EU Clinical Trials Register

Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Assess the Immune Response Following Administration of Zoster Vaccine to Subjects With Rheumatoid Arthritis Receiving Tofacitinib (CP-690,550) or Placebo With Background Methotrexate Treatment

Summary

EudraCT number	2014-000706-34
Trial protocol	GB
Global end of trial date	06 July 2015

Results information

Result version number	v1 (current)
This version publication date	07 July 2016
First version publication date	07 July 2016

Trial information

Trial identification

Sponsor protocol code	A3921237

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer, Inc., Pfizer ClinicalTrials.gov Call Center, 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)	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	13 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2015
Global end of trial reached?	Yes
Global end of trial date	06 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the effect of tofacitinib on varicella zoster virus (VZV)-specific immunoglobulin reponses 6 weeks after zoster vaccination in patients with rheumatoid arthritis (RA) on background methotrexate (MTX).

Protection of trial subjects:

A Data Monitoring Committee (DMC) was responsible for ongoing monitoring of patient safety according to the Charter. Recommendations made by the DMC to alter the conduct of the study were forwarded to the Sponsor for final decision.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2014
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	United States: 112
Worldwide total number of subjects	112
EEA total number of subjects	0

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)	77
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult subjects ≥50 years with active RA, characterized by ≥4 tender/painful joints and ≥4 swollen joints at screening or baseline before vaccination, and characterized by a screening CRP3mg/L or Clinical Disease Activity Index score10 at screening or baseline before vaccination, and had ≥4 month treatment with MTX 15-25mg/week before screening.

Pre-assignment

Screening details:

The zoster vaccine was administered at least 2 weeks (14 to 21 days) prior to initiation of CP-690,550 (tofacitinib) or placebo in rheumatoid arthritis (RA) patients on background methotrexate therapy.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Twice a Day

Arm description:

Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received placebo matched tofacitinib tablets twice a day orally for up to 12 weeks.

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

Dosage and administration details:

orally twice a day

Arm title	Tofacitinib 5 mg Twice a Day

Arm description:

Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received tofacitinib 5 mg tablets twice a day orally for up to 12 weeks.

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

Dosage and administration details:

5 mg orally twice a day

Number of subjects in period 1	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day
Started	57	55
Completed	46	50
Not completed	11	5
Adverse event, non-fatal	9	4
Lack of efficacy	2	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo Twice a Day
Reporting group description:	

Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received placebo matched tofacitinib tablets twice a day orally for up to 12 weeks.

Reporting group title	Tofacitinib 5 mg Twice a Day
Reporting group description:	

Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received tofacitinib 5 mg tablets twice a day orally for up to 12 weeks.

Reporting group values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day	Total
Number of subjects	57	55	112
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	38	77
From 65-84 years	18	17	35
85 years and over	0	0	0
Age Continuous				
Units: years			
arithmetic mean	62	61.7	
standard deviation	± 8.7	± 6.2	-
Gender, Male/Female			
Units: participants			
FEMALE	38	42	80
MALE	19	13	32

End points

End points reporting groups

Reporting group title	Placebo Twice a Day
Reporting group description:	
Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received placebo matched tofacitinib tablets twice a day orally for up to 12 weeks.	
Reporting group title	Tofacitinib 5 mg Twice a Day
Reporting group description:	
Following administration of zoster vaccine, participants with Rheumatoid Arthritis (RA) on background methotrexate received tofacitinib 5 mg tablets twice a day orally for up to 12 weeks.	

Primary: Fold Rise From Baseline in Varicella Zoster Virus (VZV)-Specific Immunoglobulin G (IgG) Levels at Week 4

End point title	Fold Rise From Baseline in Varicella Zoster Virus (VZV)-Specific Immunoglobulin G (IgG) Levels at Week 4
End point description:	
VZV-specific IgG levels as measured by enzyme-linked immunosorbent assay (ELISA). Baseline units are measured in units of glycoprotein ELISA units per milliliter (gp ELISA units/mL).	
End point type	Primary
End point timeframe:	
Baseline (pre-vaccination; Day -14), Week 4 (6 weeks post-vaccination)	

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: fold rise				
number (not applicable)				
Baseline (gp ELISA units/mL)	182.338	200.952		
Fold Rise at Week 4	1.736	2.105		

Statistical analyses

Statistical analysis title	Geometric Mean Fold Rise (GMFR) at Week 4
Statistical analysis description:	
Geometric Mean Fold Rise (GMFR) for Tofacitinib versus Placebo (Week 4)	
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMFR
Point estimate	1.213
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.033
upper limit	1.424

Secondary: Fold Rise From Baseline in VZV-Specific IgG Levels at Day 1 and Week 12

End point title	Fold Rise From Baseline in VZV-Specific IgG Levels at Day 1 and Week 12

End point description:

The evaluable immunogenicity analysis population included randomized patients who had at least 1 dose of study drug (tofacitinib or placebo) and who complied closely with protocol eligibility criteria, visit windows for study procedures, had valid assay results at the primary visits and no major protocol deviations.

End point type	Secondary

End point timeframe:

Baseline (pre-vaccination; Day -14), Day 1 (2 weeks post-vaccination), Week 12 (14 weeks post-vaccination)

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: fold rise				
number (not applicable)				
Fold Rise at Day 1 (n=53,54)	1.947	2.005		
Fold Rise at Week 12 (n=44,48)	1.496	1.636		

Statistical analyses

Statistical analysis title	GMFR at Week 12
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMFR
Point estimate	1.093
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.924
upper limit	1.294

Statistical analysis title	GMFR at Day 1
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMFR
Point estimate	1.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.877
upper limit	1.209

Secondary: Absolute Values in VZV-Specific IgG Levels at Day 1, Week 4 and Week 12

End point title	Absolute Values in VZV-Specific IgG Levels at Day 1, Week 4 and Week 12
End point description:	

The absolute geometric mean titer (GMT) of VZV-specific IgG levels was calculated from logarithmically transformed assay values.

End point type	Secondary
End point timeframe:	

Day 1 (2 weeks post-vaccination), Week 4 (6 weeks post-vaccination), Week 12 (14 weeks post-vaccination)

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: gpELISA units/mL				
geometric mean (confidence interval 80%)				

Day -14	182.338 (151.281 to 219.771)	200.952 (166.045 to 243.198)		
Day 1 (n=53,54)	361.603 (300.012 to 435.838)	384.219 (317.477 to 464.993)		
Week 4 (n=53,54)	322.486 (267.557 to 388.69)	403.422 (333.343 to 488.232)		
Week 12 (n=44,48)	278.599 (229.984 to 337.489)	312.328 (257.319 to 379.096)		

Statistical analyses

Statistical analysis title	Ratio of GMT at Day 1
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMT
Point estimate	1.063
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.821
upper limit	1.375

Statistical analysis title	Ratio of GMT at Week 4
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMT
Point estimate	1.251
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.967
upper limit	1.618

Statistical analysis title	Ratio of GMT at Week 12
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day

Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	ANCOVA
Parameter estimate	Ratio of GMT
Point estimate	1.121
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.862
upper limit	1.459

Secondary: Percentage of Patients With >=1.5 Fold Rise in VZV-Specific IgG Levels Day 1, Week 4 and Week 12

End point title	Percentage of Patients With >=1.5 Fold Rise in VZV-Specific IgG Levels Day 1, Week 4 and Week 12
End point description:	
VZV-specific IgG levels as measured by ELISA. A ratio greater than or equal to (>=) 1.5 was defined as a responder.	
End point type	Secondary
End point timeframe:	
Day 1 (2 weeks post-vaccination), Week 4 (6 weeks post-vaccination), Week 12 (14 weeks post-vaccination)	

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	54		
Units: percentage of patients				
number (not applicable)				
Day 1 (n=53,54)	47.17	55.56		
Week 4 (n=53,54)	43.4	57.41		
Week 12 (n=44,48)	43.18	45.83		

Statistical analyses

Statistical analysis title	Tofacitinib versus Placebo (Day 1)
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	80% CI based on Chan and Zhang method
Parameter estimate	Mean difference (final values)
Point estimate	8.39

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.05
upper limit	20.56

Statistical analysis title	Tofacitinib versus Placebo (Week 4)
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	80% CI based on Chan and Zhang method
Parameter estimate	Mean difference (final values)
Point estimate	14.01
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.57
upper limit	26.03

Statistical analysis title	Tofacitinib versus Placebo (Week 12)
Comparison groups	Placebo Twice a Day v Tofacitinib 5 mg Twice a Day
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Method	80% CI based on Chan and Zhang method
Parameter estimate	Mean difference (final values)
Point estimate	2.65
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-10.66
upper limit	15.83

Other pre-specified: Number of Patients With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Patients With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a patient who received study drug. An 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 are events between first dose of study drug and up to Week 16 that were absent before treatment or that worsened relative to pre-treatment state. AEs included both SAEs and non-SAEs.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: patients				
AEs	21	16		
SAEs	0	3		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients With Zoster Vaccine-Related AEs by System Organ Class

End point title	Number of Patients With Zoster Vaccine-Related AEs by System Organ Class

End point description:

Zoster vaccine-related AEs included General Disorders and Administration Site Conditions (injection site erythema, pain, pruritis, rash, swelling; vaccination site erythema, pruritus, rash), Infections and Infestations (disseminated herpes zoster), and Musculoskeletal and Connective Tissue Disorders (myalgia). All zoster vaccine-related AEs were mild, except for the herpes zoster AE classified under Infections and Infestations, which was moderate in severity.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: patients				
General and Administration Site Conditions	2	4		
Infections and Infestations	0	1		
Musculoskeletal and Connective Tissue Disorders	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients With Clinical Herpes Zoster Events by Severity

End point title	Number of Patients With Clinical Herpes Zoster Events by Severity

End point description:

Clinical herpes is manifested as mild, moderate, or severe disseminated herpes zoster.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: patients				
Mild Herpes Zoster	0	0		
Moderate Herpes Zoster	0	1		
Severe Herpes Zoster	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Patients With Clinically Significant Abnormal Laboratory Parameters

End point title	Number of Patients With Clinically Significant Abnormal Laboratory Parameters

End point description:

Patients with the following abnormalities were discontinued from the study: 2 sequential absolute neutrophil counts (ANC) <1000/mm^3; 2 sequential hemoglobin values <8.0 g/dL or decreases of >30% from baseline value; 2 sequential absolute lymphocyte count <500/mm^3; 2 sequential platelet counts <75,000/mm^3; 2 sequential alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations >=3 times the upper limit of normal (X ULN) with a total bilirubin value >=2X ULN, elevated international normalized ratio (INR), or accompanied by signs/symptoms consistent with hepatic injury; 2 sequential ALT or AST elevations >=5X ULN regardless of total bilirubin or accompanying symptoms; confirmed increases in serum creatinine (SCr) >50% over the average of screening and baseline values; a confirmed positive urine pregnancy test or refusal to use appropriate contraception in a woman of childbearing potential.

End point type	Other pre-specified

End point timeframe:

Baseline up to Week 16

End point values	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: patients	1	0		

Statistical analyses

No statistical analyses for this end point

	Placebo Twice a Day	Tofacitinib 5 mg Twice a Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: patients	1	0		

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 16

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one patient and as non-serious in another patient, or one patient may have experienced both a serious and non-serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Tofacitinib 5 mg Twice a Day

Reporting group description:

Following administration of zoster vaccine to RA patients receiving background methotrexate, patients received tofacitinib 5 mg twice a day orally for up to 12 weeks.

Reporting group title	Placebo Twice a Day

Reporting group description:

Following administration of zoster vaccine to rheumatoid arthritis (RA) patients receiving background methotrexate, patients received tofacitinib-matched placebo tablets twice a day orally for up to 12 weeks.

Serious adverse events	Tofacitinib 5 mg Twice a Day	Placebo Twice a Day	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 55 (5.45%)	0 / 57 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

	Tofacitinib 5 mg Twice a Day	Placebo Twice a Day	
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated	Additional description: adjudicated AE term "vaccine dissemination VZV"		
subjects affected / exposed	1 / 55 (1.82%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tofacitinib 5 mg Twice a Day	Placebo Twice a Day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 55 (10.91%)	9 / 57 (15.79%)	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 55 (5.45%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Rheumatoid arthritis			
subjects affected / exposed	3 / 55 (5.45%)	9 / 57 (15.79%)	
occurrences (all)	3	9	

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

 None reported