Clinical trial results:
A Phase 2a, Randomized, Placebo-controlled, Proof of Mechanism Study to Evaluate the Safety and Efficacy of AMG 557/MEDI5872 in Subjects with Primary Sjogren's Syndrome

Summary

EudraCT number	2014-003896-41
Trial protocol	GB SE
Global end of trial date	13 August 2018

Results information

Result version number	v1 (current)
This version publication date	23 August 2019
First version publication date	23 August 2019

Trial information

Trial identification

Sponsor protocol code	D5181C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02334306
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Maryland, Gaithersburg, United States, 20878
Public contact	Gabor Illei, MedImmune, LLC, +1 240 558 0038 118, information.center@astrazenea.com
Scientific contact	Gabor Illei, MedImmune, LLC, +1 240 558 0038 118, information.center@astrazenea.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 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of AMG 557/MEDI5872 compared to placebo in reducing objective measures of overall disease activity in subjects with primary Sjogren's syndrome.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Subjects signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 2015
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	France: 11
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	32
EEA total number of subjects	26

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)	27
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted across 4 countries (France, United Kingdom, Sweden, and the United States).

Pre-assignment

Screening details:

A total of 59 participants were screened in the study. Of which, 27 participants were screen failures and 32 participants were randomized and enrolled in study.

Period 1

Period 1 title	Double-blind period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received a subcutaneous (SC) dose of placebo matching with MEDI5872 every week (QW) for 3 weeks (Days 1, 8, and 15) and then every 2 weeks (Q2W) for next 9 weeks (Days 29 to 85) in double-blind period of the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo matching to MEDI5872 was administered subcutaneously QW for 3 weeks (Days 1, 8, and 15) and then Q2W for next 9 weeks (Days 29 to 85).

Arm title	MEDI5872 210 mg

Arm description:

Participants received a fixed SC dose of 210 mg MEDI5872 QW for 3 weeks (Days 1, 8, and 15) and then Q2W for next 9 weeks (Days 29 to 85) in double-blind period of the study.

Arm type	Experimental
Investigational medicinal product name	MEDI5872
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

MEDI5872 210 mg was administered subcutaneously QW for 3 weeks (Days 1, 8, and 15) and then Q2W for next 9 weeks (Days 29 to 85).

Number of subjects in period 1	Placebo	MEDI5872 210 mg
Started	16	16
Completed	15	14
Not completed	1	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Open-label period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/MEDI5872 210 mg

Arm description:

Participants who received placebo in double-blind period, received MEDI5872 QW from Days 99 to 113 and Q2W from Days 127 to 183 in open-label period of the study.

Arm type	Experimental
Investigational medicinal product name	MEDI5872
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants who received placebo in double-blind period, received MEDI5872 QW from Days 99 to 113 and Q2W from Days 127 to 183.

Arm title	MEDI5872 210 mg/MEDI5872 210 mg

Arm description:

Participants who received MEDI5872 210 mg in double-blind period, continued to receive MEDI5872 210 mg Q2W from Days 99 to 183 and received an additional dose of blinded placebo on Day 106 in open-label period of the study.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered subcutaneously on Day 106 for participants who received MEDI5872 in double-blind period.

Investigational medicinal product name	MEDI5872
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants who received MEDI5872 in double-blind period were continued to receive MEDI5872 210mg Q2W from Days 99 to 183.

Number of subjects in period 2	Placebo/MEDI5872 210 mg	MEDI5872 210 mg/MEDI5872 210 mg
Started	15	14
Completed	15	14

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received a subcutaneous (SC) dose of placebo matching with MEDI5872 every week (QW) for 3 weeks (Days 1, 8, and 15) and then every 2 weeks (Q2W) for next 9 weeks (Days 29 to 85) in double-blind period of the study.	
Reporting group title	MEDI5872 210 mg
Reporting group description:	
Participants received a fixed SC dose of 210 mg MEDI5872 QW for 3 weeks (Days 1, 8, and 15) and then Q2W for next 9 weeks (Days 29 to 85) in double-blind period of the study.	

Reporting group values	Placebo	MEDI5872 210 mg	Total
Number of subjects	16	16	32
Age categorical			
The subject analysis set for baseline characteristics was "Intent-to-treat (ITT) population". ITT population included all randomized and treated participants, grouped according to assigned treatment.			
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)	15	12	27
From 65-84 years	1	4	5
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	50.2	51.1	
standard deviation	± 12	± 14.3	-
Sex: Female, Male			
Units: Subjects			
Female	14	14	28
Male	2	2	4

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received a subcutaneous (SC) dose of placebo matching with MEDI5872 every week (QW) for 3 weeks (Days 1, 8, and 15) and then every 2 weeks (Q2W) for next 9 weeks (Days 29 to 85) in double-blind period of the study.

Reporting group title	MEDI5872 210 mg

Reporting group description:

Participants received a fixed SC dose of 210 mg MEDI5872 QW for 3 weeks (Days 1, 8, and 15) and then Q2W for next 9 weeks (Days 29 to 85) in double-blind period of the study.

Reporting group title	Placebo/MEDI5872 210 mg

Reporting group description:

Participants who received placebo in double-blind period, received MEDI5872 QW from Days 99 to 113 and Q2W from Days 127 to 183 in open-label period of the study.

Reporting group title	MEDI5872 210 mg/MEDI5872 210 mg

Reporting group description:

Participants who received MEDI5872 210 mg in double-blind period, continued to receive MEDI5872 210 mg Q2W from Days 99 to 183 and received an additional dose of blinded placebo on Day 106 in open-label period of the study.

Subject analysis set title	Any MEDI5872 210 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received at least one dose of MEDI5872 treatment either during double-blind and/or open-label period of the study.
One participant from ‘Placebo’ arm discontinued treatment before Day 99, didn’t receive MEDI5872 dose and entered in safety follow-up period.

Primary: Change From Baseline in European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) Score at Day 99

End point title	Change From Baseline in European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) Score at Day 99

End point description:

In ESSDAI, physician scores the disease activity level of 12 organ-specific domains (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, and biological), with each domain activity level as 3 or 4 levels (no, low, moderate, high) according to their severity (0 = no disease activity; 3 or 4 = high disease activity). Each domain is assigned a weight between 1 and 6, and domain score is multiplied by domain weight. Overall score is calculated as sum of all individual weighted domain scores (ranges from 0 [best] to 123 [worst activity]). A higher score indicates worsening of the disease. Adjusted mean change and standard error are presented. Intent-to-treat (ITT) population was analysed for this end point, which included all randomized and treated participants, grouped according to assigned treatment. Number to Subjects Analyzed = number of participants evaluated for this end point.

End point type	Primary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	13		
Units: Scores on a scale				
arithmetic mean (standard error)	-2.3 (± 0.8)	-3.8 (± 0.9)		

Statistical analyses

Statistical analysis title	Placebo and MEDI5872 210 mg
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.6
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	1.3

Secondary: Ratio to Baseline in Peripheral Blood Biomarkers at Day 99

End point title	Ratio to Baseline in Peripheral Blood Biomarkers at Day 99

End point description:

The peripheral blood biomarkers included total plasma cell levels (including plasma blast levels) and T follicular helper (TFH) cells. Adjusted geometric mean ratio to baseline and standard error (log) are presented. The ITT population was analysed for this end point, which included all randomized and treated participants, grouped according to assigned treatment.

End point type	Secondary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Ratio				
geometric mean (standard error)				
Plasma Cell Levels	0.70 (± 0.24)	0.65 (± 0.24)		
TFH Cells	0.94 (± 0.27)	0.62 (± 0.27)		

Statistical analyses

Statistical analysis title	Placebo and MEDI5872 210 mg
Statistical analysis description: For plasma cell levels	
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.93
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	1.64
Variability estimate	Standard error of the mean
Dispersion value	0.33

Statistical analysis title	Placebo and MEDI5872 210 mg
Statistical analysis description: For TFH cells	
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.291
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.33
upper limit	1.28
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Ratio to Baseline in Minor Salivary Gland Tissue Biomarkers at Day 99	
End point title	Ratio to Baseline in Minor Salivary Gland Tissue Biomarkers at Day 99

End point description:

The minor salivary gland biopsy biomarkers included total plasma cell levels, CD4/ inducible T-cell costimulator (ICOS) TFH cells, and PD-1/ICOS TFH cells. Adjusted geometric mean ratio to baseline and standard error (log) are presented. The ITT population was analysed for this end point, which included all randomized and treated participants, grouped according to assigned treatment. The "Number of Subjects Analyzed" denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Ratio				
geometric mean (standard error)				
Total Plasma Cells	1.32 (± 0.13)	1.15 (± 0.11)		
CD4/ICOS TFH Cells	1.76 (± 0.21)	0.75 (± 0.18)		
PD-1/ICOS TFH Cells	1.06 (± 0.19)	1.07 (± 0.16)		

Statistical analyses

Statistical analysis title	Placebo and MEDI5872 210 mg

Statistical analysis description:

For total plasma cells

Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	1.18
Variability estimate	Standard error of the mean
Dispersion value	0.17

Statistical analysis title	Placebo and MEDI5872 210 mg

Statistical analysis description: For CD4/ICOS TFH cells	
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	0.43
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.28

Statistical analysis title	Placebo and MEDI5872 210 mg
Statistical analysis description: For PD-1/ICOS TFH cells	
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.972
Method	ANCOVA
Parameter estimate	Geometric mean ratio
Point estimate	1.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.59
Variability estimate	Standard error of the mean
Dispersion value	0.26

Secondary: Ratio to Baseline in Focus Score at Day 99

End point title	Ratio to Baseline in Focus Score at Day 99

End point description:

The focus score is a semi-quantitative assessment of focal lymphocytic sialoadenitis, which is defined as the presence of >= 1 dense aggregate of 50 or more lymphocytes in a 4 mm^2 area. Higher numbers are associated with more inflammation. The ITT population was analysed for this end point, which included all randomized and treated participants, grouped according to assigned treatment. The "Number of Subjects Analyzed" denotes the number of participants evaluated for this end point.

End point type	Secondary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: Ratio				
arithmetic mean (standard deviation)	0.79 (± 0.53)	0.96 (± 0.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI) Score at Day 99

End point title	Change From Baseline in European League Against Rheumatism Sjogren's Syndrome Patient Reported Index (ESSPRI) Score at Day 99

End point description:

The ESSPRI is a patient-reported, subjective symptom index for primary Sjögren's syndrome. It consists of three questions covering the cardinal symptoms of Sjögren's syndrome: dryness, fatigue and pain (articular and/or muscular). Each domain scored on scale of 0-10 (0 =no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Adjusted mean change and standard error are presented. The ITT population was analysed for this end point, which included all randomized and treated participants, grouped according to assigned treatment.

End point type	Secondary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Scores on a scale				
arithmetic mean (standard error)	-1.0 (± 0.5)	-0.6 (± 0.5)		

Statistical analyses

Statistical analysis title	Placebo and MEDI5872 210 mg
Comparison groups	Placebo v MEDI5872 210 mg

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.574
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.8
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.7

Secondary: Percentage of ESSDAI Responders at Day 99

End point title	Percentage of ESSDAI Responders at Day 99

End point description:

In ESSDAI, physician scores the disease activity level of 12 organ-specific domains (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, and biological), with each domain activity level as 3 or 4 levels (no, low, moderate, high) according to their severity (0 = no disease activity; 3 or 4 = high disease activity). Each domain is assigned a weight between 1 and 6, and domain score is multiplied by domain weight. Overall score is calculated as sum of all individual weighted domain scores (ranges from 0 [best] to 123 [worst activity]). Participants are considered to be an ESSDAI[x] responder as they achieved a reduction of x points or more in ESSDAI score, did not prematurely discontinue the study drug, and did not receive prohibited concomitant medications. The ITT population was analysed for this end point.

End point type	Secondary

End point timeframe:

Baseline (Day 1 predose) and Day 99

End point values	Placebo	MEDI5872 210 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Percentage of participants				
number (not applicable)				
ESSDAI [3]|	18.8	43.8		
ESSDAI [4]|	18.8	43.8		

Statistical analyses

Statistical analysis title	Placebo and MEDI5872 210 mg

Statistical analysis description:

ESSDAI[4]

Comparison groups	Placebo v MEDI5872 210 mg

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	Fisher exact
Parameter estimate	Difference in precentages
Point estimate	25
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.1
upper limit	50.9

Statistical analysis title	Placebo and MEDI5872 210 mg
Statistical analysis description:	
ESSDAI [3]	
Comparison groups	Placebo v MEDI5872 210 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.252
Method	Fisher exact
Parameter estimate	Difference in percentages
Point estimate	25
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.1
upper limit	50.9

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) is 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. TEAEs are defined as events present at baseline that worsened in intensity after administration of study drug or events absent at baseline that emerged after administration of study drug.
Placebo: As-treated population (participants grouped per actual treatment received).
Any MEDI5872 210 mg: Any MEDI5872 population (participants received at least 1 dose of MEDI5872 either in double-blind and/or open-label). 1 participant from 'Placebo' discontinued treatment before Day 99 and didn't receive MEDI5872 dose in open-label period.

End point type	Secondary

End point timeframe:

Placebo arm: Day 1 (postdose) through Day 99 (predose); Any MEDI5872 210 mg arm: Day 1

(postdose) through Day 296 for MEDI5872 210 mg arm, and Day 99 (postdose) through Day 296 for participants who received placebo at double-blind period

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Placebo	Any MEDI5872 210 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	16	31		
Units: Participants				
Any TEAEs|	14	29		
Any TESAEs|	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events of Special Interest (AESIs)

End point title	Number of Participants With Adverse Events of Special Interest (AESIs)[2]

End point description:

An AESI (serious or non-serious) was one of scientific and medical interest specific to understanding of study drug and may have required close monitoring and rapid communication by investigator to the sponsor. The AESIs for this study were hepatic function abnormality meeting the definition of Hy's law, new or reactivated tuberculosis infection, malignancy, and hypersensitivity and anaphylactic reactions.
Placebo: As-treated population (participants grouped per actual treatment received).
Any MEDI5872 210 mg: Any MEDI5872 population (participants received at least 1 dose of MEDI5872 either in double-blind and/or open-label). 1 participant from 'Placebo' discontinued treatment before Day 99 and didn't receive MEDI5872 dose in open-label period.

End point type	Secondary

End point timeframe:

Placebo arm: Day 1 (postdose) through Day 99 (predose); Any MEDI5872 210 mg arm: Day 1 (postdose) through Day 296 for MEDI5872 210 mg arm, and Day 99 (postdose) through Day 296 for participants who received placebo at double-blind period

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	Placebo	Any MEDI5872 210 mg		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	16	31		
Units: Participants	1	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Placebo: Days 1 to 99;
Any MEDI5872 210 mg: Days 1 to 296 for MEDI5872 210 mg arm, and Days 99 to 296 for participants who received placebo at double-blind.
One participant from 'Placebo' discontinued before Day 99 and entered directly in safety period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Any MEDI5872 210 mg

Reporting group description:

Participants received at least one dose of MEDI5872 treatment either during double-blind and/or open-label period of the study. In double-bind period, participants received a fixed SC dose of 210 mg MEDI5872 QW for 3 weeks (Days 1, 8, and 15) and then every Q2W for 9 weeks (Days 29 to 85). In open-label period, participants who received MEDI5872 210mg in double-blinded period received MEDI5872 210mg on Days 99 and Day 113; and participants who received placebo in double-blinded period received MEDI5872 210mg QW from Days 99 to 113, later all participants received MEDI5872 210mg Q2W from Days 127 to 183 and were followed up till Day 296.

Reporting group title	Placebo

Reporting group description:

Participants received a subcutaneous (SC) dose of placebo matching with MEDI5872 every week (QW) for 3 weeks (Days 1, 8, and 15) and then every 2 weeks (Q2W) for next 9 weeks (Days 29 to 85) in double-blind period of the study.

Serious adverse events	Any MEDI5872 210 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Small intestine polyp			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (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: 0 %

Non-serious adverse events	Any MEDI5872 210 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 31 (93.55%)	14 / 16 (87.50%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Hot flush			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Facial pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Feeling hot			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			
subjects affected / exposed	0 / 31 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Injection site erythema			

subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	7	0	
Injection site haematoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Injection site rash			
subjects affected / exposed	4 / 31 (12.90%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Injection site reaction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vaccination site reaction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			

subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 31 (3.23%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Nasal congestion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 31 (6.45%)	1 / 16 (6.25%)	
occurrences (all)	2	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Stress			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood urine present			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Epicondylitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Accidental device ingestion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Face injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ligament rupture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Post procedural swelling			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Procedural complication			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Skin abrasion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Soft tissue injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Tooth avulsion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Cardiac disorders			
Palpitations			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Dysgeusia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	5 / 31 (16.13%)	2 / 16 (12.50%)	
occurrences (all)	8	2	
Sciatica			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			

subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	4 / 31 (12.90%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Dental caries			
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Diarrhoea			
subjects affected / exposed	4 / 31 (12.90%)	2 / 16 (12.50%)	
occurrences (all)	4	2	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Food poisoning			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Lip blister			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	2 / 31 (6.45%)	3 / 16 (18.75%)	
occurrences (all)	2	3	
Paraesthesia oral			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Parotid gland enlargement			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	2	
Reflux gastritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tongue blistering			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hepatic steatosis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Erythema			
subjects affected / exposed	3 / 31 (9.68%)	1 / 16 (6.25%)	
occurrences (all)	4	2	
Eczema			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	3	
Night sweats			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Papule			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	7	0	
Purpura			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Urticaria			
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 31 (12.90%)	0 / 16 (0.00%)	
occurrences (all)	5	0	
Back pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Bone pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Dupuytren's contracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Bursitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Flank pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Limb mass			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			

subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 31 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Neck pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Sjogren's syndrome			
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Tendonitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 31 (6.45%)	2 / 16 (12.50%)	
occurrences (all)	2	2	
Gastroenteritis viral			
subjects affected / exposed	2 / 31 (6.45%)	1 / 16 (6.25%)	
occurrences (all)	2	1	

Genital candidiasis				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	2	0		
Lower respiratory tract infection				
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)		
occurrences (all)	2	0		
Nasopharyngitis				
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)		
occurrences (all)	0	1		
Oral herpes				
subjects affected / exposed	3 / 31 (9.68%)	0 / 16 (0.00%)		
occurrences (all)	7	0		
Paronychia				
subjects affected / exposed	2 / 31 (6.45%)	0 / 16 (0.00%)		
occurrences (all)	2	0		
Parotitis				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Pharyngitis				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Respiratory tract infection viral				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Serratia infection				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Tongue fungal infection				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Tooth abscess				
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)		
occurrences (all)	1	0		
Urinary tract infection				
subjects affected / exposed	4 / 31 (12.90%)	1 / 16 (6.25%)		
occurrences (all)	6	1		

Upper respiratory tract infection			
subjects affected / exposed	8 / 31 (25.81%)	4 / 16 (25.00%)	
occurrences (all)	8	5	
Viral pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)	2 / 16 (12.50%)	
occurrences (all)	2	3	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	1 / 31 (3.23%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	1 / 31 (3.23%)	1 / 16 (6.25%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2014	• Added criteria for discontinuation of investigational product and for study suspension/termination, to specify the number and type of adverse events that would trigger either action. • Added a primary analysis of the primary endpoint at Study Day 99 that would not change at the final analysis, and indicated that the Sponsor would be unblinded at the primary analysis (after Study Day 99) but other study/site staff and subjects would remain blinded until the study was complete. • Added methotrexate >20 mg/week as a prohibited concomitant medication.
28 August 2015	• Modified Exclusion Criteria to exclude subjects with only systemic fungal infections and allow subjects with topical fungal infections
17 February 2016	• Modified Inclusion Criteria to raise the upper age limit from 70 to 75 years. • Modified Inclusion Criteria to lower the IgG requirement from 16g/dL to 13 g/dL, and to include a positive test for cryoglobulins. • Modified Exclusion Criteria to lower the white blood cell count from < 2000 × 10^6/L to < 1500 × 10^6/L and to lower the neutrophil count requirement from < 1500 × 10^6/L to < 1000 × 10^6/L.
24 October 2017	• Moved the exploratory endpoint of ESSDAI response to become a secondary endpoint as an objective measure of overall disease activity supporting secondary objective. • Added ESSPRI response and MDGA as a new Exploratory Endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported