Clinical trial results:
A single arm, multicenter, Phase IIa study to explore the efficacy and safety of ruxolitinib (INC424) in regularly transfused patients with thalassemia

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.novfor complete trial results.

Summary

EudraCT number	2013-002812-28
Trial protocol	IT GR
Global end of trial date	12 April 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	CINC424X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02049450
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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,

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	12 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of ruxolitinib on transfusion requirement.

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	28 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Turkey: 13
Worldwide total number of subjects	30
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

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)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 30 patients were planned to be enrolled in the study. 30 patients were analyzed in the full analysis, PK, and safety sets; 27 patients were analyzed in the per-protocol set.

Period 1

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

Arms

Arm title	INC424 (ruxolitinib) - Study Treatment

Arm description:

Regularly transfused adult patients with thalassemia and spleen enlargement

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:

Ruxolitinib (5 mg per tablet) at a starting dose of 10 mg twice daily with dose adjustments within the range of 5 to 25 mg twice daily.

Number of subjects in period 1	INC424 (ruxolitinib) - Study Treatment
Started	30
Completed	26
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Patients/guardian decision	1

Baseline characteristics

Reporting groups	
Reporting group title	INC424 (ruxolitinib) - Study Treatment
Reporting group description:	
Regularly transfused adult patients with thalassemia and spleen enlargement	

Reporting group values	INC424 (ruxolitinib) - Study Treatment	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults (18-64 years)	30	30	
Age Continuous Units: years			
arithmetic mean	25.9		
standard deviation	± 6.83	-	
Gender, Male/Female Units: Subjects			
Female	12	12	
Male	18	18	

End points

End points reporting groups

Reporting group title	INC424 (ruxolitinib) - Study Treatment
Reporting group description: Regularly transfused adult patients with thalassemia and spleen enlargement	
Subject analysis set title	10mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received INC422 10mg bid	
Subject analysis set title	15mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received INC422 15mg bid	
Subject analysis set title	20mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received INC422 20mg bid	
Subject analysis set title	5mg bid
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received INC422 5mg bid	

Primary: Change of hematocrit adjusted volume of red blood cells (RBC)

End point title	Change of hematocrit adjusted volume of red blood cells
End point description: Change of RBC transfusion requirement measured as percent change of the hematocrit-adjusted volume of transfused RBC during treatment (between week 6 and week 30) compared to baseline .	
End point type	Primary
End point timeframe: week 6, week 30	

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: The statistical analysis was descriptive. Mean percent change of RBC transfusion requirement was given with 95% confidence intervals: 95% CI as [-14.70, 2.83])

End point values	INC424 (ruxolitinib) - Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: % change of hematocrit-adjusted volume				
arithmetic mean (standard deviation)	-5.934 (± 22.1681)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in spleen volume (cm3)

End point title	Percentage change in spleen volume (cm3)

End point description:

Change of spleen volume from baseline at week 12 and week 30 as measured by magnetic imaging resonance (MRI) or computed tomography (CT).

End point type	Secondary

End point timeframe:

baseline, week 12, week 30

End point values	INC424 (ruxolitinib) - Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage change				
arithmetic mean (standard deviation)				
% change from baseline at Week 12 (n = 26)	-19.733 (± 16.0539)			
% change from baseline at Week 30 (n = 25)	-26.829 (± 16.6936)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change of mean pre-transfusion hemoglobin by 6 week time intervals

End point title	Change of mean pre-transfusion hemoglobin by 6 week time intervals

End point description:

Change from baseline in pre-transfusion hemoglobin levels

End point type	Secondary

End point timeframe:

baseline, weeks 0 - 30

End point values	INC424 (ruxolitinib) - Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage change of hemoglobin levels				
arithmetic mean (standard deviation)				

Weeks 0 - 6 (n = 27)	0.43 (± 10.135)			
Weeks 6 - 12 (n = 27)	2.87 (± 10.555)			
Weeks 12 - 18 (n = 27)	2.78 (± 11.081)			
Weeks 18 - 24 (n = 26)	-0.56 (± 9.76)			
Weeks 24 - 30 (n = 26)	0.06 (± 14.321)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in spleen length (cm) below the left coastal margin

End point title	Change in spleen length (cm) below the left coastal margin
End point description:	
Change of spleen length from baseline over time measured by palpitation by time	
End point type	Secondary
End point timeframe:	
baseline, weeks 1,2,3,4,6,12,18,24,30	

End point values	INC424 (ruxolitinib) - Study Treatment			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: percentage change in spleen length				
arithmetic mean (standard deviation)				
Week 1	-11.19 (± 15.376)			
Week 2	-22.11 (± 23.604)			
Week 3 (n = 29)	-25.01 (± 24.178)			
Week 4 (n = 29)	-26.94 (± 25.343)			
Week 6 (n = 29)	-33.85 (± 25.251)			
Week 12 (n = 29)	-49.29 (± 26.792)			
Week 18 (n = 27)	-56.32 (± 29.994)			
Week 24 (n = 27)	-56.93 (± 29.552)			
Week 30 (n = 24)	-57.4 (± 36.97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetice (PK) parameter for Cmin

End point title	Pharmacokinetice (PK) parameter for Cmin

End point description:

C min of INC424 by actual dose administered from 10mg bid to 20mg bid. Plasma PK samples were collected at Day 15 (Week 2), and Day 85 (Week 12). Cmin was collected immediately prior to dosing.

End point type	Secondary

End point timeframe:

Week 2 (Day 15), Week 12 (Day 85)

End point values	10mg bid	15mg bid	20mg bid	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	16	2	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 2 (Day 15)	7.58 (± 7.51959)	999.99 (± 99.99)	999.99 (± 99.99)	
Week 12 (Day 85)	9.13 (± 7.61039)	18.54 (± 23.9994)	20.23 (± 25.98617)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter for Cmax

End point title	Pharmacokinetics (PK) parameter for Cmax

End point description:

Cmax (1h) of INC424 by actual dose administered from 10mg bid to 20mg bid. Plasma PK samples were collected at Day 1, Week 2, and Week 12. Cmax was collected within a +/- 1 hour post dose.

End point type	Secondary

End point timeframe:

Day 1, Week 2 (Day 15), Week 12 (Day 85)

End point values	10mg bid	15mg bid	20mg bid	5mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	30	16	2	2
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	126.8 (± 58.70337)	999.99 (± 99.99)	999.99 (± 99.99)	58.2 (± 99.99)
Week 2 (Day 15)	125.24 (± 40.61805)	999.99 (± 99.99)	999.99 (± 99.99)	56.7 (± 99.99)
Week 12 (Day 85)	107.21 (± 50.07525)	245.69 (± 50.00362)	185 (± 97.58074)	999.99 (± 99.99)

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	INCB018424

Reporting group description:

INCB018424

Serious adverse events	INCB018424		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia viral			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	INCB018424		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 30 (76.67%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Weight increased			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pleuritic pain			

subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	10		
Urinary tract infection			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 December 2014	Amendment 1: The purpose of this protocol amendment was: To allow continuous use of ruxolitinib for patients who have completed 30 weeks of treatment in the study and are judged to be benefitting from study treatment according to the investigator, and are unable to access ruxolitinib outside of this clinical trial. A treatment extension phase was introduced for the patients continuing beyond Week 30 visit up to the time other alternatives to receive ruxolitinib from the sponsor become available; To update the contraception language to reflect current Novartis guidelines; To add some editorial clarifications and changes throughout the protocol to improve consistency and clarity.

Notes:

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 https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: