Clinical trial results:
An Open-Label Multiple Dose Study To Evaluate The Pharmacokinetics, Safety And Tolerability Of CP-690,550 In Pediatric Patients From 2 To Less Than 18 Years Of Age With Juvenile Idiopathic Arthritis (JIA)

Summary

EudraCT number	2011-004914-40
Trial protocol	PL HU SK IT
Global end of trial date	04 December 2015

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	13 July 2016

Trial information

Trial identification

Sponsor protocol code	A3921103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01513902
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000576-PIP01-09
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	03 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetic (PK) and safety of CP-690,550 following multiple oral doses in pediatric subjects (from 2 to less than 18 years) with active JIA.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 March 2013
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	Germany: 10
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	26
EEA total number of subjects	21

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)	18
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects aged 2 to less than (<)18 years with juvenile idiopathic arthritis (JIA) were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort I: 12 Years to <18 Years

Arm description:

CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 milliliter [mL] to 3 mL) for children weighing <40 kilogram (kg) or twice daily as oral tablets (5 milligram [mg]) for subjects weighing greater than or equal to (>=) 40 kg. Subjects who were unable to swallow tablets had the option of taking oral solution.

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	CP-690,550
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

CP-690,550 was administered orally, twice daily as oral solution.

Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	CP-690,550
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CP-690,550 was administered orally, twice daily as oral tablet.

Arm title	Cohort II: 6 Years to <12 Years

Arm description:

CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 3 mL) for subjects weighing <40 kg, oral tablets (5 mg) were used for subjects weighing >=40 kg. Subjects with a body weight of >=40 kg had the option of taking oral solution (5 mL) or tablets (5 mg).

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	CP-690,550
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

CP-690,550 was administered orally, twice daily as oral solution.

Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	CP-690,550
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

CP-690,550 was administered orally, twice daily as oral tablet.

Arm title	Cohort III: 2 Years to <6 Years

Arm description:

CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 4.5 mL) for subjects weighing <30 kg. Subjects weighing >=30 kg had the option of taking oral solution (5 mL) or tablets (5 mg).

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	CP-690,550
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

CP-690,550 was administered orally, twice daily as oral solution.

Number of subjects in period 1	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years
Started	8	9	9
Completed	8	9	9

Baseline characteristics

Reporting groups	
Reporting group title	Cohort I: 12 Years to <18 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 milliliter [mL] to 3 mL) for children weighing <40 kilogram (kg) or twice daily as oral tablets (5 milligram [mg]) for subjects weighing greater than or equal to (>=) 40 kg. Subjects who were unable to swallow tablets had the option of taking oral solution.	
Reporting group title	Cohort II: 6 Years to <12 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 3 mL) for subjects weighing <40 kg, oral tablets (5 mg) were used for subjects weighing >=40 kg. Subjects with a body weight of >=40 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	
Reporting group title	Cohort III: 2 Years to <6 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 4.5 mL) for subjects weighing <30 kg. Subjects weighing >=30 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	

Reporting group values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years
Number of subjects	8	9	9
Age categorical Units: Subjects			
Children (2-11 years)	0	9	9
Adolescents (12-17 years)	8	0	0
Age Continuous | Units: years			
arithmetic mean	14.1	9.4	4
standard deviation	± 2	± 1.8	± 1
Gender, Male/Female Units: Subjects			
Female	5	5	7
Male	3	4	2

Reporting group values	Total		
Number of subjects	26		
Age categorical Units: Subjects			
Children (2-11 years)	18		
Adolescents (12-17 years)	8		
Age Continuous | Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	17		
Male	9		

End points

End points reporting groups

Reporting group title	Cohort I: 12 Years to <18 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 milliliter [mL] to 3 mL) for children weighing <40 kilogram (kg) or twice daily as oral tablets (5 milligram [mg]) for subjects weighing greater than or equal to (>=) 40 kg. Subjects who were unable to swallow tablets had the option of taking oral solution.	
Reporting group title	Cohort II: 6 Years to <12 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 3 mL) for subjects weighing <40 kg, oral tablets (5 mg) were used for subjects weighing >=40 kg. Subjects with a body weight of >=40 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	
Reporting group title	Cohort III: 2 Years to <6 Years
Reporting group description:	
CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 4.5 mL) for subjects weighing <30 kg. Subjects weighing >=30 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	

Primary: Apparent Oral Clearance (CL/F)

End point title	Apparent Oral Clearance (CL/F)[1]
End point description:	
Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is also influenced by the fraction of the dose absorbed. Clearance was estimated by non compartmental analysis (NCA) of PK data. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. It was calculated by dividing the given oral dose by AUCtau. AUCtau is the area under the plasma concentration time-curve from time zero to end of dosing interval. The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest. Here 'number of subjects analyzed (N)' signifies those subjects who were evaluable for this outcome measure.	
End point type	Primary
End point timeframe:	
Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose	

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: Only descriptive data was planned to be reported for this endpoint

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	9	
Units: liter per hour				
geometric mean (geometric coefficient of variation)	28.09 (± 22)	25.48 (± 40)	20.53 (± 33)	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) All Causalities

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) All Causalities[2]

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent AEs included both serious and non-serious AEs. The safety analysis population included all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline up to 28 days after the last dose of study drug (Day 5)

Notes:

[2] - 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: Only descriptive data was planned to be reported for this endpoint

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: subjects				
AE	1	1	2	
SAE	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Laboratory Test Abnormalities

End point title	Number of Subjects With Laboratory Test Abnormalities[3]

End point description:

Subjects with laboratory test abnormalities of potential clinical concern without regard to baseline abnormality were reported. Criteria: Hematology(hemoglobin,hematocrit,red blood cell[RBC] count:<0.8*lower limit of normal [LLN], platelets:<0.5*LLN/greater than [>]1.75*upper limit of normal[ULN], white blood cell [WBC] count:<0.6*LLN/ >1.5*ULN, lymphocytes, total neutrophils: <0.8*LLN or >1.2*ULN, basophils, eosinophil, monocytes:>1.2*ULN); Liver Function (total bilirubin: >1.5*ULN, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase:>3.0*ULN, total protein, albumin:<0.8*LLN or >1.2*ULN);Renal Function (blood urea nitrogen, creatinine:>1.3*ULN, uric acid:>1.2*ULN);Electrolytes (sodium:<0.95*LLN or >1.05*ULN,potassium,chloride,calcium,bicarbonate:<0.9*LLN or >1.1*ULN); Clinical chemistry (glucose <0.6*LLN or >1.5*ULN, creatine kinase:>3.0*ULN); Urinalysis (Urine WBC and RBC: greater than or

End point type	Primary

End point timeframe:

Baseline up to Day 5

Notes:

[3] - 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: Only descriptive data was planned to be reported for this endpoint

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: subjects	3	1	5	

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Vital Signs Abnormalities

End point title	Number of Subjects With Clinically Significant Vital Signs Abnormalities[4]

End point description:

Criteria for vital signs of potentially clinical concern included supine/sitting pulse rate of <40 beats per minute (bpm) or >120 bpm, standing pulse rate of <40 bpm or >140 bpm, systolic blood pressure of >=30 millimeters of mercury (mmHg) change from baseline and systolic blood pressure <90 mmHg, diastolic blood pressure >=20 mmHg change from baseline and diastolic blood pressure <50 mm Hg. The safety analysis population included all subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline up to Day 5

Notes:

[4] - 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: Only descriptive data was planned to be reported for this endpoint

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to end of Dosing Interval (AUCtau)

End point title	Area Under the Curve From Time Zero to end of Dosing Interval (AUCtau)

End point description:

The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest. Here 'number of subjects analyzed (N)' signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	9	
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	156.6 (± 25)	118.8 (± 27)	142.5 (± 32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)

End point description:

The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest.

End point type	Secondary

End point timeframe:

Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	46.97 (± 40)	41.67 (± 29)	66.15 (± 28)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point description:

The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest.

End point type	Secondary

End point timeframe:

Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	9	9	
Units: hours				
median (full range (min-max))	0.75 (0.5 to 6.9)	1 (0.5 to 2.05)	0.5 (0.5 to 1.92)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Decay Half-Life (t1/2)

End point title	Plasma Decay Half-Life (t1/2)

End point description:

Plasma decay half-life is the time measured for the plasma concentration to decrease by one half. The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest. Here 'N' signifies those subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	9	
Units: hours				
arithmetic mean (standard deviation)	2.616 (± 0.454)	1.949 (± 0.294)	1.771 (± 0.406)	

Statistical analyses

No statistical analyses for this end point

Secondary: Taste Assessment

End point title	Taste Assessment

End point description:

Subjects were evaluated for taste assessment using a 5 categories questionnaire. Subjects were asked

to answer one of the following to describe the taste of oral solution of tofacitinib: Dislike very much, dislike a little, not sure, like a little, or like very much. The taste assessment was only performed for subjects who received the oral solution. Number of subjects within each category are reported. The analysis population was defined as all participants who had received at least 1 oral solution formulation of tofacitinib.

End point type	Secondary

End point timeframe:

Day 1, Day 5

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	7	9	
Units: subjects				
Day 1: Dislike very much	0	1	1	
Day 1: Dislike a little	0	0	2	
Day 1: Not sure	1	1	1	
Day 1: Like a little	1	3	1	
Day 1: Like very much	0	2	4	
Day 5: Dislike very much	0	1	0	
Day 5: Dislike a little	1	0	3	
Day 5: Not sure	1	2	1	
Day 5: Like a little	0	2	2	
Day 5: Like very much	0	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution (Vz/F)

End point title	Apparent Volume of Distribution (Vz/F)

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired plasma concentration of a drug. Apparent volume of distribution after oral dose (Vz/F) is influenced by the fraction absorbed. The PK analysis population included all enrolled and treated subjects who had at least 1 of the PK parameters of primary interest. Here 'N' signifies those subjects who were evaluable for this outcome measure

End point type	Secondary

End point timeframe:

Day 5: Pre-dose, 0.5, 1, 2, 4, 8 hours post dose

End point values	Cohort I: 12 Years to <18 Years	Cohort II: 6 Years to <12 Years	Cohort III: 2 Years to <6 Years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8	9	
Units: liter				
geometric mean (geometric coefficient of variation)	104.9 (± 35)	71 (± 40)	51.44 (± 34)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to 28 days after the last dose of study drug (Day 5)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Cohort I: 12 Years to <18 Years
Reporting group description: CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 milliliter [mL] to 3 mL) for children weighing <40 kilogram (kg) or twice daily as oral tablets (5 milligram [mg]) for subjects weighing greater than or equal to (>=) 40 kg. Subjects who were unable to swallow tablets had the option of taking oral solution.	
Reporting group title	Cohort III: 2 Years to <6 Years
Reporting group description: CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 4.5 mL) for subjects weighing <30 kg. Subjects weighing >=30 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	
Reporting group title	Cohort II: 6 Years to <12 Years
Reporting group description: CP-690,550 was administered orally, twice daily as oral solution (ranging from 1 mL to 3 mL) for subjects weighing <40 kg, oral tablets (5 mg) were used for subjects weighing >=40 kg. Subjects with a body weight of >=40 kg had the option of taking oral solution (5 mL) or tablets (5 mg).	

Serious adverse events	Cohort I: 12 Years to <18 Years	Cohort III: 2 Years to <6 Years	Cohort II: 6 Years to <12 Years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort I: 12 Years to <18 Years	Cohort III: 2 Years to <6 Years	Cohort II: 6 Years to <12 Years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 9 (22.22%)	1 / 9 (11.11%)
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 9 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	0 / 9 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 9 (11.11%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 January 2012	Add certain prohibited treatment for psoriases, added apparent volume of distribution (Vz/F) to the parameters to be analyzed.
02 November 2012	Exclusion criteria on lymphocytes levels added, section on infections added.
14 July 2014	Revision of dosing scheme

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported