Clinical trial results:
Evaluation of the Efficacy and Safety of GS-5745 as Add-On Therapy to a Tumor Necrosis Factor Inhibitor and Methotrexate Regimen in Subjects with Moderate to Severe Rheumatoid Arthritis

Summary

EudraCT number	2016-000897-39
Trial protocol	HU DE BE
Global end of trial date	07 August 2017

Results information

Result version number	v1
This version publication date	16 June 2018
First version publication date	16 June 2018

Trial information

Trial identification

Sponsor protocol code	GS-US-373-1499

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02862574
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	07 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2017
Global end of trial reached?	Yes
Global end of trial date	07 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of andecaliximab (GS-5745) versus placebo as an add-on therapy to a tumor necrosis factor (TNF) inhibitor and methotrexate in adults with moderate to severe rheumatoid arthritis (RA).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy:

Participants remained on their current treatment regimen of a TNF inhibitor and methotrexate.

Evidence for comparator: -

Actual start date of recruitment	15 December 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	United States: 15
Worldwide total number of subjects	15
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)	13
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States. The first participant was screened on 15 December 2016. The last study visit occurred on 07 August 2017.

Pre-assignment

Screening details:

28 participants were screened.

Period 1

Period 1 title	Double-Blind Treatment 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	Andecaliximab 300 mg

Arm description:

Andecaliximab 300 mg for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Experimental
Investigational medicinal product name	Andecaliximab
Investigational medicinal product code	
Other name	GS-5745
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

300 mg administered once weekly

Arm title	Andecaliximab 150 mg

Arm description:

Andecaliximab 150 mg + placebo for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Experimental
Investigational medicinal product name	Andecaliximab
Investigational medicinal product code	
Other name	GS-5745
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

150 mg administered once weekly

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once weekly

Arm title	Placebo

Arm description:

Placebo once weekly for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once weekly

Number of subjects in period 1	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo
Started	5	5	5
Completed	2	3	1
Not completed	3	2	4
Adverse event, non-fatal	-	1	-
Study Terminated by Sponsor	3	1	4

Period 2

Period 2 title	Open-Label Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Andecaliximab 300 mg to Andecaliximab 300 mg

Arm description:

Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Experimental
Investigational medicinal product name	Andecaliximab
Investigational medicinal product code	
Other name	GS-5745
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

300 mg administered once weekly

Arm title	Andecaliximab 150 mg to Andecaliximab 300 mg

Arm description:

Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Experimental

Investigational medicinal product name	Andecaliximab
Investigational medicinal product code	
Other name	GS-5745
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

150 mg administered once weekly

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once weekly

Arm title	Placebo to Andecaliximab 300 mg

Arm description:

Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered once weekly

Number of subjects in period 2	Andecaliximab 300 mg to Andecaliximab 300 mg	Andecaliximab 150 mg to Andecaliximab 300 mg	Placebo to Andecaliximab 300 mg
Started	2	3	1
Completed	0	0	0
Not completed	2	3	1
Study Terminated by Sponsor	2	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Andecaliximab 300 mg
Reporting group description:	
Andecaliximab 300 mg for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 150 mg
Reporting group description:	
Andecaliximab 150 mg + placebo for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Placebo
Reporting group description:	
Placebo once weekly for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	

Reporting group values	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo
Number of subjects	5	5	5
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54	57	58
standard deviation	± 16.3	± 9.3	± 5.6
Gender categorical Units: Subjects			
Female	3	4	4
Male	2	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	0
Not Hispanic or Latino	5	3	5
Race Units: Subjects			
White	3	5	4
Black	2	0	1
Disease Activity Score Creactive Protein (DAS28(CRP))			
The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient’s Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and C-Reactive Protein (CRP) for a total possible score of 2 to 10. Higher values indicate higher disease activity.			
Units: units on a scale			
arithmetic mean	5.79	5.90	5.69
standard deviation	± 0.814	± 0.752	± 0.887

Reporting group values	Total		
Number of subjects	15		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	11		
Male	4		
Ethnicity Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	13		
Race Units: Subjects			
White	12		
Black	3		
Disease Activity Score Creactive Protein (DAS28(CRP))			
The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient’s Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and C-Reactive Protein (CRP) for a total possible score of 2 to 10. Higher values indicate higher disease activity.			
Units: units on a scale arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Andecaliximab 300 mg
Reporting group description:	
Andecaliximab 300 mg for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 150 mg
Reporting group description:	
Andecaliximab 150 mg + placebo for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Placebo
Reporting group description:	
Placebo once weekly for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 300 mg to Andecaliximab 300 mg
Reporting group description:	
Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 150 mg to Andecaliximab 300 mg
Reporting group description:	
Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Placebo to Andecaliximab 300 mg
Reporting group description:	
Andecaliximab 300 mg for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	

Primary: Change From Baseline in DAS28(CRP) at Week 12

End point title	Change From Baseline in DAS28(CRP) at Week 12[1]
End point description:	
The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient’s Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and CRP for a total possible score of 1 to 9.4. Higher values indicate higher disease activity. A negative change from baseline indicates improvement. Participants in the Full Analysis Set (all randomized participants who received at least 1 dose of study drug) with available data were analyzed.	
End point type	Primary
End point timeframe:	
Baseline; Week 12	

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 comparison was planned or performed.

End point values	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	3	3	
Units: units on a scale				
arithmetic mean (standard deviation)	0.13 (± 0.115)	-1.51 (± 0.670)	-0.36 (± 0.353)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants That Achieve DAS28(CRP) ≤ 3.2 at Week 12

End point title	Percentage of Participants That Achieve DAS28(CRP) ≤ 3.2 at Week 12

End point description:

The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient’s Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and CRP for a total possible score of 1 to 9.4. Higher values indicate higher disease activity. A negative change from baseline indicates improvement. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: percentage of participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants That Achieve DAS28(CRP) < 2.6 at Week 12

End point title	Percentage of Participants That Achieve DAS28(CRP) < 2.6 at Week 12

End point description:

The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient’s Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and CRP for a total possible score of 1 to 9.4. Higher values indicate higher disease activity. A negative change from baseline indicates improvement. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: percentage of participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Andecaliximab

End point title	Plasma Concentration of Andecaliximab

End point description:

The plasma concentrations of andecaliximab were not collected and were not analyzed.

End point type	Secondary

End point timeframe:

Day 4 or 6 (± 1 day)

End point values	Andecaliximab 300 mg	Andecaliximab 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[2] - The plasma concentrations of andecaliximab were not collected and were not analyzed.

[3] - The plasma concentrations of andecaliximab were not collected and were not analyzed.

[4] - The plasma concentrations of andecaliximab were not collected and were not analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to the last dose date (maximum: 127 days) plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set: participants who received at least 1 dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Andecaliximab 300 mg (Double-Blind)
Reporting group description:	
Andecaliximab 300 mg for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 150 mg (Double-Blind)
Reporting group description:	
Andecaliximab 150 mg + placebo for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Placebo (Double-Blind)
Reporting group description:	
Placebo once weekly for 12 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	
Reporting group title	Andecaliximab 300 mg (Open-Label)
Reporting group description:	
Andecaliximab 300 mg administered via subcutaneous injection once weekly for up to 52 weeks, in addition to participant's current regimen of a TNF inhibitor and methotrexate	

Serious adverse events	Andecaliximab 300 mg (Double-Blind)	Andecaliximab 150 mg (Double-Blind)	Placebo (Double-Blind)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Andecaliximab 300 mg (Open-Label)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Andecaliximab 300 mg (Double-Blind)	Andecaliximab 150 mg (Double-Blind)	Placebo (Double-Blind)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	2 / 5 (40.00%)	2 / 5 (40.00%)
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Andecaliximab 300 mg (Open-Label)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Rash papular subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1 0 / 6 (0.00%) 0		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2016	Amendment #1 was initiated to add study drug administration visits to the Schedule of Assessments and to eliminate an un-needed visit. Several points were clarified and several clerical errors were corrected such as biomarker collection time-points.
23 September 2016	The following changes were made to enhance safety monitoring: ● Added chest x-ray at screening to further exclude active TB or lung disease and annually to monitor for re-activation of disease ● Added annual QuantiFERON-TB Gold test to monitor for re-activation of tuberculosis (TB) ● Added reflex testing for Hepatitis B and C every 3 months if subjects test positive for serology at screening ● Added erythrocyte sedimentation rate (ESR) at all study visits to correlate sedimentation rates with C-Reactive protein (CRP)levels ● Added pregnancy precaution requirements for methotrexate (MTX) ● Added additional hematology and chemistry lab draws at Open Label Extension (OLE) weeks 19, 30, 42, and 54 to monitor for infection. Additional instructions were added for potential re-screening of eligible subjects

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 June 2017	Gilead made a decision to discontinue the development of andecaliximab in rheumatoid arthritis. This decision was not due to any safety concerns with andecaliximab or with study procedures. As a result of the decision, Study GS-US-373-1499 was terminated.	-

Notes:

Limitations and caveats

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

Because the study was terminated early by the sponsor and only 15 participants were enrolled, no formal statistical testing was completed for the final analysis.

Notes: