



## Clinical trial results:

**A randomized, double blind, placebo-controlled, multicenter, Phase III study investigating the efficacy and safety of ruxolitinib in early myelofibrosis patients with high molecular risk mutations (ReTHINK)**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results**

## Summary

|                          |                                        |
|--------------------------|----------------------------------------|
| EudraCT number           | 2014-004928-21                         |
| Trial protocol           | ES SE GB AT BE HU GR FR PT FI DK PL IT |
| Global end of trial date | 23 October 2017                        |

## Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 08 November 2018 |
| First version publication date | 08 November 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CINC424A2353 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02598297 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                                                                                                              |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma, AG                                                                                                                          |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                                                                                                 |
| Public contact               | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a> |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a> |

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:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 23 October 2017 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 23 October 2017 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of ruxolitinib in delaying progression of MF from early disease to advanced disease.

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                          | 03 February 2016 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Austria: 1            |
| Country: Number of subjects enrolled | Belgium: 4            |
| Country: Number of subjects enrolled | Canada: 1             |
| Country: Number of subjects enrolled | Denmark: 1            |
| Country: Number of subjects enrolled | France: 2             |
| Country: Number of subjects enrolled | Germany: 4            |
| Country: Number of subjects enrolled | United Kingdom: 1     |
| Country: Number of subjects enrolled | Greece: 5             |
| Country: Number of subjects enrolled | Hong Kong: 1          |
| Country: Number of subjects enrolled | Israel: 6             |
| Country: Number of subjects enrolled | Italy: 4              |
| Country: Number of subjects enrolled | Japan: 4              |
| Country: Number of subjects enrolled | Poland: 3             |
| Country: Number of subjects enrolled | Russian Federation: 2 |
| Country: Number of subjects enrolled | Spain: 3              |
| Country: Number of subjects enrolled | Sweden: 3             |
| Country: Number of subjects enrolled | Turkey: 4             |

|                                    |    |
|------------------------------------|----|
| Worldwide total number of subjects | 49 |
| EEA total number of subjects       | 31 |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| 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)                      | 24 |
| From 65 to 84 years                       | 25 |
| 85 years and over                         | 0  |

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## Subject disposition

### Recruitment

Recruitment details:

Approximately 320 male or female adults (age 18 or over) with a confirmed diagnosis of MF were planned to be enrolled. The target population was not met due to early study termination. A total of 49 subjects were enrolled in the study, 25 in the ruxolitinib arm and 24 in the placebo arm.

### Pre-assignment

Screening details:

Approximately 320 male or female adults (age 18 or over) with a confirmed diagnosis of MF were planned to be enrolled. The target population was not met due to early study termination. A total of 49 subjects were enrolled in the study, 25 in the ruxolitinib arm and 24 in the placebo arm.

### Period 1

|                              |                                        |
|------------------------------|----------------------------------------|
| Period 1 title               | Overall Study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Investigator, Carer, Assessor, Subject |

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | Ruxolitinib (INC424) |

Arm description:

Two tablets of ruxolitinib 5 mg were administered orally twice per 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:

Treatment period 1: Two tablets of ruxolitinib 5 mg were administered orally twice per day.

Treatment period 2: tablets of either 5, 15, 20 mg twice orally per day based on platelet counts

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Ruxolitinib Placebo |
|------------------|---------------------|

Arm description:

Two tablets of 5mg placebo were administered orally twice per day

|                                        |                     |
|----------------------------------------|---------------------|
| Arm type                               | Placebo             |
| Investigational medicinal product name | Ruxolitinib Placebo |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Tablet              |
| Routes of administration               | Oral use            |

Dosage and administration details:

Treatment period 1: Two tablets of placebo 5 mg were administered orally twice per day.

Treatment period 2: tablets of either 5, 15, 20 mg twice orally per day based on platelet counts

| <b>Number of subjects in period 1</b> | Ruxolitinib (INC424) | Ruxolitinib Placebo |
|---------------------------------------|----------------------|---------------------|
| Started                               | 25                   | 24                  |
| Not treated with study drug           | 1                    | 0                   |
| Subjects followed for survival        | 1                    | 0                   |
| Completed                             | 0                    | 0                   |
| Not completed                         | 25                   | 24                  |
| Physician decision                    | 1                    | -                   |
| Study terminated by Sponsor           | 21                   | 23                  |
| Adverse event, non-fatal              | 1                    | 1                   |
| Followed for survival                 | 1                    | -                   |
| Subject/guardian decision             | 1                    | -                   |

## Baseline characteristics

### Reporting groups

|                                                                        |                      |
|------------------------------------------------------------------------|----------------------|
| Reporting group title                                                  | Ruxolitinib (INC424) |
| Reporting group description:                                           |                      |
| Two tablets of ruxolitinib 5 mg were administered orally twice per day |                      |
| Reporting group title                                                  | Ruxolitinib Placebo  |
| Reporting group description:                                           |                      |
| Two tablets of 5mg placebo were administered orally twice per day      |                      |

| Reporting group values     | Ruxolitinib (INC424) | Ruxolitinib Placebo | Total |
|----------------------------|----------------------|---------------------|-------|
| Number of subjects         | 25                   | 24                  | 49    |
| Age categorical            |                      |                     |       |
| Units: Subjects            |                      |                     |       |
| Adults (18-64 years)       | 14                   | 10                  | 24    |
| From 65-84 years           | 11                   | 14                  | 25    |
| Age Continuous             |                      |                     |       |
| Units: Years               |                      |                     |       |
| arithmetic mean            | 59.0                 | 67.4                |       |
| standard deviation         | ± 14.23              | ± 7.72              | -     |
| Sex: Female, Male          |                      |                     |       |
| Units: Subjects            |                      |                     |       |
| Female                     | 12                   | 7                   | 19    |
| Male                       | 13                   | 17                  | 30    |
| Race/Ethnicity, Customized |                      |                     |       |
| Units: Subjects            |                      |                     |       |
| Caucasian                  | 19                   | 23                  | 42    |
| Asian                      | 4                    | 1                   | 5     |
| Other                      | 1                    | 0                   | 1     |
| Missing                    | 1                    | 0                   | 1     |

## End points

### End points reporting groups

|                                                                                                        |                      |
|--------------------------------------------------------------------------------------------------------|----------------------|
| Reporting group title                                                                                  | Ruxolitinib (INC424) |
| Reporting group description:<br>Two tablets of ruxolitinib 5 mg were administered orally twice per day |                      |
| Reporting group title                                                                                  | Ruxolitinib Placebo  |
| Reporting group description:<br>Two tablets of 5mg placebo were administered orally twice per day      |                      |

### Primary: Progression free survival (PFS-1)

|                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                        | Progression free survival (PFS-1) <sup>[1]</sup> |
| End point description:<br>Progression free survival (PFS-1) from date of randomization until the occurrence of any of the criteria for disease progression: • Progressive splenomegaly • Circulating peripheral blast counts > 10% • Leukemic transformation • Hb < 10g/dl with absolute decrease of at least 3 g/dl from baseline • White blood cell (WBC) counts > 25 x 10 <sup>3</sup> /µL • MF-7 score ≥ 30 • Death from any cause |                                                  |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                         | Primary                                          |
| End point timeframe:<br>From randomization till disease progression (estimated to be assessed up 48 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 statistical analysis was performed for this endpoint as the study terminated early.

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Participants         | 0                    | 0                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to primary progression (TTP)

|                                                                                                                                                 |                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                                 | Time to primary progression (TTP) |
| End point description:<br>TTP is defined as time from randomization until disease progression as defined for PFS-1 excluding death as an event. |                                   |
| End point type                                                                                                                                  | Secondary                         |
| End point timeframe:<br>From randomization till progression (estimated to be assessed up to 48 months)                                          |                                   |

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Months               | 0                    | 0                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage Change in spleen volume from baseline

|                                                                                                      |                                                  |
|------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| End point title                                                                                      | Percentage Change in spleen volume from baseline |
| End point description:<br>Change in spleen volume (by MRI/CT) from baseline                          |                                                  |
| End point type                                                                                       | Secondary                                        |
| End point timeframe:<br>From baseline and assessed on 12 week intervals until end of treatment (EOT) |                                                  |

| End point values                       | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|----------------------------------------|----------------------|---------------------|--|--|
| Subject group type                     | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed            | 25                   | 24                  |  |  |
| Units: Percentage change from baseline |                      |                     |  |  |
| arithmetic mean (standard deviation)   |                      |                     |  |  |
| Week 12 (N = 19, 19)                   | -10.8 (± 24.45)      | 9.1 (± 12.34)       |  |  |
| Week 24 (N = 13, 8)                    | -17.8 (± 18.83)      | 17.6 (± 17.78)      |  |  |
| Week 36 (N = 7, 2)                     | -18.4 (± 31.62)      | 32.5 (± 18.81)      |  |  |
| Week 48 (N = 2, 0)                     | -23.5 (± 10.57)      | 999 (± 999)         |  |  |
| End of Treatment (EOT) (N = 10, 9)     | -11.6 (± 8.08)       | 18.1 (± 18.58)      |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change in symptoms from baseline using MF-7

|                                                                                                                                                                                                                                                                                                                                                         |                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                         | Percentage change in symptoms from baseline using MF-7 |
| End point description:<br>Percentage change from Baseline in MF-7 total symptom score and 7 individual symptoms at each visit was summarized with descriptive statistics. For this scale, symptoms range from 0 to 10 for the severity experienced within the past 24 hours, with 0 being for absence of symptoms and 10 for worst imaginable symptoms. |                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                          | Secondary                                              |



End point timeframe:

From Baseline and assessed every 4 weeks until end of treatment

| End point values                            | Ruxolitinib<br>(INC424) | Ruxolitinib<br>Placebo |  |  |
|---------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                 | 25 <sup>[2]</sup>       | 24 <sup>[3]</sup>      |  |  |
| Units: Percentage change in scores          |                         |                        |  |  |
| arithmetic mean (standard deviation)        |                         |                        |  |  |
| TSD change from baseline @ W12              | -0.3 (± 4.45)           | 0.5 (± 6.08)           |  |  |
| TSD change from baseline @ W24              | 0.5 (± 3.71)            | -0.8 (± 6.44)          |  |  |
| TSD change from baseline @ W48              | -0.3 (± 3.06)           | 999 (± 999)            |  |  |
| TSD change from BL @ EOT                    | 1.1 (± 4.40)            | 3.3 (± 9.53)           |  |  |
| Tiredness: Baseline (BL)                    | 1.8 (± 1.45)            | 1.5 (± 1.53)           |  |  |
| Tiredness: change from baseline @ W12       | 0.1 (± 1.47)            | 0.4 (± 1.27)           |  |  |
| Tiredness: change from baseline @ W24       | -0.1 (± 0.76)           | 1.1 (± 2.52)           |  |  |
| Tiredness: change from baseline @ W48       | -0.3 (± 0.58)           | 999 (± 999)            |  |  |
| Tiredness change from BL @ EOT              | 0.8 (± 1.32)            | 1.1 (± 2.28)           |  |  |
| Filling up quickly when you eat (FUQWYE):BL | 1.0 (± 1.41)            | 0.8 (± 1.27)           |  |  |
| FUQWYE: change from BL @W12                 | 0.1 (± 1.49)            | -0.1 (± 2.09)          |  |  |
| FUQWYE: change from BL @W24                 | -0.2 (± 0.99)           | 0.1 (± 1.17)           |  |  |
| FUQWYE: change from BL @W48                 | 0.7 (± 1.15)            | 999 (± 999)            |  |  |
| FUQWYE: change from BL @ EOT                | 0.2 (± 1.08)            | 0.3 (± 2.29)           |  |  |
| Abdominal discomfort (AD): BL               | 0.7 (± 1.43)            | 0.6 (± 1.10)           |  |  |
| Abdominal discomfort change from BL @W12    | -0.1 (± 1.66)           | -0.1 (± 0.85)          |  |  |
| Abdominal discomfort change from BL @W24    | 0.0 (± 1.15)            | -0.3 (± 0.71)          |  |  |
| Abdominal discomfort change from BL @W48    | 0.0 (± 0.00)            | 999 (± 999)            |  |  |
| AD: change from BL @ EOT                    | 0.1 (± 0.92)            | 0.3 (± 1.40)           |  |  |
| Night sweat (NS): Baseline (BL)             | 0.7 (± 1.07)            | 1.1 (± 1.45)           |  |  |
| Night sweat change from BL @W12             | -0.1 (± 0.71)           | -0.3 (± 1.29)          |  |  |
| Night sweat change from BL @W24             | 0.5 (± 1.45)            | -0.7 (± 1.41)          |  |  |
| Night sweat change from BL @W48             | -0.3 (± 0.58)           | 999 (± 999)            |  |  |
| Night Sweat: change from BL @ EOT           | 0.0 (± 0.85)            | 0.3 (± 2.12)           |  |  |
| Itching (Pruritus):BL                       | 0.9 (± 1.42)            | 0.6 (± 0.93)           |  |  |
| Itching (Pruritus): change from BL @W12     | -0.3 (± 0.67)           | 0.1 (± 1.45)           |  |  |
| Itching (Pruritus): change from BL @W24     | 0.4 (± 0.77)            | -0.3 (± 1.22)          |  |  |
| Itching (Pruritus): change from BL @W48     | -1.0 (± 1.73)           | 999 (± 999)            |  |  |
| Itching: change from BL @ EOT               | 0.1 (± 1.03)            | 0.4 (± 1.75)           |  |  |
| Bone Pain: BL                               | 0.9 (± 1.35)            | 0.9 (± 1.33)           |  |  |
| Bone Pain: change from BL @W12              | -0.4 (± 1.01)           | 0.3 (± 1.56)           |  |  |
| Bone Pain: change from BL @W24              | -0.2 (± 1.17)           | -0.8 (± 1.79)          |  |  |
| Bone Pain: change from BL @W48              | 0.7 (± 1.15)            | 999 (± 999)            |  |  |
| Bone Pain: change from BL @ EOT             | 0.1 (± 0.96)            | 0.6 (± 1.50)           |  |  |

|                                              |               |              |  |  |
|----------------------------------------------|---------------|--------------|--|--|
| Pain under ribs on left side (PUROLS):<br>BL | 0.7 (± 1.18)  | 0.4 (± 0.82) |  |  |
| PUROLS: change from BL @W12                  | 0.4 (± 1.01)  | 0.1 (± 0.76) |  |  |
| PUROLS: change from BL @W24                  | 0.0 (± 0.41)  | 0.1 (± 1.17) |  |  |
| PUROLS: change from BL @W48                  | 0.0 (± 0.00)  | 999 (± 999)  |  |  |
| PUROLS: change from BL @ EOT                 | -0.2 (± 0.68) | 0.3 (± 1.00) |  |  |

Notes:

[2] - Baseline n = 25

Week 12 (n= 19)

Week 24 (n = 13)

Week 48 (n = 3)

EOT (n = 15)

[3] - Baseline n = 24

Week 12 (n= 20)

Week 24 (n = 9)

Week 48 (n = 0)

EOT (n = 16)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage change in symptoms from baseline using EQ-5D

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Percentage change in symptoms from baseline using EQ-5D |
|-----------------|---------------------------------------------------------|

End point description:

EQ-5D profiles were tabulated at baseline and each scheduled assessment. EQ visual analogue scale values were summarized descriptively by arm for each scheduled visit. The 5 scores for mobility, self-care, usual activities, pain/discomfort and anxiety/depression are all self-explanatory (eg "I have no problems walking" to "I am unable to walk"), except for the following overall health check, where 100 is the best of health, and 0 is the worst health, Only the categories with non-zero counts are presented with these results.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline and assessed every 4 weeks until end of treatment

| End point values                      | Ruxolitinib<br>(INC424) | Ruxolitinib<br>Placebo |  |  |
|---------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                    | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed           | 25                      | 24                     |  |  |
| Units: Participants                   |                         |                        |  |  |
| Mobility- Baseline: No problem        | 17                      | 18                     |  |  |
| Mobility- Baseline: Slight problems   | 4                       | 5                      |  |  |
| Mobility- Baseline: Moderate problems | 1                       | 1                      |  |  |
| Mobility- Baseline: Extreme problems  | 1                       | 0                      |  |  |
| Mobility - Week 4: No prob.           | 17                      | 14                     |  |  |
| Mobility - Week 4: Slight problems    | 4                       | 7                      |  |  |
| Mobility - Week 4: Moderate problems  | 1                       | 2                      |  |  |
| Mobility - Week 8: No problem         | 17                      | 15                     |  |  |
| Mobility - Week 8: Slight problems    | 3                       | 6                      |  |  |
| Mobility - Week 8: Moderate problems  | 0                       | 1                      |  |  |
| Mobility - Week 12: No problem        | 15                      | 12                     |  |  |
| Mobility - Week 12: Slight problems   | 4                       | 6                      |  |  |
| Mobility - Week 12: Moderate problems | 0                       | 2                      |  |  |
| Mobility - Week 16: No problem        | 12                      | 10                     |  |  |

|                                                |    |    |  |  |
|------------------------------------------------|----|----|--|--|
| Mobility - Week 16: Slight problems            | 2  | 7  |  |  |
| Mobility - Week 16: Moderate problems          | 1  | 0  |  |  |
| Mobility - Week 20: No problem                 | 12 | 5  |  |  |
| Mobility - Week 20: Slight problems            | 2  | 6  |  |  |
| Mobility - Week 24: No problem                 | 12 | 5  |  |  |
| Mobility - Week 24: Slight problems            | 1  | 3  |  |  |
| Mobility - Week 24: Moderate problems          | 0  | 1  |  |  |
| Mobility - Week 32: No problem                 | 8  | 1  |  |  |
| Mobility - Week 32: Slight problems            | 0  | 1  |  |  |
| Mobility - Week 32: Moderate problems          | 1  | 0  |  |  |
| Mobility - Week 40: No problem                 | 5  | 0  |  |  |
| Mobility - Week 40: Slight problems            | 1  | 0  |  |  |
| Mobility - Week 48: No problem                 | 2  | 0  |  |  |
| Mobility - Week 48: Slight problems            | 1  | 0  |  |  |
| Mobility - EOT: No problem                     | 11 | 12 |  |  |
| Mobility - EOT: Slight problems                | 4  | 3  |  |  |
| Mobility - EOT: Moderate problems              | 0  | 1  |  |  |
| Mobility- 30 day safety FU: No problem         | 2  | 3  |  |  |
| Mobility- 30 day safety FU: Slight problems    | 1  | 0  |  |  |
| Self-care - Baseline: No problem               | 23 | 22 |  |  |
| Self-care - Baseline: Slight problems          | 0  | 2  |  |  |
| Self-care - Week 4: No problem                 | 21 | 20 |  |  |
| Self-care - Week 4: Slight problems            | 0  | 3  |  |  |
| Self-care - Week 4: Moderate problems          | 1  | 0  |  |  |
| Self-care - Week 8: No problem                 | 19 | 21 |  |  |
| Self-care - Week 8: Slight problems            | 1  | 1  |  |  |
| Self-care - Week 12: No problem                | 17 | 19 |  |  |
| Self-care - Week 12: Slight problems           | 1  | 1  |  |  |
| Self-care - Week 12: Moderate problems         | 1  | 0  |  |  |
| Self-care - Week 16: No problem                | 15 | 16 |  |  |
| Self-care - Week 16: Slight problems           | 0  | 1  |  |  |
| Self-care - Week 20: No problem                | 14 | 11 |  |  |
| Self-care - Week 24: No problem                | 12 | 9  |  |  |
| Self-care - Week 24: Slight problems           | 1  | 0  |  |  |
| Self-care - Week 32: No problem                | 8  | 2  |  |  |
| Self-care - Week 32: Slight problems           | 1  | 0  |  |  |
| Self-care - Week 40: No problem                | 5  | 0  |  |  |
| Self-care - Week 40: Slight problems           | 1  | 0  |  |  |
| Self-care - Week 48: No problem                | 3  | 0  |  |  |
| Self-care - EOT: No problem                    | 14 | 15 |  |  |
| Self-care - EOT: Slight problems               | 1  | 1  |  |  |
| Self-care - 30 day Safety FU: No problem       | 3  | 3  |  |  |
| Usual activities -Baseline: No problem         | 18 | 21 |  |  |
| Usual activities -Baseline: Slight problems    | 4  | 3  |  |  |
| Usual activities - Baseline: Moderate problems | 1  | 0  |  |  |
| Usual activities - Week 4: No problem          | 20 | 18 |  |  |
| Usual activities - Week 4: Slight problems     | 1  | 4  |  |  |

|                                                   |    |    |  |  |
|---------------------------------------------------|----|----|--|--|
| Usual activities - Week 4: Moderate problems      | 1  | 0  |  |  |
| Usual activities - Week 4: Severe problems        | 0  | 1  |  |  |
| Usual activities - Week 8: No problem             | 20 | 18 |  |  |
| Usual activities - Week 8: Slight problems        | 0  | 3  |  |  |
| Usual activities - Week 8: Moderate problems      | 0  | 1  |  |  |
| Usual activities - Week 12: No problem            | 16 | 16 |  |  |
| Usual activities - Week 12: Slight problems       | 3  | 3  |  |  |
| Usual activities - Week 12: Moderate problems     | 0  | 1  |  |  |
| Usual activities - Week 16: No problem            | 13 | 14 |  |  |
| Usual activities - Week 16: Slight problems       | 2  | 3  |  |  |
| Usual activities - Week 20: No problem            | 13 | 9  |  |  |
| Usual activities - Week 20: Slight problems       | 1  | 2  |  |  |
| Usual activities - Week 24: No problem            | 12 | 9  |  |  |
| Usual activities - Week 24: Slight problems       | 1  | 0  |  |  |
| Usual activities - Week 32: No problem            | 8  | 2  |  |  |
| Usual activities - Week 32: Slight problems       | 1  | 0  |  |  |
| Usual activities - Week 40: No problem            | 5  | 0  |  |  |
| Usual activities - Week 40: Slight problems       | 1  | 0  |  |  |
| Usual activities - Week 48: No problem            | 3  | 0  |  |  |
| Usual activities - EOT: No problem                | 12 | 13 |  |  |
| Usual activities -EOT: Slight problems            | 3  | 3  |  |  |
| Usual activities - 30 day Safety FU: No problem   | 2  | 3  |  |  |
| Usual activities - 30 say Safety FU: Slight probs | 1  | 0  |  |  |
| Pain/Discomfort - Baseline: No problem            | 13 | 11 |  |  |
| Pain/Discomfort - Baseline: Slight problems       | 8  | 12 |  |  |
| Pain/Discomfort - Baseline: Moderate problems     | 2  | 1  |  |  |
| Pain/Discomfort - Week 4: No problem              | 11 | 15 |  |  |
| Pain/Discomfort - Week 4: Slight problems         | 10 | 6  |  |  |
| Pain/Discomfort - Week 4: Moderate problems       | 1  | 2  |  |  |
| Pain/Discomfort - Week 8: No problem              | 14 | 13 |  |  |
| Pain/Discomfort - Week 8: Slight problems         | 5  | 7  |  |  |
| Pain/Discomfort - Week 8: Moderate problems       | 1  | 2  |  |  |
| Pain/Discomfort - Week 12: No problem             | 12 | 10 |  |  |
| Pain/Discomfort - Week 12: Slight problems        | 7  | 6  |  |  |
| Pain/Discomfort - Week 12: Moderate problems      | 0  | 4  |  |  |
| Pain/Discomfort - Week 16: No problem             | 9  | 11 |  |  |

|                                                    |    |    |  |  |
|----------------------------------------------------|----|----|--|--|
| Pain/Discomfort - WK16: Slight problems            | 6  | 3  |  |  |
| Pain/Discomfort - WK16: Moderate problems          | 0  | 3  |  |  |
| Pain/Discomfort - WK20: No problem                 | 8  | 8  |  |  |
| Pain/Discomfort - WK20: Slight problems            | 6  | 3  |  |  |
| Pain/Discomfort - WK24: No problem                 | 9  | 7  |  |  |
| Pain/Discomfort - WK24: Slight problems            | 4  | 2  |  |  |
| Pain/Discomfort - WK32: No problem                 | 7  | 2  |  |  |
| Pain/Discomfort - WK32: Slight problems            | 2  | 0  |  |  |
| Pain/Discomfort - WK40: No problem                 | 4  | 0  |  |  |
| Pain/Discomfort - WK40: Slight problems            | 2  | 0  |  |  |
| Pain/Discomfort - WK48: No problem                 | 3  | 0  |  |  |
| Pain/Discomfort - EOT: No problem                  | 8  | 10 |  |  |
| Pain/Discomfort - EOT: Slight problems             | 7  | 3  |  |  |
| Pain/Discomfort - EOT: Moderate problems           | 0  | 3  |  |  |
| Pain/Discomfort - 30 day Safety FU: No problem     | 1  | 2  |  |  |
| Pain/Discomfort - 30 day safety FU: Slight probs   | 2  | 0  |  |  |
| Pain/Discomfort - 30 day Safety FU: Moderate probs | 0  | 1  |  |  |
| Anxiety/Depression - Baseline: No problem          | 14 | 18 |  |  |
| Anxiety/Depression - Baseline: Slight problems     | 6  | 3  |  |  |
| Anxiety/Depression - Baseline: Moderate problems   | 3  | 3  |  |  |
| Anxiety/Depression - WK4: No problem               | 13 | 15 |  |  |
| Anxiety/Depression - WK4: Slight problems          | 7  | 6  |  |  |
| Anxiety/Depression - WK4: Moderate problems        | 2  | 2  |  |  |
| Anxiety/Depression - WK8: No problem               | 11 | 16 |  |  |
| Anxiety/Depression - WK8: Slight problems          | 8  | 2  |  |  |
| Anxiety/Depression - WK8: Moderate problems        | 1  | 4  |  |  |
| Anxiety/Depression - WK12: No problem              | 8  | 13 |  |  |
| Anxiety/Depression - WK12: Slight problems         | 10 | 3  |  |  |
| Anxiety/Depression -WK12: Moderate problems        | 1  | 4  |  |  |
| Anxiety/Depression - WK16: No problem              | 10 | 10 |  |  |
| Anxiety/Depression - WK16: Slight problems         | 5  | 5  |  |  |
| Anxiety/Depression - WK16: Moderate problems       | 0  | 2  |  |  |
| Anxiety/Depression -WK20: No problem               | 10 | 8  |  |  |
| Anxiety/Depression - WK20: Slight problems         | 4  | 3  |  |  |

|                                                   |    |    |  |  |
|---------------------------------------------------|----|----|--|--|
| Anxiety/Depression - WK24: No problem             | 11 | 7  |  |  |
| Anxiety/Depression - WK24: Slight problems        | 2  | 2  |  |  |
| Anxiety/Depression - WK32: No problem             | 7  | 2  |  |  |
| Anxiety/Depression - WK32: Slight problems        | 2  | 0  |  |  |
| Anxiety/Depression - WK40: No problem             | 5  | 0  |  |  |
| Anxiety/Depression - WK40: Slight problems        | 1  | 0  |  |  |
| Anxiety/Depression - WK48: No problem             | 3  | 0  |  |  |
| Anxiety/Depression - EOT: No problem              | 11 | 12 |  |  |
| Anxiety/Depression - EOT: Slight probs            | 4  | 3  |  |  |
| Anxiety/Depression - EOT: Moderate probs          | 0  | 1  |  |  |
| Anxiety/Depression - 30 day Safety FU: No probs   | 2  | 2  |  |  |
| Anxiety/Depression-30 day Safety FU: Slight probs | 1  | 0  |  |  |
| Anxiety/Depression-30 day Safety FU: Severe probs | 0  | 1  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

To evaluate the effect of ruxolitinib on overall survival

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Time from randomization to date of death due to any cause (estimated to be assessed up to 48 months).

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Participants         | 0                    | 0                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma ruxolitinib concentrations

|                                                                                                    |                                   |
|----------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                    | Plasma ruxolitinib concentrations |
| End point description:<br>Characterize pharmacokinetics (PK)by utilizing a population PK approach. |                                   |
| End point type                                                                                     | Secondary                         |
| End point timeframe:<br>Week 12, Wk 48                                                             |                                   |

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Participants         | 0                    | 0                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS-2)

|                                                                                                                                                                                                     |                                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| End point title                                                                                                                                                                                     | Progression free survival (PFS-2) |
| End point description:<br>PFS-2 assessed by 25% increase over new baseline of PFS-1 in any of the following: • Progressive splenomegaly • 25 % increase in MF-7 score with absolute score $\geq 30$ |                                   |
| End point type                                                                                                                                                                                      | Secondary                         |
| End point timeframe:<br>From date of randomization until second disease progression or death, whichever comes first (estimated to be assessed up to 72 months)                                      |                                   |

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Participants         | 0                    | 0                   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Quality-adjusted life years from baseline

|                                                                                                                                                                                                                                                                                                                                        |                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                        | Quality-adjusted life years from baseline |
| End point description:<br>EQ-5D-5L (EuroQol-5D-5L, is a standardized instrument for measuring health outcomes, is consists of a descriptive system and a visual analogue scale - scores can be summarized into a single index score that provides a simple measure of health for clinical and economic appraisal ) The EQ-5D-5L health |                                           |

states will be converted into index values (utilities) from which the QALY (Quality - adjusted life years) will be calculated. QALY will be summarized descriptively by treatment arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from Baseline compared with scheduled study visits at the following intervals every 4 weeks up to week 24, every 8 weeks up to Week 48, every 12 weeks past Wk 48 until End of treatment and 30 day follow up visit

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Participants         | 0                    | 0                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first progressive splenomegaly (TTPS)

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Time to first progressive splenomegaly (TTPS) |
|-----------------|-----------------------------------------------|

End point description:

Time to first progressive splenomegaly as determined by spleen volume (by Magnetic Resonance Imaging (MRI)/Computed Tomography (CT)).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From randomization until earliest time to progressive splenomegaly (estimated to be assessed up to 48 months)

| End point values            | Ruxolitinib (INC424) | Ruxolitinib Placebo |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 25                   | 24                  |  |  |
| Units: Months               | 0                    | 0                   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to first symptomatic progression (TTSP)

|                 |                                              |
|-----------------|----------------------------------------------|
| End point title | Time to first symptomatic progression (TTSP) |
|-----------------|----------------------------------------------|

End point description:

Time to first symptomatic progression as determined by Myelofibrosis 7 Item Symptom Scale (MF-7)

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



---

End point timeframe:

From randomization until symptomatic progression (MF-7)(estimated to be assessed up to 48 months)

---

| <b>End point values</b>     | Ruxolitinib<br>(INC424) | Ruxolitinib<br>Placebo |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 25                      | 24                     |  |  |
| Units: Months               | 0                       | 0                      |  |  |

### **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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit, up to about 48 months.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 20.1   |

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description:

PLACEBO

|                       |        |
|-----------------------|--------|
| Reporting group title | INC424 |
|-----------------------|--------|

Reporting group description:

INC424

| Serious adverse events                                              | PLACEBO        | INC424         |  |
|---------------------------------------------------------------------|----------------|----------------|--|
| Total subjects affected by serious adverse events                   |                |                |  |
| subjects affected / exposed                                         | 1 / 24 (4.17%) | 2 / 24 (8.33%) |  |
| number of deaths (all causes)                                       | 0              | 0              |  |
| number of deaths resulting from adverse events                      | 0              | 0              |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                |  |
| Gastric cancer                                                      |                |                |  |
| subjects affected / exposed                                         | 0 / 24 (0.00%) | 1 / 24 (4.17%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Injury, poisoning and procedural complications                      |                |                |  |
| Tendon rupture                                                      |                |                |  |
| subjects affected / exposed                                         | 0 / 24 (0.00%) | 1 / 24 (4.17%) |  |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0          |  |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0          |  |
| Respiratory, thoracic and mediastinal disorders                     |                |                |  |
| Pneumonitis                                                         |                |                |  |

|                                                 |                |                |  |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 24 (4.17%) | 0 / 24 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | PLACEBO          | INC424           |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 11 / 24 (45.83%) | 17 / 24 (70.83%) |  |
| Vascular disorders                                    |                  |                  |  |
| Hypertension                                          |                  |                  |  |
| subjects affected / exposed                           | 3 / 24 (12.50%)  | 3 / 24 (12.50%)  |  |
| occurrences (all)                                     | 3                | 0                |  |
| Blood and lymphatic system disorders                  |                  |                  |  |
| Thrombocytopenia                                      |                  |                  |  |
| subjects affected / exposed                           | 2 / 24 (8.33%)   | 0 / 24 (0.00%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| Anaemia                                               |                  |                  |  |
| subjects affected / exposed                           | 6 / 24 (25.00%)  | 7 / 24 (29.17%)  |  |
| occurrences (all)                                     | 6                | 0                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Fatigue                                               |                  |                  |  |
| subjects affected / exposed                           | 4 / 24 (16.67%)  | 3 / 24 (12.50%)  |  |
| occurrences (all)                                     | 4                | 0                |  |
| Pyrexia                                               |                  |                  |  |
| subjects affected / exposed                           | 0 / 24 (0.00%)   | 2 / 24 (8.33%)   |  |
| occurrences (all)                                     | 0                | 0                |  |
| Respiratory, thoracic and mediastinal disorders       |                  |                  |  |
| Cough                                                 |                  |                  |  |
| subjects affected / exposed                           | 0 / 24 (0.00%)   | 3 / 24 (12.50%)  |  |
| occurrences (all)                                     | 0                | 0                |  |
| Skin and subcutaneous tissue disorders                |                  |                  |  |
| Night sweats                                          |                  |                  |  |
| subjects affected / exposed                           | 2 / 24 (8.33%)   | 1 / 24 (4.17%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| Pruritus                                              |                  |                  |  |

|                                                  |                      |                     |  |
|--------------------------------------------------|----------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 24 (12.50%)<br>3 | 0 / 24 (0.00%)<br>0 |  |
| Infections and infestations                      |                      |                     |  |
| Nasopharyngitis                                  |                      |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)       | 4 / 24 (16.67%)     |  |
| occurrences (all)                                | 0                    | 0                   |  |
| Respiratory tract infection                      |                      |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)       | 2 / 24 (8.33%)      |  |
| occurrences (all)                                | 0                    | 0                   |  |
| Urinary tract infection                          |                      |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)       | 2 / 24 (8.33%)      |  |
| occurrences (all)                                | 0                    | 0                   |  |
| Upper respiratory tract infection                |                      |                     |  |
| subjects affected / exposed                      | 0 / 24 (0.00%)       | 3 / 24 (12.50%)     |  |
| occurrences (all)                                | 0                    | 0                   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <a href="https://www.novctrd.com/CtrdWeb/home.nov">https://www.novctrd.com/CtrdWeb/home.nov</a> for complete trial results |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes: