Clinical trial results:
A Randomized, Double-Blind, Double-Dummy, Active Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of ABBV-3373 in Subjects with Moderate to Severe Rheumatoid Arthritis

Summary

EudraCT number	2018-003053-21
Trial protocol	PL
Global end of trial date	26 August 2020

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	M16-560

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03823391
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.com
Scientific contact	Global Medical Services, AbbVie, 001 800-633-9110, abbvieclinicaltrials@abbvie.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	26 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the safety, tolerability, and efficacy of ABBV-3373 administered every other week (EOW) intravenously (IV) in subjects with moderately to severely active rheumatoid arthritis (RA) on background methotrexate (MTX).
2. To compare clinical efficacy of ABBV-3373 with adalimumab and to test the concept that an anti-tumor necrosis factor (TNF) antibody-drug-conjugate (ADC) has the potential to provide superior efficacy than the traditional anti-TNF antibody in RA.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy:

Subjects must have been on oral or parenteral methotrexate (MTX) therapy ≥ 3 months and on a stable prescription of 15 to 25 mg/week (or ≥ 10 mg/week in subjects intolerant of MTX at doses ≥ 15 mg/week) for ≥ 4 weeks prior to the first dose of study drug. Subjects were expected to be able to continue on stable dose of MTX for the duration of study participation.

Evidence for comparator: -

Actual start date of recruitment	27 March 2019
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	Hungary: 15
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	48
EEA total number of subjects	18

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)	38
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with moderately to severely active rheumatoid arthritis (RA) on background methotrexate were enrolled at 14 sites in the United States and Puerto Rico, Poland, Hungary, and Israel.

Pre-assignment

Screening details:

Subjects were randomly assigned in a 2:1 ratio to either ABBV-3373 or adalimumab. Randomization was stratified by current use of systemic glucocorticoid and prior exposure to non-anti-TNF biologics or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) for less than 3 months and terminated not due to lack of efficacy or intolerance.

Period 1

Period 1 title	Period 1: Baseline to Week 12
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab

Arm description:

Participants received 80 mg adalimumab by subcutaneous injection once every other week (EOW) and placebo to ABBV-3373 by intravenous infusion EOW for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	HUMIRA™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered at 80 mg EOW for 12 weeks.

Investigational medicinal product name	Placebo to ABBV-3373
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered EOW for 12 weeks.

Arm title	ABBV-3373

Arm description:

Participants received 100 mg ABBV-3373 by intravenous infusion EOW and placebo to adalimumab by subcutaneous injection EOW for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABBV-3373
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: Administered at 100 mg EOW for 12 weeks.	
Investigational medicinal product name	Placebo to Adalimumab
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 EOW for 12 weeks.	

Number of subjects in period 1	Adalimumab	ABBV-3373
Started	17	31
Completed	17	31

Period 2	
Period 2 title	Period 2: Week 12 to Week 24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor
Arms	
Are arms mutually exclusive?	Yes
Arm title	Adalimumab / Adalimumab
Arm description: Participants continued to receive 80 mg adalimumab by subcutaneous injection EOW from Week 12 to Week 24.	
Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	HUMIRA™
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details: Administered at 80 mg EOW for 12 weeks.	
Arm title	ABBV-3373 / Placebo
Arm description: Participants received placebo to adalimumab by subcutaneous injection EOW from Week 12 to Week 24.	
Arm type	Experimental

Investigational medicinal product name	Placebo to Adalimumab
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 EOW for 12 weeks.

Number of subjects in period 2	Adalimumab / Adalimumab	ABBV-3373 / Placebo
Started	17	31
Completed	15	30
Not completed	2	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab
Reporting group description:	
Participants received 80 mg adalimumab by subcutaneous injection once every other week (EOW) and placebo to ABBV-3373 by intravenous infusion EOW for 12 weeks.	
Reporting group title	ABBV-3373
Reporting group description:	
Participants received 100 mg ABBV-3373 by intravenous infusion EOW and placebo to adalimumab by subcutaneous injection EOW for 12 weeks.	

Reporting group values	Adalimumab	ABBV-3373	Total
Number of subjects	17	31	48
Age categorical Units: Subjects			
< 40 years	0	5	5
40 - 65 years	13	21	34
≥ 65 years	4	5	9
Age continuous Units: years			
arithmetic mean	54.0	52.8	
standard deviation	± 10.21	± 13.14	-
Gender categorical Units: Subjects			
Female	14	24	38
Male	3	7	10
Race Units: Subjects			
White	16	28	44
Black	1	2	3
Other	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	3	8	11
Not Hispanic or Latino	14	23	37
Baseline Use of Systemic Glucocorticoids			
Randomization was stratified by current use of systemic glucocorticoid (≤ 7.5 mg/day prednisone equivalent) for treatment of rheumatoid arthritis at Baseline).			
Units: Subjects			
Yes	5	11	16
No	12	20	32
Prior Exposure to Non-anti-TNF or Targeted Synthetic DMARDs			
Randomization was stratified by prior exposure to non-anti-TNF biologics or targeted synthetic DMARDs (< 3 months and terminated not due to lack of efficacy or intolerance).			
Units: Subjects			
Yes	0	0	0
No	17	31	48

Duration of RA Symptoms			
Units: years			
arithmetic mean	5.9	8.0	
standard deviation	± 3.22	± 8.73	-
Duration of RA Diagnosis			
Units: years			
arithmetic mean	3.5	5.0	
standard deviation	± 3.09	± 6.02	-
Disease Activity Score 28 C-reactive protein (DAS28[CRP])			
The DAS28 (CRP) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (0-100 mm), and high-sensitivity C-reactive protein (hsCRP) (in mg/L). Scores on the DAS28 (CRP) range from 0.96 to approximately 10, where higher scores indicate more disease activity.			
Units: scores on a scale			
arithmetic mean	5.6	5.6	
standard deviation	± 0.71	± 0.92	-

End points

End points reporting groups

Reporting group title	Adalimumab
Reporting group description:	
Participants received 80 mg adalimumab by subcutaneous injection once every other week (EOW) and placebo to ABBV-3373 by intravenous infusion EOW for 12 weeks.	
Reporting group title	ABBV-3373
Reporting group description:	
Participants received 100 mg ABBV-3373 by intravenous infusion EOW and placebo to adalimumab by subcutaneous injection EOW for 12 weeks.	
Reporting group title	Adalimumab / Adalimumab
Reporting group description:	
Participants continued to receive 80 mg adalimumab by subcutaneous injection EOW from Week 12 to Week 24.	
Reporting group title	ABBV-3373 / Placebo
Reporting group description:	
Participants received placebo to adalimumab by subcutaneous injection EOW from Week 12 to Week 24.	

Primary: Change from Baseline to Week 12 in Disease Activity Score (DAS) 28 (C-reactive Protein [CRP])

End point title	Change from Baseline to Week 12 in Disease Activity Score (DAS) 28 (C-reactive Protein [CRP])[1]
End point description:	
The DAS28 (CRP) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (measured on a visual analog scale [VAS] from 0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 (CRP) range from 0.96 to approximately 10, where higher scores indicate more disease activity. A negative change from Baseline in DAS28 (CRP) indicates improvement in disease activity. Subjects in the full analysis set (randomized subjects who received at least 1 dose of the study drug) with non-missing Baseline and at least one post-baseline value are included in the analysis.	
End point type	Primary
End point timeframe:	
Baseline and 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: Two primary comparisons were performed between ABBV-3373 and adalimumab. The first was the comparison of ABBV-3373 to historical adalimumab reference value -2.13 based on a meta-analysis from 3 historical adalimumab studies. The second comparison was ABBV-3373 to adalimumab with combined in-trial and historical adalimumab data in which the success criterion was posterior probability of ABBV-3373 better than adalimumab >95%. The results of these analyses are reported in the attachment below.	

