



## Clinical trial results:

**An open-label, multi-center, Expanded Treatment Protocol (ETP) of ruxolitinib in patients with Polycythemia Vera who are Hydroxyurea resistant or intolerant and for whom no treatment alternatives are available**

### Summary

EudraCT number	2014-001309-42
Trial protocol	AT NO SK PT SE BE BG
Global end of trial date	29 December 2017

### Results information

Result version number	v1 (current)
This version publication date	04 January 2019
First version publication date	04 January 2019

### Trial information

#### Trial identification

Sponsor protocol code	CINC424B2001X
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02292446
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma AG, 1 888-669-6682, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 1 888-669-6682, novartis.email@novartis.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	29 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 December 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

Provide early access and to evaluate the safety of ruxolitinib in patients with PV who were HU resistant or intolerant and who had no other standard treatment options

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Thailand: 2
Worldwide total number of subjects	161
EEA total number of subjects	129

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	74
From 65 to 84 years	83
85 years and over	4

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

161 patients were included in the ruxolitinib arm and 100% of the patient's received the treatment

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	All patients
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Arm description:

All patients will receive ruxolitinib at a starting dose of 10 mg twice daily which could be titrated to most appropriate dose. Dose was not to exceed 25 mg bid nor be less than 5 mg once a day

Arm type	Experimental
Investigational medicinal product name	ruxolitinib
Investigational medicinal product code	INC424
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Supplied to the Investigators as 5 mg, 10 mg and 20 mg tablets. Starting dose of ruxolitinib was 10 mg bid. A standardized dosing paradigm was used to determine dose adjustments so that each patient was titrated to their most appropriate dose. The ruxolitinib dose was not to exceed 25 mg bid nor be less than 5 mg once a day unless there was an adverse event that warranted interruption

Number of subjects in period 1	All patients
Started	161
Completed	141
Not completed	20
Adverse event, serious fatal	1
Consent withdrawn by subject	3
Disease progression	2
Adverse event, non-fatal	12
Subject/guardian decision	2

## Baseline characteristics

### Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients will receive ruxolitinib at a starting dose of 10 mg twice daily which could be titrated to most appropriate dose. Dose was not to exceed 25 mg bid nor be less than 5 mg once a day

Reporting group values	All patients	Total	
Number of subjects	161	161	
Age, Customized			
Units: Subjects			
18-64	74	74	
65 -84	83	83	
>=85	4	4	
Sex: Female, Male			
Units: Subjects			
Female	65	65	
Male	96	96	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	128	128	
Asian	3	3	
Other	30	30	
Number of participants resistant or intolerant to hydroxyurea (HU)			
Definition of resistant or intolerant was based on physician's evaluation			
Units: Subjects			
Resistant to hydroxyurea	60	60	
Intolerant to hydroxyurea	101	101	
Number of participants' frequency of phlebotomy in 52 weeks prior to screening			
Units: Subjects			
1 phlebotomy	21	21	
2 phlebotomies	19	19	
>=3 phlebotomies	74	74	
Missing	47	47	

## End points

### End points reporting groups

Reporting group title	All patients
Reporting group description:	
All patients will receive ruxolitinib at a starting dose of 10 mg twice daily which could be titrated to most appropriate dose. Dose was not to exceed 25 mg bid nor be less than 5 mg once a day	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Hematocrit level at baseline	
Subject analysis set title	Post-baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Post-baseline hematocrit value	
Subject analysis set title	Change
Subject analysis set type	Full analysis
Subject analysis set description:	
Change from baseline	

### Primary: Number of Participants with Adverse Events - all grades

End point title	Number of Participants with Adverse Events - all grades <sup>[1]</sup>
End point description:	
Summary of adverse events (all grades).	
End point type	Primary
End point timeframe:	
0 to 39 months	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: No analysis was done for this End Point	

<b>End point values</b>	All patients			
Subject group type	Reporting group			
Number of subjects analysed	161			
Units: participants				
Adverse events	143			
Serious adverse events	26			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in hematocrit levels at all visits

End point title	Change from baseline in hematocrit levels at all visits
End point description:	
Change in hematocrit levels from Baseline to each visit were measured	
End point type	Secondary

End point timeframe:  
Up to approximately 26 months

End point values	Baseline	Post-baseline	Change	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	161	161	161	
Units: percentage				
arithmetic mean (standard deviation)				
Week 4 n=154	45.26 (± 5.246)	43.70 (± 5.220)	-1.55 (± 3.652)	
Week 8 n=144	45.21 (± 5.136)	40.73 (± 4.967)	-4.48 (± 5.055)	
Week 12 n=118	45.44 (± 5.324)	39.97 (± 5.419)	-5.47 (± 6.522)	
Week 16 n=107	45.64 (± 5.395)	39.32 (± 5.454)	-6.32 (± 6.928)	
Week 20 n=90	45.96 (± 5.353)	40.47 (± 5.323)	-5.49 (± 6.840)	
Week 24 n=79	45.93 (± 5.109)	40.32 (± 4.960)	-5.62 (± 6.073)	
Week 36 n=48	45.30 (± 4.602)	40.43 (± 4.959)	-4.86 (± 6.184)	
Week 48 n=37	45.41 (± 4.714)	39.82 (± 4.959)	-5.59 (± 6.318)	
Week 60 n=23	46.56 (± 5.299)	40.60 (± 5.105)	40.60 (± 5.929)	
Week 72 n=18	47.66 (± 5.377)	40.59 (± 4.056)	-7.07 (± 6.388)	
Week 84 n=15	48.15 (± 5.758)	41.93 (± 5.097)	-6.23 (± 6.492)	
Week 96 n=12	50.03 (± 4.702)	40.82 (± 4.496)	-9.21 (± 6.861)	
EOT n=154	45.38 (± 5.202)	39.93 (± 5.730)	-5.45 (± 5.847)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in spleen length

End point title	Change from baseline in spleen length
End point description:	
Change in spleen length from Baseline to each visit	
End point type	Secondary
End point timeframe:	
Up to approximately 26 months	

End point values	Baseline	Post-baseline	Change	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	161	161	161	
Units: cm				
arithmetic mean (standard deviation)				
Week 12 n=105	23.92 (± 14.618)	16.83 (± 12.931)	-7.09 (± 12.770)	
Week 24 n=75	22.66 (± 14.319)	16.26 (± 13.896)	-6.40 (± 14.101)	
Week 36 n=43	22.14 (± 13.994)	18.76 (± 16.880)	-3.38 (± 14.438)	
Week 48 n=36	22.14 (± 13.994)	18.76 (± 16.880)	-3.38 (± 14.438)	
Week 60 n=23	20.00 (± 13.007)	17.35 (± 12.357)	-2.65 (± 13.753)	
Week 72 n=17	18.41 (± 13.148)	13.47 (± 11.441)	-4.94 (± 13.840)	
Week 84 n=14	19.57 (± 14.233)	13.36 (± 9.443)	-6.21 (± 12.135)	
Week 96 n=12	19.92 (± 14.494)	12.33 (± 8.026)	-7.58 (± 11.237)	
End of treatment n=109	3.03 (± 3.419)	0.54 (± 1.661)	-2.49 (± 3.025)	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

End point title	Change from baseline in Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)
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End point description:

The MPN-SAF (Appendix 6) was a disease specific questionnaire comprised of 10 items that measures fatigue related to MPN disease and the severity of nine of the most prevalent associated symptoms including: early satiety, abdominal discomfort, inactivity, concentration, night sweats, itching, bone pain, fever and weight loss. There were three recall periods used in this questionnaire, which were 24 hours for fatigue, the past week for symptoms of early satiety, abdominal discomfort, inactivity, concentration, night sweats, itching, bone pain and fever, and the past 6 months for weight loss. Each item was scored on a scale ranging from 0 (no fatigue/absent) to 10 (As bad as you can imagine/worst imaginable). The MPN-SAF TSS was computed as the average of the observed items multiplied by 10 to achieve a 0-to-100 scale. The MPN-SAF TSS thus had a possible score range of 0 to 100.

End point type	Secondary
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End point timeframe:

Up to approximately 26 months

End point values	Baseline	Post-baseline	Change	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	161	161	161	
Units: scores				
arithmetic mean (standard deviation)				
Week 12 n=114	23.92 (± 14.618)	16.83 (± 12.931)	-7.09 (± 12.770)	
Week 24 n=75	22.66 (± 14.319)	16.26 (± 13.896)	-6.40 (± 14.101)	
Week 36 n=43	21.87 (± 13.228)	16.70 (± 14.419)	-5.18 (± 10.929)	
Week 48 n=36	22.14 (± 13.994)	18.76 (± 16.880)	-3.38 (± 14.438)	
Week 60 n=23	20.00 (± 13.007)	17.35 (± 12.357)	-2.65 (± 13.753)	
Week 72 n=17	18.41 (± 13.148)	13.47 (± 11.441)	-4.94 (± 13.840)	
Week 84 n=14	19.57 (± 14.233)	13.36 (± 9.443)	-6.21 (± 12.135)	
Week 96 n=12	19.92 (± 14.494)	12.33 (± 8.026)	-7.58 (± 11.237)	
End of treatment	22.86 (± 14.225)	18.12 (± 15.130)	-4.74 (± 13.954)	

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit up to approximately 26 months

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

### Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients will receive ruxolitinib at a starting dose of 10 mg twice daily which could be titrated to most appropriate dose. Dose was not to exceed 25 mg bid nor be less than 5 mg once a day

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 161 (16.15%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cancer			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Squamous cell carcinoma subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 161 (1.24%) 0 / 2 0 / 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 1 / 2 0 / 0		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 1 / 1 0 / 0		
Psychiatric disorders Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 0 / 1 0 / 0		
Injury, poisoning and procedural complications Accident	Additional description: Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally re		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 0 / 1 0 / 0		
Acetabulum fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 0 / 1 0 / 0		
Overdose subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 161 (0.62%) 1 / 1 0 / 0		
Skin injury			

subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bundle branch block bilateral			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Eye disorders			
Cataract			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haematoma			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 161 (1.24%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 161 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 161 (66.46%)		
Investigations			
Weight increased			
subjects affected / exposed	13 / 161 (8.07%)		
occurrences (all)	14		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	9 / 161 (5.59%) 10		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)	12 / 161 (7.45%) 14  27 / 161 (16.77%) 33		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Thrombocytosis subjects affected / exposed occurrences (all)	35 / 161 (21.74%) 41  11 / 161 (6.83%) 13		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)	12 / 161 (7.45%) 12  14 / 161 (8.70%) 15		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)	14 / 161 (8.70%) 16  15 / 161 (9.32%) 22		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)  Epistaxis	9 / 161 (5.59%) 9		

subjects affected / exposed occurrences (all)	9 / 161 (5.59%) 11		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	13 / 161 (8.07%) 14		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 161 (5.59%) 12		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2016	Changes were made to the inclusion criteria: requirement of a treatment history for PV that met the definition of resistance or intolerance to hydroxyurea was removed; confirmed diagnosis of PV according to the revised WHO criteria with resistance or intolerance to hydroxyurea was updated; requirement of palpable spleen was removed which allowed patients without splenomegaly to enter the trial. Hemoglobin parameter was added in the laboratory assessment. This parameter was judged as important to assess safety. The paragraph "Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event" was removed. The sample size was revised to 500 from 1500.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported