF (N=99)	PET-MF (N=47)	Total (N=464)
	2	16 (13.0)	4 (7.3)	2 (10.0)	22 (11.1)
	3	1 (0.8)	1 (1.8)	0	2 (1.0)
	4	0	0	0	0
	5	0	0	0	0
	-missing	31	5	5	41

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis
PET-MF = Post essential thrombocytemia myelofibrosis

Spleen size (or volume) reduction

Table 10-16: Change in palpable spleen length - Arm A and Arm B (FAS)

	Enlarged spleen palpable,% (n)	Median spleen length [cm] (range) n (pats with assessment)*	Median difference to BL [cm] (range) n (pats with assessment)
Arm A			
BL visit	83.0 (239/288)	13.5 (0.0; 30.0) (n=175)	
Month1	83.9 (78/93)	12.0 (0.0; 29.0) (n=61)	-3.0 (-12.0; 8.0) (n=48)
Month 2	72.6 (45/64)	6.0 (0.0; 30.0) (n=35)	-4.1 (-13.0; 2.0) (n=30)
Month 3	77.8 (105/136)	10.0 (1.5; 25.0) (n=72)	-3.0 (-20.0; 8.5) (n=56)
Month 6	68.5 (87/129)	7.0 (0.0; 84.0) (n=63)	-4.0 (-12.0; 8.0) (n=46)
Month 9	66.7 (80/120)	9.0 (0.0; 30.0) (n=59)	-4.0 (-15.0; 9.0) (n=43)
Month 12	59.2 (71/120)	10.5 (0.0; 26.0) (n=54)	-3.0 (-13.0; 14.0) (n=43)
Month 18	64.2 (61/95)	7.0 (2.0; 31.0) (n=55)	-4.0 (-18.0; 17.0) (n=41)
Month 24	57.6 (49/85)	7.0 (0.0; 23.0) (n=35)	-3.0 (-16.0; 7.0) (n=22)
Month 30	66.7 (46/69)	8.0 (2.0; 25.0) (n=29)	-2.5 (-19.0; 10.6) (n=20)
Month 36	49.0 (25/52)	7.5 (2.0; 20.0) (n=22)	-7.0 (-12.5; 7.0) (n=13)
Last post BL visit	68.4 (238/350)	11.0 (1.0; 31.0) (n=175)	-2.0 (-20.0; 18.0) (n=115)
Arm B			
BL visit	60.5 (107/178)	13.0 (0.0; 26.0) (n=64)	
Month1	53.8 (28/53)	10.0 (0.0; 18.0) (n=18)	0.0 (-3.0; 0.0) (n=13)
Month 2	53.5 (23/43)	8.7 (1.0; 18.0) (n= 14)	0.0 (-3.0; 0.0) (n=8)
Month 3	43.7 (38/88)	11.0 (1.5; 25.0) (n=29)	0.0 (-5.0; 8.0) (n=13)
Month 6	49.4 (41/86)	7.5 (1.0; 19.0) (n=26)	0.0 (-4.0; 2.0) (n=15)
Month 9	44.6 (37/86)	9.0 (0.0; 23.0) (n=23)	0.0 (-4.0; 9.5) (n=13)
Month 12	36.7 (29/80)	12.6 (0.0; 21.0) (n=21)	0.0 (-5.0; 10.3) (n=14)
Month 18	48.6 (36/75)	8.0 (0.0; 21.0) (n=21)	-0.5 (-4.0; 2.0) (n=14)
Month 24	42.6 (29/68)	5.0 (0.0; 25.0) (n=18)	0.0 (-18.0; 6.0) (n=11)
Month 30	41.8 (33/79)	7.0 (0.0; 21.0) (n=17)	-1.9 (-4.0; 4.0) (n= 9)
Month 36	35.6 (21/59)	6.0 (0.0; 19.0) (n=15)	-1.0 (-6.0; 7.0) (n= 7)
Last post BL visit	50.7 (141/282)	11.0 (1.0; 25.0) (n=81)	0.0 (18.0; 10.3) (n=31)

Abbreviations: BL = baseline, FAS = Full Analysis Set

* patients with implausible spleen values were set to missing for this analysis

NOVARTIS

Change in the number of patients with constitutional symptoms

Full analysis set Arm A				
Symptom	**P-MF (N=325)**	**PPV-MF (N=99)**	**PET-MF (N=55)**	**Total (N=479)**
Constitutional symptoms, n (%)				
Baseline visit	212 (65.2%)	66 (66.7%)	35 (63.6%)	313 (65.3%)
FU Month 1	113 (39.6%)	39 (47.6%)	20 (40.8%)	172 (41.3%)
FU Month 2	88 (33.7%)	29 (37.2%)	19 (43.2%)	136 (35.5%)
FU Month 3	80 (27.8%)	36 (40.9%)	16 (35.6%)	132 (31.4%)
FU Month 6	71 (26.9%)	26 (34.2%)	14 (31.8%)	111 (28.9%)
FU Month 9	58 (25.3%)	20 (26.3%)	10 (26.3%)	88 (25.7%)
FU Month 12	43 (19.7%)	16 (22.5%)	7 (20.0%)	66 (20.4%)
FU Month 18	39 (20.9%)	12 (17.6%)	10 (30.3%)	61 (21.2%)
FU Month 24	37 (23.1%)	10 (17.2%)	6 (22.2%)	53 (21.6%)
FU Month 30	26 (19.0%)	13 (22.8%)	5 (19.2%)	44 (20.0%)
FU Month 36	21 (16.4%)	17 (32.7%)	6 (24.0%)	44 (21.5%)

Full analysis set Arm B				
Symptom	**P-MF (N=318)**	**PPV-MF (N=99)**	**PET-MF (N=47)**	**Total (N=464)**
Constitutional symptoms, n (%)				
Baseline visit	132 (41.5%)	26 (26.3%)	22 (46.8%)	180 (38.8%)
FU Month 1	85 (34.3%)	17 (24.3%)	15 (40.5%)	117 (33.0%)
FU Month 2	59 (25.8%)	16 (22.2%)	10 (30.3%)	85 (25.4%)
FU Month 3	83 (30.5%)	18 (22.5%)	11 (28.9%)	112 (28.7%)
FU Month 6	61 (23.4%)	10 (11.1%)	9 (24.3%)	80 (20.6%)
FU Month 9	47 (19.3%)	14 (16.7%)	9 (25.7%)	70 (19.3%)
FU Month 12	43 (17.8%)	8 (9.8%)	8 (22.9%)	59 (16.4%)
FU Month 18	40 (18.7%)	5 (6.3%)	7 (21.2%)	52 (16.0%)
FU Month 24	43 (22.3%)	9 (12.5%)	10 (33.3%)	62 (21.0%)
FU Month 30	24 (14.4%)	5 (7.4%)	4 (13.8%)	33 (12.5%)
FU Month 36	22 (14.3%)	5 (8.3%)	5 (20.0%)	32 (13.4%)

Abbreviations: PMF = Primary Myelofibrosis, PPV-MF = Post Polycythemia Vera Myelofibrosis, PET-MF = Post-Essential Thrombocytemia Myelofibrosis

Safety and tolerability

Please refer to the safety section to see the number of Adverse Events, serious Adverse Events, Adverse Drug reaction and serious Adverse Drug Reactions.

Assessment of the Quality of Life (QoL) : Myeloproliferative Neoplasm - Symptom Assessment Form (MPN-SAF)

Table 10-21: Course of MPN-SAF total symptom score* (FAS)

Visit	n	Mean ± SD	Min	Median	Max	probt
Arm A (N=479)						
Baseline	332	28.5 ± 18.9	0.0	25.6	93.0	-
Difference to baseline						
Month 1	242	-6.8 ± 14.6	-72.2	-5.1	33.1	<.0001
Month 3	238	-7.8 ± 17.0	-70.7	-6.2	34.2	<.0001
Month 6	211	-7.6 ± 16.4	-74.2	-4.8	51.2	<.0001
Month 12	174	-7.7 ± 15.3	-75.4	-6.5	44.7	<.0001
Month 24	120	-5.2 ± 18.1	-70.4	-2.9	36.2	0.0022
Month 36	91	-4.4 ± 16.7	-75.4	-3.9	45.7	0.0150
Arm B (N=464)						
Baseline	284	21.2 ± 16.5	0.0	18.2	78.7	-
Difference to baseline						
Month 1	181	-1.8 ± 10.1	-46.4	-1.4	22.4	0.0146
Month 3	172	-0.6 ± 12.3	-44.0	0.0	41.3	0.5329
Month 6	171	-1.5 ± 12.5	-45.7	-0.8	37.8	0.1267
Month 12	167	-2.1 ± 12.6	-48.3	0.0	29.3	0.0312
Month 24	117	0.5 ± 15.6	-50.2	0.2	46.3	0.7314
Month 36	89	0.3 ± 13.5	-52.6	1.0	36.3	0.8176

Abbreviations: FAS = full analysis set, MPN-SAF = Myeloproliferative Neoplasm-Symptom Assessment Form
probt: 1-sample t-test (Ho: mean=0)
*Score ranges from 0-10 with score 0= absent symptom/no issue, score 10 = worst imaginable symptom

NOVARTIS

Assessment of the Quality of Life (QoL) : Short Form-36 (SF-36)

Table 10-24: SF-36* summary scores – Arm A and Arm B (FAS)

Arm A (N=479)	Baseline	Month 12	Month 24	Month 36
Physical component summary				
n, mean ± SD	332, 37.8 ± 10.2	203, 40.5 ± 10.6	153, 40.9 ± 10.8	116, 40.9 ± 11.1
median (range)	36.6 (14.9; 61.2)	40.3 (17.1; 60.2)	40.9 (17.9; 60.5)	42.1 (13.7; 60.3)
Difference to BL				
n, mean ± SD	-	175, 1.9 ± 9.3	133, 1.6 ± 10.2	96, 1.5 ± 11.1
median (range)		1.1 (-17.3; 34.7)	0.6 (-20.7; 36.6)	0.8 (-28.1; 32.1)
Mental component summary				
n, mean ± SD	332, 39.4 ± 14.7	203, 44.1 ± 12.1	153, 43.4 ± 13.0	116, 43.4 ± 12.8
median (range)	41.7 (4.3; 70.5)	46.2 (12.4; 67.4)	46.3 (11.2; 67.6)	46.6 (10.9; 66.0)
Difference to BL				
n, mean ± SD	-	175, 2.6 ± 13.6	133, 2.3 ± 13.9	96, -0.3 ± 11.7
median (range)		0.8 (-27.9; 49.9)	1.2 (-22.9; 50.0)	1.2 (-34.9; 34.9)
Arm B (N=464)	**Baseline**	**Month 12**	**Month 24**	**Month 36**
Physical component summary				
n, mean ± SD	283, 39.6 ± 10.2	200, 39.9 ± 10.5	158, 39.8 ± 10.2	107, 39.6 ± 9.5
median (range)	39.4 (17.9; 62.3)	40.7 (15.2; 63.4)	39.3 (17.5; 57.8)	39.0 (16.3; 58.1)
Difference to BL				
n, mean ± SD	-	162, -0.8 ± 8.5	129, -1.9 ± 8.3	92, -1.3 ± 9.0
median (range)		-0.8 (-24.0; 25.8)	-1.8 (-24.8; 20.8)	-1.5 (-27.0; 21.9)
Mental component summary				
n, mean ± SD	283, 44.2 ± 13.6	200, 45.2 ± 13.7	158, 45.0 ± 13.6	107, 43.1 ± 14.0
median (range)	45.9 (8.4; 68.2)	48.6 (4.9; 71.1)	47.8 (3.3; 66.3)	46.2 (13.4; 64.5)
Difference to BL		1		
n, mean ± SD	-	162, 0.4 ± 12.0	129, -1.9 ± 11.9	92, -2.2 ± 13.0
median (range)		-0.3 (-49.0; 34.0)	-0.3 (-47.9; 31.3)	-1.0 (-39.2; 32.4)

Abbreviations: FAS = full analysis set, SF-36 = short form health survey 36 items
*SF-36 normed by German population and myelofibrosis type, score ranges from 0-100 with 0=maximum disability, 100=no disability

Overall Survival

Full analysis set Arm A			
	P-MF (N=325)	**PPV-MF (N=99)**	**PET-MF (N=55)**
6 months	275	86	46
12 months	230	75	38
18 months	187	69	34
24 months	169	61	30
30 months	142	60	29
36 months	83	41	21
P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis *PET-MF = Post essential thrombocytemia myelofibrosis*			

Full analysis set Arm B			
	P-MF (N=318)	**PPV-MF (N=99)**	**PET-MF (N=47)**
6 months	283	93	40
12 months	249	89	36
18 months	225	81	35
24 months	201	77	32

Full analysis set Arm B			
	P-MF (N=318)	**PPV-MF (N=99)**	**PET-MF (N=47)**
30 months	174	70	30
36 months	111	43	16

P-MF = Primary myelofibrosis, PPV-MF = Post Polycythemia Vera-myelofibrosis
PET-MF = Post essential thrombocytemia myelofibrosis

.

Secondary Outcome Result(s)

No data identified.

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

NOVARTIS

Safety Results

Table 10-27: Summary of adverse events per treatment arm (FAS)

	Arm A (N=479)	Arm B (N=464)
Number of patients with: n (%)		
AE	433 (90.4)	400 (86.2)
nsAE	400 (83.5)	347 (74.8)
nsADR	307 (64.1)	228 (49.1)
nsAEnr	324 (67.6)	287 (61.9)
SAE	254 (53.0)	242 (52.2)
SADR	131 (27.3)	97 (20.9)
SAEnr	223 (46.6)	210 (45.3)
Number of events:		
AE	3437	2393
nsAE	2271	1685
nsADR	916	584
nsAEnr	1355	1101
SAE	1166	708
SADR	405	224
SAEnr	761	484

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, FAS = Full Analysis Set, nr = not related, ns = non-serious, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event
AEs without information on relation to study drug or seriousness were considered as related or serious.

NOVARTIS

Table 10-30: Adverse events in Arm A by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1) PT							
Number of patients with at least one AE, n (%)	**324 (67.6)**	**307 (64.1)**	**400 (83.5)**	**223 (46.6)**	**131 (27.3)**	**254 (53.0)**	**433 (90.4)**
Blood and lymphatic system disorders	**106 (22.1)**	**187 (39.0)**	**234 (48.9)**	**31 (6.5)**	**32 (6.7)**	**58 (12.1)**	**260 (54.3)**
Anemia	46 (9.6)	102 (21.3)	137 (28.6)	12 (2.5)	13 (2.7)	25 (5.2)	155 (32.4)
Thrombocytopenia	21 (4.4)	116 (24.2)	133 (27.8)	5 (1.0)	11 (2.3)	16 (3.3)	139 (29.0)
Splenomegaly	34 (7.1)	13 (2.7)	44 (9.2)	3 (0.6)	3 (0.6)	6 (1.3)	50 (10.4)
Leukocytosis	8 (1.7)	5 (1.0)	12 (2.5)	4 (0.8)	2 (0.4)	6 (1.3)	17 (3.5)
Thrombocytosis	9 (1.9)	2 (0.4)	11 (2.3)	1 (0.2)	-	1 (0.2)	12 (2.5)
Leukopenia	3 (0.6)	4 (0.8)	7 (1.5)	-	-	-	7 (1.5)
Hemolysis	2 (0.4)	3 (0.6)	5 (1.0)	-	-	-	5 (1.0)
General disorders and administration site conditions	**116 (24.2)**	**67 (14.0)**	**161 (33.6)**	**64 (13.4)**	**28 (5.8)**	**81 (16.9)**	**213 (44.5)**
Fatigue	42 (8.8)	23 (4.8)	63 (13.2)	2 (0.4)	1 (0.2)	3 (0.6)	66 (13.8)
Asthenia	30 (6.3)	27 (5.6)	53 (11.1)	4 (0.8)	5 (1.0)	9 (1.9)	62 (12.9)
General physical health deterioration	13 (2.7)	3 (0.6)	16 (3.3)	20 (4.2)	5 (1.0)	23 (4.8)	37 (7.7)
Pyrexia	13 (2.7)	3 (0.6)	16 (3.3)	11 (2.3)	5 (1.0)	16 (3.3)	32 (6.7)
Oedema peripheral	10 (2.1)	3 (0.6)	13 (2.7)	7 (1.5)	2 (0.4)	9 (1.9)	21 (4.4)
Death	-	-	-	14 (2.9)	6 (1.3)	20 (4.2)	20 (4.2)
Pain	13 (2.7)	2 (0.4)	15 (3.1)	2 (0.4)	1 (0.2)	3 (0.6)	17 (3.5)
Chills	7 (1.5)	1 (0.2)	8 (1.7)	-	1 (0.2)	1 (0.2)	9 (1.9)
Multiple organ dysfunction syndrome	-	-	-	7 (1.5)	1 (0.2)	8 (1.7)	8 (1.7)
Gait disturbance	3 (0.6)	-	3 (0.6)	2 (0.4)	-	2 (0.4)	5 (1.0)
Infections and infestations	**109 (22.8)**	**21 (4.4)**	**122 (25.5)**	**78 (16.3)**	**26 (5.4)**	**91 (19.0)**	**182 (38.0)**
Pneumonia	12 (2.5)	1 (0.2)	13 (2.7)	23 (4.8)	6 (1.3)	28 (5.8)	38 (7.9)
Urinary tract infection	20 (4.2)	-	20 (4.2)	10 (2.1)	8 (1.7)	17 (3.5)	35 (7.3)
Nasopharyngitis	23 (4.8)	2 (0.4)	25 (5.2)	-	-	-	25 (5.2)
Herpes zoster	6 (1.3)	11 (2.3)	17 (3.5)	5 (1.0)	-	5 (1.0)	21 (4.4)
Bronchitis	18 (3.8)	-	18 (3.8)	1 (0.2)	-	1 (0.2)	19 (4.0)
Sepsis	-	-	-	12 (2.5)	4 (0.8)	16 (3.3)	16 (3.3)
Infection	6 (1.3)	-	6 (1.3)	3 (0.6)	3 (0.6)	6 (1.3)	12 (2.5)
Cystitis	10 (2.1)	-	10 (2.1)	-	-	-	10 (2.1)

NOVARTIS

Table 10-30: Adverse events in Arm A by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1)							
PT							
Upper respiratory tract infection	7 (1.5)	-	7 (1.5)	1 (0.2)	-	1 (0.2)	8 (1.7)
Gastroenteritis	4 (0.8)	1 (0.2)	5 (1.0)	2 (0.4)	-	2 (0.4)	7 (1.5)
Urosepsis	-	-	-	5 (1.0)	2 (0.4)	7 (1.5)	7 (1.5)
Peritonitis	-	-	-	3 (0.6)	3 (0.6)	6 (1.3)	6 (1.3)
Respiratory tract infection	5 (1.0)	-	5 (1.0)	-	-	-	5 (1.0)
Septic shock	-	-	-	3 (0.6)	2 (0.4)	5 (1.0)	5 (1.0)
Investigations	**72 (15.0)**	**79 (16.5)**	**136 (28.4)**	**29 (6.1)**	**52 (10.9)**	**69 (14.4)**	**173 (36.1)**
Hemoglobin decreased	12 (2.5)	19 (4.0)	29 (6.1)	7 (1.5)	23 (4.8)	30 (6.3)	56 (11.7)
Weight increased	4 (0.8)	23 (4.8)	27 (5.6)	-	-	-	27 (5.6)
Weight decreased	13 (2.7)	5 (1.0)	18 (3.8)	2 (0.4)	2 (0.4)	4 (0.8)	22 (4.6)
C-reactive protein increased	4 (0.8)	4 (0.8)	8 (1.7)	4 (0.8)	9 (1.9)	13 (2.7)	21 (4.4)
Blood creatinine increased	12 (2.5)	2 (0.4)	12 (2.5)	2 (0.4)	2 (0.4)	4 (0.8)	16 (3.3)
White blood cell count increased	2 (0.4)	2 (0.4)	4 (0.8)	3 (0.6)	10 (2.1)	11 (2.3)	15 (3.1)
Platelet count decreased	2 (0.4)	2 (0.4)	4 (0.8)	-	9 (1.9)	9 (1.9)	13 (2.7)
Blood lactate dehydrogenase increased	6 (1.3)	-	6 (1.3)	2 (0.4)	3 (0.6)	5 (1.0)	11 (2.3)
Hematocrit decreased	-	6 (1.3)	6 (1.3)	-	4 (0.8)	4 (0.8)	10 (2.1)
Gamma-glutamyltransferase increased	3 (0.6)	5 (1.0)	8 (1.7)	-	1 (0.2)	1 (0.2)	9 (1.9)
Red blood cell count decreased	2 (0.4)	2 (0.4)	4 (0.8)	-	5 (1.0)	5 (1.0)	9 (1.9)
Serum ferritin increased	5 (1.0)	3 (0.6)	8 (1.7)	-	1 (0.2)	1 (0.2)	9 (1.9)
Blood uric acid increased	4 (0.8)	1 (0.2)	5 (1.0)	2 (0.4)	1 (0.2)	3 (0.6)	8 (1.7)
Blood potassium increased	3 (0.6)	-	3 (0.6)	-	3 (0.6)	3 (0.6)	6 (1.3)
Gastrointestinal disorders	**81 (16.9)**	**54 (11.3)**	**116 (24.2)**	**41 (8.6)**	**18 (3.8)**	**50 (10.4)**	**142 (29.6)**
Diarrhoea	24 (5.0)	16 (3.3)	37 (7.7)	8 (1.7)	4 (0.8)	11 (2.3)	45 (9.4)
Nausea	15 (3.1)	15 (3.1)	30 (6.3)	2 (0.4)	1 (0.2)	3 (0.6)	32 (6.7)
Abdominal pain	13 (2.7)	11 (2.3)	22 (4.6)	7 (1.5)	-	7 (1.5)	28 (5.8)
Constipation	7 (1.5)	4 (0.8)	11 (2.3)	4 (0.8)	-	4 (0.8)	15 (3.1)
Abdominal pain upper	8 (1.7)	3 (0.6)	11 (2.3)	2 (0.4)	2 (0.4)	4 (0.8)	14 (2.9)
Vomiting	6 (1.3)	2 (0.4)	8 (1.7)	4 (0.8)	2 (0.4)	5 (1.0)	13 (2.7)
Abdominal discomfort	7 (1.5)	4 (0.8)	10 (2.1)	1 (0.2)	1 (0.2)	2 (0.4)	12 (2.5)

NOVARTIS

Table 10-30: Adverse events in Arm A by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1)							
PT							
Ascites	2 (0.4)	-	2 (0.4)	6 (1.3)	-	6 (1.3)	8 (1.7)
Dyspepsia	5 (1.0)	1 (0.2)	6 (1.3)	1 (0.2)	-	1 (0.2)	7 (1.5)
Gastrooesophageal reflux disease	4 (0.8)	2 (0.4)	6 (1.3)	1 (0.2)	-	1 (0.2)	7 (1.5)
Abdominal distension	4 (0.8)	1 (0.2)	5 (1.0)	-	1 (0.2)	1 (0.2)	6 (1.3)
Flatulence	2 (0.4)	3 (0.6)	5 (1.0)	1 (0.2)	-	1 (0.2)	6 (1.3)
Respiratory, thoracic and mediastinal disorders	**65 (13.6)**	**24 (5.0)**	**82 (17.1)**	**37 (7.7)**	**19 (4.0)**	**52 (10.9)**	**118 (24.6)**
Dyspnoea	23 (4.8)	8 (1.7)	30 (6.3)	12 (2.5)	6 (1.3)	15 (3.1)	42 (8.8)
Epistaxis	17 (3.5)	10 (2.1)	26 (5.4)	5 (1.0)	1 (0.2)	6 (1.3)	32 (6.7)
Dyspnoea exertional	13 (2.7)	6 (1.3)	19 (4.0)	1 (0.2)	-	1 (0.2)	20 (4.2)
Cough	15 (3.1)	3 (0.6)	18 (3.8)	1 (0.2)	-	1 (0.2)	19 (4.0)
Pulmonary embolism	-	1 (0.2)	1 (0.2)	9 (1.9)	4 (0.8)	13 (2.7)	14 (2.9)
Pleural effusion	-	-	-	5 (1.0)	3 (0.6)	8 (1.7)	8 (1.7)
Respiratory failure	-	1 (0.2)	1 (0.2)	3 (0.6)	2 (0.4)	5 (1.0)	6 (1.3)
Oropharyngeal pain	4 (0.8)	1 (0.2)	5 (1.0)	-	-	-	5 (1.0)
Pulmonary oedema	-	-	-	4 (0.8)	1 (0.2)	5 (1.0)	5 (1.0)
Nervous system disorders	**50 (10.4)**	**51 (10.6)**	**89 (18.6)**	**26 (5.4)**	**11 (2.3)**	**31 (6.5)**	**112 (23.4)**
Dizziness	20 (4.2)	23 (4.8)	42 (8.8)	3 (0.6)	1 (0.2)	4 (0.8)	46 (9.6)
Headache	9 (1.9)	23 (4.8)	32 (6.7)	2 (0.4)	-	2 (0.4)	33 (6.9)
Paraesthesia	2 (0.4)	4 (0.8)	6 (1.3)	-	1 (0.2)	1 (0.2)	7 (1.5)
Polyneuropathy	3 (0.6)	2 (0.4)	5 (1.0)	-	1 (0.2)	1 (0.2)	6 (1.3)
Hypoaesthesia	-	4 (0.8)	4 (0.8)	-	1 (0.2)	1 (0.2)	5 (1.0)
Syncope	2 (0.4)	-	2 (0.4)	3 (0.6)	-	3 (0.6)	5 (1.0)
Musculoskeletal and connective tissue disorders	**71 (14.8)**	**31 (6.5)**	**93 (19.4)**	**18 (3.8)**	**8 (1.7)**	**25 (5.2)**	**108 (22.5)**
Bone pain	19 (4.0)	9 (1.9)	27 (5.6)	-	1 (0.2)	1 (0.2)	28 (5.8)
Pain in extremity	13 (2.7)	5 (1.0)	18 (3.8)	1 (0.2)	1 (0.2)	2 (0.4)	20 (4.2)
Back pain	13 (2.7)	3 (0.6)	16 (3.3)	2 (0.4)	-	2 (0.4)	18 (3.8)
Muscle spasms	8 (1.7)	4 (0.8)	12 (2.5)	-	-	-	12 (2.5)
Arthralgia	6 (1.3)	5 (1.0)	10 (2.1)	1 (0.2)	-	1 (0.2)	11 (2.3)
Osteoarthritis	4 (0.8)	1 (0.2)	5 (1.0)	1 (0.2)	2 (0.4)	3 (0.6)	8 (1.7)

Table 10-30: Adverse events in Arm A by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1) **PT**							
Intervertebral disc protrusion	4 (0.8)	-	4 (0.8)	1 (0.2)	-	1 (0.2)	5 (1.0)
Skin and subcutaneous tissue disorders	**63 (13.2)**	**39 (8.1)**	**93 (19.4)**	**2 (0.4)**	**4 (0.8)**	**6 (1.3)**	**98 (20.5)**
Pruritus	21 (4.4)	16 (3.3)	33 (6.9)	-	1 (0.2)	1 (0.2)	34 (7.1)
Night sweats	22 (4.6)	8 (1.7)	29 (6.1)	-	-	-	29 (6.1)
Rash	5 (1.0)	7 (1.5)	12 (2.5)	-	-	-	12 (2.5)
Hyperhidrosis	6 (1.3)	3 (0.6)	9 (1.9)	-	-	-	9 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**25 (5.2)**	**5 (1.0)**	**29 (6.1)**	**56 (11.7)**	**16 (3.3)**	**68 (14.2)**	**89 (18.6)**
Myelofibrosis	6 (1.3)	3 (0.6)	9 (1.9)	21 (4.4)	-	21 (4.4)	30 (6.3)
Acute myeloid leukemia	1 (0.2)	-	1 (0.2)	3 (0.6)	3 (0.6)	6 (1.3)	7 (1.5)
Primary myelofibrosis	2 (0.4)	-	2 (0.4)	2 (0.4)	3 (0.6)	5 (1.0)	7 (1.5)
Transformation to acute myeloid leukemia	-	-	-	6 (1.3)	1 (0.2)	7 (1.5)	7 (1.5)
Squamous cell carcinoma of skin	3 (0.6)	-	3 (0.6)	3 (0.6)	-	3 (0.6)	6 (1.3)
Basal cell carcinoma	3 (0.6)	-	3 (0.6)	2 (0.4)	-	2 (0.4)	5 (1.0)
Myeloproliferative neoplasm	-	-	-	2 (0.4)	3 (0.6)	5 (1.0)	5 (1.0)
Second primary malignancy	2 (0.4)	-	2 (0.4)	3 (0.6)	-	3 (0.6)	5 (1.0)
Metabolism and nutrition disorders	**47 (9.8)**	**17 (3.5)**	**63 (13.2)**	**20 (4.2)**	**4 (0.8)**	**23 (4.8)**	**78 (16.3)**
Iron overload	14 (2.9)	8 (1.7)	22 (4.6)	3 (0.6)	-	3 (0.6)	25 (5.2)
Decreased appetite	7 (1.5)	2 (0.4)	9 (1.9)	-	-	-	9 (1.9)
Gout	5 (1.0)	1 (0.2)	6 (1.3)	2 (0.4)	-	2 (0.4)	8 (1.7)
Hyperkalemia	3 (0.6)	1 (0.2)	4 (0.8)	2 (0.4)	2 (0.4)	4 (0.8)	8 (1.7)
Hyperuricemia	3 (0.6)	2 (0.4)	5 (1.0)	2 (0.4)	1 (0.2)	3 (0.6)	8 (1.7)
Hypokalemia	6 (1.3)	-	6 (1.3)	2 (0.4)	-	2 (0.4)	8 (1.7)
Cardiac disorders	**16 (3.3)**	**7 (1.5)**	**23 (4.8)**	**45 (9.4)**	**15 (3.1)**	**54 (11.3)**	**69 (14.4)**
Cardiac failure	2 (0.4)	-	2 (0.4)	17 (3.5)	2 (0.4)	19 (4.0)	21 (4.4)
Atrial fibrillation	6 (1.3)	-	6 (1.3)	10 (2.1)	4 (0.8)	13 (2.7)	18 (3.8)
Angina pectoris	1 (0.2)	2 (0.4)	3 (0.6)	3 (0.6)	1 (0.2)	4 (0.8)	7 (1.5)
Coronary artery disease	-	-	-	6 (1.3)	1 (0.2)	7 (1.5)	7 (1.5)
Vascular disorders	**25 (5.2)**	**14 (2.9)**	**37 (7.7)**	**22 (4.6)**	**11 (2.3)**	**30 (6.3)**	**64 (13.4)**

NOVARTIS

Table 10-30: Adverse events in Arm A by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1)							
PT							
Hematoma	5 (1.0)	7 (1.5)	11 (2.3)	1 (0.2)	4 (0.8)	4 (0.8)	15 (3.1)
Hypertension	7 (1.5)	2 (0.4)	9 (1.9)	4 (0.8)	-	4 (0.8)	13 (2.7)
Deep vein thrombosis	3 (0.6)	1 (0.2)	4 (0.8)	5 (1.0)	2 (0.4)	7 (1.5)	10 (2.1)
Hypertensive crisis	-	-	-	4 (0.8)	2 (0.4)	5 (1.0)	5 (1.0)
Injury, poisoning and procedural complications	**29 (6.1)**	**1 (0.2)**	**30 (6.3)**	**27 (5.6)**	**8 (1.7)**	**32 (6.7)**	**58 (12.1)**
Fall	7 (1.5)	-	7 (1.5)	12 (2.5)	5 (1.0)	16 (3.3)	23 (4.8)
Facial bones fracture	2 (0.4)	-	2 (0.4)	3 (0.6)	-	3 (0.6)	5 (1.0)
Renal and urinary disorders	**21 (4.4)**	**4 (0.8)**	**25 (5.2)**	**23 (4.8)**	**8 (1.7)**	**29 (6.1)**	**51 (10.6)**
Acute kidney injury	1 (0.2)	-	1 (0.2)	8 (1.7)	2 (0.4)	10 (2.1)	11 (2.3)
Renal failure	1 (0.2)	-	1 (0.2)	6 (1.3)	2 (0.4)	8 (1.7)	9 (1.9)
Psychiatric disorders	**25 (5.2)**	**8 (1.7)**	**32 (6.7)**	**1 (0.2)**	**3 (0.6)**	**4 (0.8)**	**35 (7.3)**
Sleep disorder	10 (2.1)	2 (0.4)	12 (2.5)	-	-	-	12 (2.5)
Depression	9 (1.9)	1 (0.2)	10 (2.1)	-	1 (0.2)	1 (0.2)	11 (2.3)
Hepatobiliary disorders	**8 (1.7)**	**1 (0.2)**	**9 (1.9)**	**7 (1.5)**	**3 (0.6)**	**9 (1.9)**	**17 (3.5)**
Cholelithiasis	2 (0.4)	-	2 (0.4)	3 (0.6)	1 (0.2)	4 (0.8)	6 (1.3)
Eye disorders	**13 (2.7)**	**3 (0.6)**	**14 (2.9)**	**1 (0.2)**	**1 (0.2)**	**2 (0.4)**	**16 (3.3)**
Visual impairment	4 (0.8)	2 (0.4)	5 (1.0)	-	-	-	5 (1.0)
Ear and labyrinth disorders	**9 (1.9)**	**1 (0.2)**	**10 (2.1)**	**3 (0.6)**	**1 (0.2)**	**3 (0.6)**	**13 (2.7)**
Vertigo	6 (1.3)	1 (0.2)	7 (1.5)	1 (0.2)	-	1 (0.2)	8 (1.7)
Immune system disorders	**4 (0.8)**	-	**4 (0.8)**	**5 (1.0)**	-	**5 (1.0)**	**8 (1.7)**
Surgical and medical procedures	**3 (0.6)**	-	**3 (0.6)**	**5 (1.0)**	-	**5 (1.0)**	**8 (1.7)**
Reproductive system and breast disorders	**4 (0.8)**	**1 (0.2)**	**5 (1.0)**	**2 (0.4)**	-	**2 (0.4)**	**7 (1.5)**

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, FAS = Full Analysis Set, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SOC = System Organ Class

NOVARTIS

Table 10-31: Adverse events in Arm B by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1) PT							
Number of patients with at least one AE, n (%)	**287 (61.9)**	**228 (49.1)**	**347 (74.8)**	**210 (45.3)**	**97 (20.9)**	**242 (52.2)**	**400 (86.2)**
Blood and lymphatic system disorders	**88 (19.0)**	**116 (25.0)**	**178 (38.4)**	**18 (3.9)**	**20 (4.3)**	**37 (8.0)**	**196 (42.2)**
Anemia	30 (6.5)	76 (16.4)	102 (22.0)	5 (1.1)	7 (1.5)	12 (2.6)	112 (24.1)
Thrombocytopenia	11 (2.4)	39 (8.4)	49 (10.6)	3 (0.6)	6 (1.3)	9 (1.9)	57 (12.3)
Splenomegaly	31 (6.7)	10 (2.2)	40 (8.6)	3 (0.6)	1 (0.2)	4 (0.9)	44 (9.5)
Leukocytosis	8 (1.7)	2 (0.4)	10 (2.2)	2 (0.4)	1 (0.2)	3 (0.6)	13 (2.8)
Thrombocytosis	6 (1.3)	3 (0.6)	9 (1.9)	-	-	-	9 (1.9)
Pancytopenia	2 (0.4)	3 (0.6)	5 (1.1)	2 (0.4)	1 (0.2)	3 (0.6)	8 (1.7)
General disorders and administration site conditions	**72 (15.5)**	**60 (12.9)**	**116 (25.0)**	**48 (10.3)**	**23 (5.0)**	**63 (13.6)**	**158 (34.1)**
Fatigue	20 (4.3)	29 (6.3)	47 (10.1)	-	1 (0.2)	1 (0.2)	48 (10.3)
Asthenia	24 (5.2)	13 (2.8)	36 (7.8)	3 (0.6)	1 (0.2)	4 (0.9)	39 (8.4)
General physical health deterioration	12 (2.6)	2 (0.4)	14 (3.0)	20 (4.3)	3 (0.6)	23 (5.0)	36 (7.8)
Death	-	-	-	20 (4.3)	10 (2.2)	30 (6.5)	30 (6.5)
Pyrexia	10 (2.2)	5 (1.1)	14 (3.0)	6 (1.3)	2 (0.4)	8 (1.7)	21 (4.5)
Oedema peripheral	13 (2.8)	2 (0.4)	15 (3.2)	1 (0.2)	1 (0.2)	2 (0.4)	17 (3.7)
Pain	3 (0.6)	4 (0.9)	7 (1.5)	-	2 (0.4)	2 (0.4)	9 (1.9)
Multiple organ dysfunction syndrome	-	-	-	3 (0.6)	3 (0.6)	6 (1.3)	6 (1.3)
Chills	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)	1 (0.2)	2 (0.4)	5 (1.1)
Infections and infestations	**93 (20.0)**	**11 (2.4)**	**99 (21.3)**	**67 (14.4)**	**15 (3.2)**	**76 (16.4)**	**157 (33.8)**
Pneumonia	9 (1.9)	-	9 (1.9)	25 (5.4)	6 (1.3)	29 (6.3)	37 (8.0)
Nasopharyngitis	23 (5.0)	-	23 (5.0)	-	-	-	23 (5.0)
Urinary tract infection	15 (3.2)	2 (0.4)	17 (3.7)	3 (0.6)	-	3 (0.6)	20 (4.3)
Herpes zoster	9 (1.9)	3 (0.6)	12 (2.6)	2 (0.4)	4 (0.9)	6 (1.3)	18 (3.9)
Bronchitis	8 (1.7)	2 (0.4)	10 (2.2)	7 (1.5)	2 (0.4)	8 (1.7)	17 (3.7)
Sepsis	-	-	-	12 (2.6)	1 (0.2)	13 (2.8)	13 (2.8)
Infection	4 (0.9)	-	4 (0.9)	2 (0.4)	2 (0.4)	4 (0.9)	8 (1.7)
Cystitis	6 (1.3)	-	6 (1.3)	1 (0.2)	-	1 (0.2)	7 (1.5)
Gastrointestinal disorders	**73 (15.7)**	**38 (8.2)**	**100 (21.6)**	**22 (4.7)**	**5 (1.1)**	**26 (5.6)**	**117 (25.2)**
Nausea	14 (3.0)	10 (2.2)	24 (5.2)	1 (0.2)	1 (0.2)	2 (0.4)	26 (5.6)
Diarrhoea	16 (3.4)	6 (1.3)	22 (4.7)	2 (0.4)	1 (0.2)	3 (0.6)	25 (5.4)

NOVARTIS

Table 10-31: Adverse events in Arm B by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1) **PT**							
Abdominal pain upper	12 (2.6)	1 (0.2)	13 (2.8)	1 (0.2)	2 (0.4)	3 (0.6)	15 (3.2)
Vomiting	8 (1.7)	4 (0.9)	12 (2.6)	2 (0.4)	-	2 (0.4)	14 (3.0)
Abdominal discomfort	7 (1.5)	5 (1.1)	11 (2.4)	-	-	-	11 (2.4)
Abdominal pain	5 (1.1)	2 (0.4)	7 (1.5)	1 (0.2)	1 (0.2)	2 (0.4)	9 (1.9)
Ascites	4 (0.9)	-	4 (0.9)	4 (0.9)	-	4 (0.9)	8 (1.7)
Constipation	4 (0.9)	4 (0.9)	8 (1.7)	-	-	-	8 (1.7)
Abdominal distension	4 (0.9)	3 (0.6)	7 (1.5)	-	-	-	7 (1.5)
Dyspepsia	3 (0.6)	4 (0.9)	7 (1.5)	-	-	-	7 (1.5)
Gastrooesophageal reflux disease	3 (0.6)	2 (0.4)	5 (1.1)	1 (0.2)	-	1 (0.2)	6 (1.3)
Musculoskeletal and connective tissue disorders	**77 (16.6)**	**33 (7.1)**	**99 (21.3)**	**16 (3.4)**	**2 (0.4)**	**18 (3.9)**	**108 (23.3)**
Pain in extremity	15 (3.2)	8 (1.7)	22 (4.7)	2 (0.4)	-	2 (0.4)	24 (5.2)
Bone pain	10 (2.2)	11 (2.4)	21 (4.5)	-	-	-	21 (4.5)
Arthralgia	17 (3.7)	1 (0.2)	18 (3.9)	1 (0.2)	-	1 (0.2)	18 (3.9)
Back pain	11 (2.4)	2 (0.4)	13 (2.8)	2 (0.4)	-	2 (0.4)	14 (3.0)
Muscle spasms	7 (1.5)	5 (1.1)	12 (2.6)	-	-	-	12 (2.6)
Osteoarthritis	7 (1.5)	1 (0.2)	8 (1.7)	3 (0.6)	-	3 (0.6)	10 (2.2)
Intervertebral disc protrusion	4 (0.9)	-	4 (0.9)	2 (0.4)	-	2 (0.4)	6 (1.3)
Musculoskeletal discomfort	4 (0.9)	2 (0.4)	6 (1.3)	-	-	-	6 (1.3)
Myalgia	5 (1.1)	2 (0.4)	6 (1.3)	-	-	-	6 (1.3)
Investigations	**47 (10.1)**	**36 (7.8)**	**74 (15.9)**	**4 (0.9)**	**37 (8.0)**	**39 (8.4)**	**100 (21.6)**
Hemoglobin decreased	6 (1.3)	11 (2.4)	15 (3.2)	2 (0.4)	15 (3.2)	17 (3.7)	32 (6.9)
C-reactive protein increased	9 (1.9)	-	9 (1.9)	1 (0.2)	3 (0.6)	4 (0.9)	13 (2.8)
Platelet count decreased	2 (0.4)	5 (1.1)	6 (1.3)	-	7 (1.5)	7 (1.5)	13 (2.8)
Weight decreased	9 (1.9)	3 (0.6)	12 (2.6)	-	-	-	12 (2.6)
White blood cell count increased	7 (1.5)	-	7 (1.5)	-	5 (1.1)	5 (1.1)	11 (2.4)
Weight increased	2 (0.4)	7 (1.5)	9 (1.9)	1 (0.2)	-	1 (0.2)	10 (2.2)
Blood lactate dehydrogenase increased	1 (0.2)	1 (0.2)	2 (0.4)	1 (0.2)	5 (1.1)	6 (1.3)	8 (1.7)
Gamma-glutamyltransferase increased	2 (0.4)	5 (1.1)	7 (1.5)	-	1 (0.2)	1 (0.2)	8 (1.7)
Aspartate aminotransferase increased	3 (0.6)	2 (0.4)	5 (1.1)	-	2 (0.4)	2 (0.4)	7 (1.5)
Blood creatinine increased	3 (0.6)	2 (0.4)	5 (1.1)	-	2 (0.4)	2 (0.4)	7 (1.5)

NOVARTIS

Table 10-31: Adverse events in Arm B by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1)							
PT							
Red blood cell count decreased	-	-	-	-	7 (1.5)	7 (1.5)	7 (1.5)
Alanine aminotransferase increased	3 (0.6)	2 (0.4)	5 (1.1)	-	1 (0.2)	1 (0.2)	6 (1.3)
Serum ferritin increased	3 (0.6)	2 (0.4)	5 (1.1)	-	1 (0.2)	1 (0.2)	6 (1.3)
Hematocrit decreased	-	1 (0.2)	1 (0.2)	-	4 (0.9)	4 (0.9)	5 (1.1)
Liver function test increased	3 (0.6)	1 (0.2)	4 (0.9)	-	1 (0.2)	1 (0.2)	5 (1.1)
Nervous system disorders	**44 (9.5)**	**34 (7.3)**	**69 (14.9)**	**23 (5.0)**	**7 (1.5)**	**28 (6.0)**	**89 (19.2)**
Dizziness	13 (2.8)	17 (3.7)	29 (6.3)	2 (0.4)	-	2 (0.4)	31 (6.7)
Headache	7 (1.5)	11 (2.4)	18 (3.9)	-	1 (0.2)	1 (0.2)	19 (4.1)
Paraesthesia	5 (1.1)	2 (0.4)	7 (1.5)	-	1 (0.2)	1 (0.2)	8 (1.7)
Polyneuropathy	5 (1.1)	1 (0.2)	6 (1.3)	-	-	-	6 (1.3)
Cerebrovascular accident	-	-	-	5 (1.1)	-	5 (1.1)	5 (1.1)
Syncope	3 (0.6)	-	3 (0.6)	2 (0.4)	-	2 (0.4)	5 (1.1)
Respiratory, thoracic and mediastinal disorders	**53 (11.4)**	**23 (5.0)**	**68 (14.7)**	**21 (4.5)**	**10 (2.2)**	**30 (6.5)**	**88 (19.0)**
Dyspnoea	20 (4.3)	4 (0.9)	24 (5.2)	8 (1.7)	1 (0.2)	9 (1.9)	32 (6.9)
Dyspnoea exertional	14 (3.0)	7 (1.5)	19 (4.1)	2 (0.4)	-	2 (0.4)	21 (4.5)
Epistaxis	8 (1.7)	5 (1.1)	13 (2.8)	-	1 (0.2)	1 (0.2)	14 (3.0)
Cough	10 (2.2)	3 (0.6)	13 (2.8)	-	-	-	13 (2.8)
Pleural effusion	5 (1.1)	-	5 (1.1)	1 (0.2)	-	1 (0.2)	6 (1.3)
Pulmonary embolism	-	-	-	5 (1.1)	1 (0.2)	6 (1.3)	6 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**25 (5.4)**	**6 (1.3)**	**31 (6.7)**	**48 (10.3)**	**7 (1.5)**	**54 (11.6)**	**82 (17.7)**
Myelofibrosis	7 (1.5)	2 (0.4)	9 (1.9)	8 (1.7)	1 (0.2)	9 (1.9)	18 (3.9)
Primary myelofibrosis	1 (0.2)	2 (0.4)	3 (0.6)	5 (1.1)	1 (0.2)	6 (1.3)	9 (1.9)
Acute myeloid leukemia	1 (0.2)	-	1 (0.2)	5 (1.1)	1 (0.2)	6 (1.3)	7 (1.5)
Basal cell carcinoma	4 (0.9)	1 (0.2)	5 (1.1)	1 (0.2)	1 (0.2)	2 (0.4)	7 (1.5)
Blast cell crisis	1 (0.2)	-	1 (0.2)	5 (1.1)	-	5 (1.1)	6 (1.3)
Squamous cell carcinoma of skin	1 (0.2)	-	1 (0.2)	3 (0.6)	2 (0.4)	5 (1.1)	6 (1.3)
Metabolism and nutrition disorders	**57 (12.3)**	**13 (2.8)**	**66 (14.2)**	**10 (2.2)**	**3 (0.6)**	**13 (2.8)**	**73 (15.7)**
Iron overload	21 (4.5)	2 (0.4)	23 (5.0)	3 (0.6)	1 (0.2)	4 (0.9)	27 (5.8)
Decreased appetite	7 (1.5)	2 (0.4)	9 (1.9)	-	-	-	9 (1.9)

NOVARTIS

Table 10-31: Adverse events in Arm B by primary SOC and most common PTs (≥ 1.0% in any AE, by patient, FAS) – multipage table

	nsAEnr	nsADR	nsAE	SAEnr	SADR	SAE	Any AE
Primary SOC (MedDRA v24.1) PT							
Vitamin d deficiency	9 (1.9)	-	9 (1.9)	-	-	-	9 (1.9)
Folate deficiency	7 (1.5)	1 (0.2)	8 (1.7)	-	-	-	8 (1.7)
Vitamin b12 deficiency	3 (0.6)	2 (0.4)	5 (1.1)	-	-	-	5 (1.1)
Skin and subcutaneous tissue disorders	**41 (8.8)**	**26 (5.6)**	**63 (13.6)**	**3 (0.6)**	**1 (0.2)**	**4 (0.9)**	**67 (14.4)**
Pruritus	8 (1.7)	11 (2.4)	18 (3.9)	-	-	-	18 (3.9)
Night sweats	11 (2.4)	6 (1.3)	17 (3.7)	-	-	-	17 (3.7)
Rash	4 (0.9)	1 (0.2)	5 (1.1)	-	-	-	5 (1.1)
Cardiac disorders	**18 (3.9)**	**3 (0.6)**	**20 (4.3)**	**31 (6.7)**	**7 (1.5)**	**35 (7.5)**	**50 (10.8)**
Cardiac failure	4 (0.9)	1 (0.2)	5 (1.1)	15 (3.2)	2 (0.4)	16 (3.4)	21 (4.5)
Atrial fibrillation	6 (1.3)	-	6 (1.3)	7 (1.5)	1 (0.2)	8 (1.7)	13 (2.8)
Vascular disorders	**23 (5.0)**	**14 (3.0)**	**36 (7.8)**	**8 (1.7)**	**5 (1.1)**	**13 (2.8)**	**47 (10.1)**
Hypertension	11 (2.4)	8 (1.7)	18 (3.9)	1 (0.2)	2 (0.4)	3 (0.6)	21 (4.5)
Hematoma	5 (1.1)	5 (1.1)	10 (2.2)	1 (0.2)	1 (0.2)	2 (0.4)	12 (2.6)
Injury, poisoning and procedural complications	**20 (4.3)**	**2 (0.4)**	**22 (4.7)**	**23 (5.0)**	**3 (0.6)**	**25 (5.4)**	**46 (9.9)**
Fall	6 (1.3)	-	6 (1.3)	4 (0.9)	1 (0.2)	5 (1.1)	11 (2.4)
Renal and urinary disorders	**17 (3.7)**	**3 (0.6)**	**20 (4.3)**	**12 (2.6)**	**4 (0.9)**	**15 (3.2)**	**34 (7.3)**
Renal failure	5 (1.1)	1 (0.2)	6 (1.3)	2 (0.4)	1 (0.2)	3 (0.6)	9 (1.9)
Psychiatric disorders	**16 (3.4)**	**6 (1.3)**	**22 (4.7)**	**2 (0.4)**	-	**2 (0.4)**	**23 (5.0)**
Sleep disorder	5 (1.1)	5 (1.1)	10 (2.2)	-	-	-	10 (2.2)
Depression	4 (0.9)	-	4 (0.9)	1 (0.2)	-	1 (0.2)	5 (1.1)
Eye disorders	**11 (2.4)**	**1 (0.2)**	**12 (2.6)**	-	**1 (0.2)**	**1 (0.2)**	**13 (2.8)**
Hepatobiliary disorders	**6 (1.3)**	**1 (0.2)**	**7 (1.5)**	**4 (0.9)**	**1 (0.2)**	**5 (1.1)**	**12 (2.6)**
Reproductive system and breast disorders	**3 (0.6)**	**3 (0.6)**	**6 (1.3)**	**2 (0.4)**	**1 (0.2)**	**3 (0.6)**	**9 (1.9)**
Surgical and medical procedures	**2 (0.4)**	-	**2 (0.4)**	**6 (1.3)**	**1 (0.2)**	**7 (1.5)**	**9 (1.9)**
Ear and labyrinth disorders	**4 (0.9)**	**2 (0.4)**	**6 (1.3)**	-	**1 (0.2)**	**1 (0.2)**	**7 (1.5)**
Endocrine disorders	**3 (0.6)**	**1 (0.2)**	**4 (0.9)**	**1 (0.2)**	-	**1 (0.2)**	**5 (1.1)**

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, FAS = Full Analysis Set, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SOC = System Organ Class
AEs without information on relation to study drug or seriousness were considered as related or serious.

NOVARTIS

Table 10-38: Outcome of adverse events, total (by event, N=3437) – Arm A (FAS)

	nsAEnr	nsADR	SAEnr	SADR	Any AE
PT					
Outcome		**Number (%) of events:**			
Total					
Recovered	648 (18.9)	402 (11.7)	396 (11.5)	83 (2.4)	1529 (44.5)
Recovered with sequelae	3 (0.1)	-	16 (0.5)	-	19 (0.6)
Improved	130 (3.8)	121 (3.5)	89 (2.6)	38 (1.1)	378 (11.0)
Not recovered	471 (13.7)	335 (9.7)	70 (2.0)	17 (0.5)	893 (26.0)
Worsened	15 (0.4)	14 (0.4)	4 (0.1)	3 (0.1)	36 (1.0)
Fatal	-	-	165 (4.8)	48 (1.4)	213 (6.2)
Unknown	83 (2.4)	43 (1.3)	20 (0.6)	3 (0.1)	149 (4.3)
Missing	5 (0.1)	1 (0.0)	1 (0.0)	213 (6.2)	220 (6.4)

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, FAS = Full Analysis Set, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SOC = System Organ Class

Table 10-39: Outcome of adverse events, total (by event, N=2393) – Arm B (FAS)

	nsAEnr	nsADR	SAEnr	SADR	Any AE
PT					
Outcome		**Number (%) of events:**			
Total					
Recovered	484 (20.2)	212 (8.9)	249 (10.4)	39 (1.6)	984 (41.1)
Recovered with sequelae	5 (0.2)	-	11 (0.5)	2 (0.1)	18 (0.8)
Improved	91 (3.8)	64 (2.7)	40 (1.7)	6 (0.3)	201 (8.4)
Not recovered	389 (16.3)	222 (9.3)	52 (2.2)	4 (0.2)	667 (27.9)
Worsened	20 (0.8)	23 (1.0)	5 (0.2)	1 (0.0)	49 (2.0)
Fatal	-	-	109 (4.6)	22 (0.9)	131 (5.5)
Unknown	106 (4.4)	61 (2.5)	18 (0.8)	4 (0.2)	189 (7.9)
Missing	6 (0.3)	2 (0.1)	-	146 (6.1)	154 (6.4)

Abbreviations: ADR = Adverse Drug Reaction, AE = Adverse Event, FAS = Full Analysis Set, MedDRA = Medical Dictionary for Regulatory Activities, nr = not related, ns = non-serious, PT = Preferred Term, SADR = Serious Adverse Drug Reaction, SAE = Serious Adverse Event, SOC = System Organ Class

All-Cause Mortality

165 SAE not related with fatal outcome (experienced by 90 patients) were reported in Arm A

48 SADRs with fatal outcome (experienced by 25 patients) were reported an Arm A: in 39 events the causality regarding treatment with ruxolitinib was assessed as “not assessable”, for 2 events causality was not reported, and in 7 events causality was assessed as “related”. The 7 related PTs were: “cerebrovascular accident”, “infection”, “septic shock”, “pneumonia”, “blood potassium increased”, “red blood cell count decreased”, and “myeloproliferative neo-plasm”

110 SAE not related with fatal outcome (experienced by 69 patients) were reported in Arm B

23 SADRs with fatal outcome (experienced by 18 patients) were documented in Arm B: in 20 events the causality regarding treatment with ruxolitinib was assessed as “not assessable” and in 3 events causality was assessed as “related”. The 3 related PTs were: “C-reactive protein increased”, “infection”, and “hematoma”.

Other Relevant Findings

Not Applicable

Conclusion:

This large NIS confirms the safety and efficacy of ruxolitinib in a representative real-world cohort of myelofibrosis patients with or without prior treatment with a JAK-inhibitor.

Date of Clinical Trial Report

16 Aug 2023