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: scores on a scale				
least squares mean (standard error)	-2.51 (± 0.293)	-2.65 (± 0.215)		

Attachments (see zip file)	Primary Analysis of the Primary Endpoint/Primary Analysis of

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 12 in Clinical Disease Activity Index (CDAI)

End point title	Change from Baseline to Week 12 in Clinical Disease Activity Index (CDAI)

End point description:

The clinical disease activity index (CDAI) is a composite index for assessing disease activity based on the summation of the counts of tender joint count (out of 28 evaluated joints) and swollen joint count (out of 28 evaluated joints), Patient Global Assessment of Disease Activity and Physician Global Assessment of Disease Activity both measured on a VAS from 0 to 10 cm. The total CDAI score ranges from 0 to 76 with higher scores indicating higher disease activity. A negative change from Baseline indicates improvement in disease activity.
Subjects in the full analysis set with non-missing Baseline and at least one post-baseline value were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: score on a scale				
least squares mean (standard error)	-26.30 (± 2.656)	-27.99 (± 1.955)		

Statistical analyses

Statistical analysis title	In-study Analysis of CDAI
Comparison groups	Adalimumab v ABBV-3373
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.601 [2]
Method	Mixed-effect model repeated measurement
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-1.69

Confidence interval	
level	90 %
sides	2-sided
lower limit	-7.08
upper limit	3.7
Variability estimate	Standard error of the mean
Dispersion value	3.207

Notes:

[2] - Mixed-effect model repeated measurement (MMRM) analysis with unstructured variance-covariance matrix, including treatment, visit, stratification factors, and treatment-by-visit interaction as fixed factors and Baseline value as covariate.

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI)

End point title	Change from Baseline in Simplified Disease Activity Index (SDAI)

End point description:

The SDAI is the numerical sum of five outcome parameters: tender and swollen joint count (based on a 28-joint assessment), Patient Global Assessment of Disease Activity and Physician Global Assessment of Disease Activity both measured on a VAS from 0-10 cm and level of CRP (in mg/dL; normal < 1 mg/dL). The SDAI has a range from 0 to 86, with higher scores indicating higher disease activity. A negative change from Baseline indicates improvement in disease activity.
Subjects in the full analysis set with non-missing Baseline and at least one post-baseline value were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: score on a scale				
least squares mean (standard error)	-27.42 (± 2.659)	-28.50 (± 1.961)		

Statistical analyses

Statistical analysis title	In-study Analysis of SDAI
Comparison groups	Adalimumab v ABBV-3373
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.737 [3]
Method	Mixed-effect model repeated measurement
Parameter estimate	LS Mean Difference
Point estimate	-1.08

Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.47
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	3.205

Notes:

[3] - Mixed-effect model repeated measurement (MMRM) analysis with unstructured variance-covariance matrix, including treatment, visit, stratification factors, and treatment-by-visit interaction as fixed factors and Baseline value as covariate.

Secondary: Change from Baseline to Week 12 in DAS28 (Erythrocyte Sedimentation Rate [ESR])

End point title	Change from Baseline to Week 12 in DAS28 (Erythrocyte Sedimentation Rate [ESR])

End point description:

The DAS28 (ESR) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (measured on a VAS from 0-100 mm), and ESR (in mm/hr). Scores on the DAS28 (ESR) range from 0 to approximately 10, where higher scores indicate more disease activity. A negative change from Baseline indicates improvement in disease activity. Subjects in the full analysis set with non-missing Baseline and at least one post-baseline value were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: score on a scale				
least squares mean (standard error)	-2.55 (± 0.344)	-2.76 (± 0.254)		

Statistical analyses

Statistical analysis title	In-study Analysis of DAS28 (ESR)
Comparison groups	Adalimumab v ABBV-3373
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.612 [4]
Method	Mixed-effect model repeated measurement
Parameter estimate	LS Mean Difference
Point estimate	-0.21

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.92
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.418

Notes:

[4] - Mixed-effect model repeated measurement analysis with unstructured variance-covariance matrix, including treatment, visit, stratification factors, and treatment-by-visit interaction as fixed factors and Baseline value as covariate.

Secondary: Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28 (CRP) at Week 12

End point title	Percentage of Participants Achieving Low Disease Activity (LDA) Based on DAS28 (CRP) at Week 12

End point description:

The DAS28 (CRP) is a composite index used to assess rheumatoid arthritis disease activity, calculated based on the tender joint count (out of 28 evaluated joints), swollen joint count (out of 28 evaluated joints), Patient's Global Assessment of Disease Activity (measured on a VAS from 0-100 mm), and hsCRP (in mg/L). Scores on the DAS28 (CRP) range from 0.96 to approximately 10, where higher scores indicate more disease activity.
A DAS28 (CRP) score less than or equal to 3.2 indicates low disease activity.
Subjects in the full analysis set; participants who prematurely discontinued from study drug prior to Week 12 or for whom DAS28 (CRP) data were missing at Week 12 were considered non-responders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: percentage of participants				
number (confidence interval 90%)	58.8 (39.2 to 78.5)	54.8 (40.1 to 69.5)		

Statistical analyses

Statistical analysis title	In-study Analysis of LDA
Comparison groups	Adalimumab v ABBV-3373
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.877 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-4

Confidence interval	
level	90 %
sides	2-sided
lower limit	-28.5
upper limit	20.5

Notes:

[5] - Cochran-Mantel-Haenszel test adjusting for stratification factors

Secondary: Percentage of Participants with an American College of Rheumatology 50% (ACR50) Response at Week 12

End point title	Percentage of Participants with an American College of Rheumatology 50% (ACR50) Response at Week 12

End point description:

Participants who met the following 3 conditions for improvement from Baseline were classified as meeting the ACR50 response criteria:
1. ≥ 50% improvement in 68-tender joint count;
2. ≥ 50% improvement in 66-swollen joint count; and
3. ≥ 50% improvement in at least 3 of the 5 following parameters:
- Physician global assessment of disease activity
- Patient global assessment of disease activity
- Patient assessment of pain
- Health Assessment Questionnaire - Disability Index (HAQ-DI)
- High-sensitivity C-reactive protein (hsCRP).

Subjects in the full analysis set; participants who prematurely discontinued from study drug prior to Week 12 or for whom ACR data were missing at Week 12 were considered non-responders.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Adalimumab	ABBV-3373		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	31		
Units: percentage of participants				
number (confidence interval 90%)	64.7 (45.6 to 83.8)	51.6 (36.8 to 66.4)		

Statistical analyses

Statistical analysis title	In-study Analysis of ACR50
Comparison groups	Adalimumab v ABBV-3373
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.426 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response Rate Difference
Point estimate	-13.1

Confidence interval	
level	90 %
sides	2-sided
lower limit	-37.2
upper limit	11

Notes:

[6] - Cochran-Mantel-Haenszel test adjusting for stratification factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 70 days after last dose; the treatment duration was 12 weeks in each period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Period 1: ABBV-3373

Reporting group description:

Participants received 100 mg ABBV-3373 by intravenous infusion EOW and placebo to adalimumab by subcutaneous injection EOW for 12 weeks.

Reporting group title	Period 1: Adalimumab

Reporting group description:

Participants received 80 mg adalimumab by subcutaneous injection EOW and placebo to ABBV-3373 by intravenous infusion EOW for 12 weeks.

Reporting group title	Period 2: ABBV-3773 / Placebo

Reporting group description:

Participants received placebo to adalimumab by subcutaneous injection EOW from Week 12 to Week 24.

Reporting group title	Period 2: Adalimumab / Adalimumab

Reporting group description:

Participants continued to receive 80 mg adalimumab by subcutaneous injection EOW from Week 12 to Week 24.

Serious adverse events	Period 1: ABBV-3373	Period 1: Adalimumab	Period 2: ABBV-3773 / Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	0 / 17 (0.00%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
ANAPHYLACTIC SHOCK			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
BREAST ABSCESS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (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
BRONCHITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (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
PNEUMONIA			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 2: Adalimumab / Adalimumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 16 (12.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
ANAPHYLACTIC SHOCK			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

BREAST ABSCESS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
BRONCHITIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Period 1: ABBV-3373	Period 1: Adalimumab	Period 2: ABBV-3773 / Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 31 (12.90%)	12 / 17 (70.59%)	7 / 30 (23.33%)
Investigations			
BLOOD PRESSURE INCREASED			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
MYCOPLASMA TEST POSITIVE			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			

HYPERTENSION			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
HEADACHE			
subjects affected / exposed	2 / 31 (6.45%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
HYPOAESTHESIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
SCIATICA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
LEUKOPENIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
INFUSION SITE BRUISING			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
INJECTION SITE PRURITUS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
PYREXIA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
TYPE I HYPERSENSITIVITY			

subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
PERIORBITAL SWELLING			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
MOUTH SWELLING			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
NAUSEA			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
BRONCHIAL HYPERREACTIVITY			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
PRURITUS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL PAIN			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
MYALGIA			

subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
OSTEOARTHRITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 31 (3.23%)	0 / 17 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
NASOPHARYNGITIS			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
ORAL HERPES			
subjects affected / exposed	0 / 31 (0.00%)	1 / 17 (5.88%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
SINUSITIS			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	1 / 30 (3.33%)
occurrences (all)	0	0	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 31 (0.00%)	0 / 17 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 31 (6.45%)	2 / 17 (11.76%)	1 / 30 (3.33%)
occurrences (all)	2	2	1

Non-serious adverse events	Period 2: Adalimumab / Adalimumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 16 (75.00%)		
Investigations			

BLOOD PRESSURE INCREASED subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
LIVER FUNCTION TEST ABNORMAL subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
MYCOPLASMA TEST POSITIVE subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Vascular disorders HYPERTENSION subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
Nervous system disorders HEADACHE subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
HYPOAESTHESIA subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
SCIATICA subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Blood and lymphatic system disorders LEUKOPENIA subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
General disorders and administration site conditions INFUSION SITE BRUISING subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0		
INJECTION SITE PRURITUS subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
OEDEMA PERIPHERAL			

subjects affected / exposed occurrences (all) PYREXIA subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Immune system disorders DRUG HYPERSENSITIVITY subjects affected / exposed occurrences (all) TYPE I HYPERSENSITIVITY subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 0 / 16 (0.00%) 0		
Eye disorders PERIORBITAL SWELLING subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Gastrointestinal disorders ABDOMINAL DISCOMFORT subjects affected / exposed occurrences (all) MOUTH SWELLING subjects affected / exposed occurrences (all) NAUSEA subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Respiratory, thoracic and mediastinal disorders BRONCHIAL HYPERREACTIVITY subjects affected / exposed occurrences (all) OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders PRURITUS			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
MYALGIA			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
OSTEOARTHRITIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
RHEUMATOID ARTHRITIS			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
GASTROENTERITIS VIRAL			
subjects affected / exposed	0 / 16 (0.00%)		
occurrences (all)	0		
NASOPHARYNGITIS			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
ORAL HERPES			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
SINUSITIS			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
UPPER RESPIRATORY TRACT INFECTION			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2019	The purpose of this version was to communicate new safety findings regarding a case of anaphylactic shock throughout the protocol.
20 November 2019	Major changes included: - changed study from Phase 1b to Phase 2a; - added a secondary objective to compare adalimumab with synthetic control to establish assay sensitivity; - added clarifications for potentially used concomitant medications; - updated statistical details for clarity; - removed interim efficacy analysis.
14 March 2020	The purpose of this version was to add the evaluation of another ADC cohort (ABBV-154) in addition to the ABBV-3373 cohort.
26 August 2020	The purpose of this version was to remove the ABBV-154 cohort.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported