Clinical trial results:
A Phase 4, Double-Blind, Randomized, Placebo-Controlled Multicenter Study to Assess the Safety and Efficacy of Adalimumab Used in Conjunction with Surgery in Subjects with Moderate to Severe Hidradenitis Suppurativa

Summary

EudraCT number	2015-005161-23
Trial protocol	DK SE NL GB DE IE PT GR BE ES CZ IT
Global end of trial date	17 October 2019
Results information	
Result version number	v1 (current)
This version publication date	22 May 2020
First version publication date	22 May 2020

Trial information

Trial identification	
Sponsor protocol code	M15-574
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02808975
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
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,
Scientific contact	Christine Jean, AbbVie, christine.jean@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	17 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was an interventional, randomized, double-blind (DB), placebo-controlled study. The study duration included a 30-day Screening Period, an initial 12-week DB treatment pre-surgery period (Period A), a 2-week peri-operative period with continuation of weekly DB study drug administration (Period B), and a subsequent 10-week DB treatment post-operative period (Period C). The projected size of the surgical excision established by the designated surgeon during the Screening Period was recorded. In Period B, the designated surgeon measured and recorded the surface area of the actual surgery, with surgery occurring during Week 13. Surgery and post-operative management (e.g., hospitalization, surgical wound care) was per local practice. No study drug was administered at Week 24, the final study visit. Participants were able to begin commercial product (as prescribed by the participants's physician) after all Week 24 procedures were completed.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2016
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	Canada: 14
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	United States: 14
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Belgium: 1

Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Greece: 23
Worldwide total number of subjects	206
EEA total number of subjects	157

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)	206
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a 30-day screening period.

Pre-assignment

Screening details:

Eligible subjects must have had skin lesions diagnostic of Hidradenitis Suppurativa (HS) for at least 1 year prior to the Baseline visit and a requirement for surgery of HS lesions in a single axilla or unilateral inguinal region.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Period A: Day 1- 4 subcutaneous (SC) injections; Week 2- 2 SC injections; Weeks 4-12- 1 SC injection each week
Period B: Weeks 13-14- 1 SC injection each week
Period C: Weeks 15-23- 1 SC injection each week

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:

Subcutaneous injections administered as described in arm description

Arm title	Adalimumab

Arm description:

Period A: Day 1- 4 subcutaneous (SC) 40 mg injections; Week 2- 2 SC 40 mg injections; Weeks 4-12- 1 SC 40 mg injection each week
Period B: Weeks 13-14- 1 SC 40 mg injection each week
Period C: Weeks 15-23- 1 SC 40 mg injection each week

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:

Subcutaneous injections administered as described in arm description

Number of subjects in period 1	Placebo	Adalimumab
Started	103	103
Completed	81	84
Not completed	22	19
Adverse event, non-fatal	3	4
Other, not specified	5	1
Planned HS surgery performed prior to Week 13	1	-
Withdrew consent	9	8
Lost to follow-up	4	6

Baseline characteristics

Reporting groups

Reporting group title	Placebo

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) injections; Week 2- 2 SC injections; Weeks 4-12- 1 SC injection each week
Period B: Weeks 13-14- 1 SC injection each week
Period C: Weeks 15-23- 1 SC injection each week

Reporting group title	Adalimumab

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) 40 mg injections; Week 2- 2 SC 40 mg injections; Weeks 4-12- 1 SC 40 mg injection each week
Period B: Weeks 13-14- 1 SC 40 mg injection each week
Period C: Weeks 15-23- 1 SC 40 mg injection each week

Reporting group values	Placebo	Adalimumab	Total
Number of subjects	103	103	206
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36.8	38.5	
standard deviation	± 10.81	± 11.71	-
Gender categorical Units: Subjects			
Female	55	51	106
Male	48	52	100

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) injections; Week 2- 2 SC injections; Weeks 4-12- 1 SC injection each week
Period B: Weeks 13-14- 1 SC injection each week
Period C: Weeks 15-23- 1 SC injection each week

Reporting group title	Adalimumab

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) 40 mg injections; Week 2- 2 SC 40 mg injections; Weeks 4-12- 1 SC 40 mg injection each week
Period B: Weeks 13-14- 1 SC 40 mg injection each week
Period C: Weeks 15-23- 1 SC 40 mg injection each week

Primary: Percentage of Participants Achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12

End point title	Percentage of Participants Achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12

End point description:

HiSCR is defined as at least a 50% reduction in the abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline.

End point type	Primary

End point timeframe:

At Week 12

End point values	Placebo	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[1]	103[2]		
Units: percentage of participants				
number (confidence interval 95%)	34.0 (24.8 to 43.1)	47.6 (37.9 to 57.2)		

Notes:

[1] - All participants who were randomized at Baseline; non-responder imputation used for missing data

[2] - All participants who were randomized at Baseline; non-responder imputation used for missing data

Statistical analyses

Statistical analysis title	Superiority statistical analysis
Comparison groups	Placebo v Adalimumab

Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - Across all strata, P-value calculated from Cochran-Mantel-Haenszel test adjusted for strata. Stratum containing zero count: 0.1 added to each cell.

Secondary: Percentage of Participants Achieving HiSCR-es at Week 12

End point title	Percentage of Participants Achieving HiSCR-es at Week 12

End point description:

Hidradenitis Suppurativa Clinical Response-es (HiSCR-es) is defined as at least a 50% reduction in the abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, excluding the Hidradenitis Suppurativa surgical site.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Placebo	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[4]	103[5]		
Units: percentage of participants				
number (confidence interval 95%)	35.0 (25.7 to 44.2)	47.6 (37.9 to 57.2)		

Notes:

[4] - All participants who were randomized at Baseline; non-responder imputation used for missing data

[5] - All participants who were randomized at Baseline; non-responder imputation used for missing data

Statistical analyses

Statistical analysis title	Superiority statistical analysis
Comparison groups	Placebo v Adalimumab
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [6]
Method	Cochran-Mantel-Haenszel

Notes:

[6] - Across all strata, P-value calculated from Cochran-Mantel-Haenszel test adjusted for strata. Stratum containing zero count: 0.1 added to each cell.

Secondary: Percentage of Participants Achieving HiSCR-es at Week 24

End point title	Percentage of Participants Achieving HiSCR-es at Week 24

End point description:

Hidradenitis Suppurativa Clinical Response-es (HiSCR-es) is defined as at least a 50% reduction in the abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline, excluding the Hidradenitis Suppurativa surgical site.

End point type	Secondary

End point timeframe:

At Week 24

End point values	Placebo	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[7]	103[8]		
Units: percentage of participants				
number (confidence interval 95%)	31.1 (22.1 to 40.0)	51.5 (41.8 to 61.1)		

Notes:

[7] - All participants who were randomized at Baseline; non-responder imputation used for missing data

[8] - All participants who were randomized at Baseline; non-responder imputation used for missing data

Statistical analyses

Statistical analysis title	Superiority statistical analysis
Comparison groups	Placebo v Adalimumab
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [9]
Method	Cochran-Mantel-Haenszel

Notes:

[9] - Across all strata, P-value calculated from Cochran-Mantel-Haenszel test adjusted for strata. Stratum containing zero count: 0.1 added to each cell.

Secondary: Percent change in the surface area of the Hidradenitis Suppurativa (HS) surgical site from Baseline to Week 12

End point title	Percent change in the surface area of the Hidradenitis Suppurativa (HS) surgical site from Baseline to Week 12

End point description:

The projected size of the surgical excision established by the designated surgeon during the Screening Period (calculated from a tracing of the outer perimeter onto an acetate sheet or equivalent) was recorded by the study physician. The change in the surface area of the projected HS surgical site from Baseline to Week 12 was documented.

End point type	Secondary

End point timeframe:

From Baseline to Week 12

End point values	Placebo	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79[10]	76[11]		
Units: percent change from Baseline				
least squares mean (confidence interval 95%)	26.233 (-31.684 to 84.150)	68.190 (8.485 to 127.896)		

Notes:

[10] - Observed case (OC) analysis; all participants who were randomized at the Baseline visit

[11] - Observed case (OC) analysis; all participants who were randomized at the Baseline visit

Statistical analyses

Statistical analysis title	Superiority statistical analysis
Comparison groups	Placebo v Adalimumab
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313 [12]
Method	ANCOVA

Notes:

[12] - Across all strata, P-values are calculated from ANCOVA with stratum, baseline value, and treatment in the model.

Secondary: Percentage of Participants at Week 12 That Require a Less Extensive Surgery than the Surgical Plan (Determined at Baseline) or No Surgery

End point title	Percentage of Participants at Week 12 That Require a Less Extensive Surgery than the Surgical Plan (Determined at Baseline) or No Surgery

End point description:

The projected size of the surgical excision established by the designated surgeon during the Screening Period (calculated from a tracing of the outer perimeter onto an acetate sheet or equivalent) was recorded by the study physician. The change in the surface area of the projected HS surgical site from Baseline to Week 12 was documented, and the percentage of participants at Week 12 requiring a less extensive surgery than the surgical plan (determined at Baseline) or no surgery as determined by the designated surgeon was recorded.

End point type	Secondary

End point timeframe:

At Week 12

End point values	Placebo	Adalimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[13]	82[14]		
Units: percentage of participants				
number (confidence interval 95%)	43.7 (33.3 to 54.1)	46.3 (35.5 to 57.1)		

Notes:

[13] - Observed case (OC) analysis; all participants who were randomized at the Baseline visit

[14] - Observed case (OC) analysis; all participants who were randomized at the Baseline visit

Statistical analyses

Statistical analysis title	Superiority statistical analysis
Comparison groups	Placebo v Adalimumab
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.746 [15]
Method	Cochran-Mantel-Haenszel

Notes:

[15] - Across all strata, P-value calculated from Cochran-Mantel-Haenszel test adjusted for strata. Stratum containing zero count: 0.1 added to each cell.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the first dose of study drug until 70 days after the last dose of study drug, up to 33 weeks.

Adverse event reporting additional description:

TEAEs and SAEs are defined as any adverse event (AE) with an onset date that is on or after the first dose of study drug until 70 days after the last dose of study drug and were collected whether elicited or spontaneously reported by the participant.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) injections; Week 2- 2 SC injections; Weeks 4-12- 1 SC injection each week
Period B: Weeks 13-14- 1 SC injection each week
Period C: Weeks 15-23- 1 SC injection each week

Reporting group title	Adalimumab

Reporting group description:

Period A: Day 1- 4 subcutaneous (SC) 40 mg injections; Week 2- 2 SC 40 mg injections; Weeks 4-12- 1 SC 40 mg injection each week
Period B: Weeks 13-14- 1 SC 40 mg injection each week
Period C: Weeks 15-23- 1 SC 40 mg injection each week

Serious adverse events	Placebo	Adalimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 103 (2.91%)	7 / 103 (6.80%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Testis cancer			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular disorder			

subjects affected / exposed	1 / 103 (0.97%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	2 / 103 (1.94%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Blastocystis infection			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 103 (0.97%)	0 / 103 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 103 (0.00%)	1 / 103 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Adalimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 103 (41.75%)	48 / 103 (46.60%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	8 / 103 (7.77%)	14 / 103 (13.59%)	
occurrences (all)	9	14	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 103 (5.83%)	2 / 103 (1.94%)	
occurrences (all)	7	2	
Headache			
subjects affected / exposed	14 / 103 (13.59%)	13 / 103 (12.62%)	
occurrences (all)	29	13	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 103 (3.88%)	6 / 103 (5.83%)	
occurrences (all)	4	6	
Skin and subcutaneous tissue disorders			
Hidradenitis			
subjects affected / exposed	15 / 103 (14.56%)	14 / 103 (13.59%)	
occurrences (all)	19	17	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed occurrences (all)	1 / 103 (0.97%) 1	6 / 103 (5.83%) 6	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	19 / 103 (18.45%) 24	19 / 103 (18.45%) 23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2016	- Updated Benefits and Risks to include all known potential risks associated with adalimumab - Clarified requirements regarding tuberculosis (TB) screening and prophylaxis requirements - Excluded subjects with suspicion of sepsis, cytomegalovirus infection, listeriosis, or other opportunistic infections (exclusion criterion #15) - Excluded subjects with interstitial lung disease (ILD) (exclusion criterion #19) - Specified that breastfeeding should be avoided for at least 5 months following the last dose of adalimumab (exclusion criterion #21) - Updated prohibited therapy, to define high-dose systemic corticosteroids - Updated contraception recommendations - Specified that patients that develop TB or any other serious or opportunistic infection must discontinue study treatment - Updated Adverse Events of Serious Interest (AESI) to include data collection and analysis of AEs concerning the surgical site
30 November 2016	- Updated Screening Period to be no less than 7 days - Clarified that stratification at randomization was for worst Hurley stage across all body regions (not only the surgical site) - Excluded subjects over 65 years old (inclusion criterion #1) - Clarified details regarding serum and urine pregnancy testing - Clarified non-authorized surgery details for exclusion (exclusion criterion #4) - Clarified referring surgeon responsibilities, including who calculates the size of the actual surgical surface area - Clarified timing of visit windows - Clarified prior, concomitant, and prohibited therapy - Added digital imaging at Week 20
13 December 2017	- Updated the planned number of sites - Added that the 95% confidence interval (CI) of treatment difference will also be provided - Added a sensitivity analysis controlling for change from baseline in body weight using logistic regression models, for the primary efficacy endpoint - Incorporated changes form Administrative Change 1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported