



Clinical trial results:

Randomized controlled 12 months trial with etanercept (enbrel®) vs. sulfasalazine followed by an open-label extension with etanercept up to week 540 in early axial spondyloarthritis with focus on improvement of acute inflammatory lesions as detected by MRI (ESTHER)

Summary

EudraCT number	2005-002320-34
Trial protocol	DE
Global end of trial date	01 October 2018

Results information

Result version number	v1 (current)
This version publication date	26 November 2021
First version publication date	26 November 2021
Summary attachment (see zip file)	FinalStudyReport (FinalStudyReport_ESTHER.pdf)

Trial information

Trial identification

Sponsor protocol code	M01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00844142
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité
Sponsor organisation address	Hindenburgdamm 30, Berlin, Germany,
Public contact	Prof. Dr. Joachim Sieper, Charité, 0049 03084454547, joachim.sieper@charite.de
Scientific contact	Prof. Dr. Joachim Sieper, Charité, 0049 03084454547, joachim.sieper@charite.de

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	01 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2013
Global end of trial reached?	Yes
Global end of trial date	01 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy – to assess efficacy of etanercept vs. sulfasalazine when added to NSAIDs in patients with moderate to severe active early axial spondyloarthritis duration of ongoing axial symptoms of less than 5 years.

Primary outcome is change of active inflammatory lesions in sacroiliac joints and spine as detected by MRI at 12 months and at week 216, sustained reduction of active inflammation up to week 540.

Protection of trial subjects:

Adverse events, vital signs, physical examination results, and clinical laboratory values.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Scientific research
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

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)	76

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 study centers in Germany, between 5th of December 2005 (first patient first visit) and recruitment was finished with the screening on 05 May 2008.

Pre-assignment

Screening details:

A total of 101 subjects entered the screening period (5th of May 2008), of whom 24 withdrew before randomization. The remaining 77 subjects were randomized and received at least one dose of study drug

Period 1

Period 1 title	Week 48
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm1

Arm description:

receive etanercept 2x25 mg weekly subcutaneous injection

Arm type	Treatment
Investigational medicinal product name	Enbrel
Investigational medicinal product code	WAY-143050
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

etanercept 2x25 mg weekly

Arm title	Arm2
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Arm description:

receive sulfasalazine up to 2 g/day (up to 3 g/ per day)

Arm type	Active comparator
Investigational medicinal product name	Sulfasalazine
Investigational medicinal product code	59238.00.00
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500-0-0 mg/day in the first week; 500-0-500 mg/day in the second week; 500-0-1000mg/day in the third; 1000-0-1000 mg/day in the fourth week.

In therapy refractory cases it is allowed to increase the dosage to 1000 – 1000 – 1000 mg/ day from week 12

Number of subjects in period 1	Arm1	Arm2
Started	40	36
Completed	35	31
Not completed	5	5
Pregnancy	2	-
Intolerance	-	1
Lost to follow-up	3	2
Lymphoma	-	1
Lack of efficacy	-	1

Period 2

Period 2 title	Long term follow-up tp year 10
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm1

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Enbrel
Investigational medicinal product code	WAY-143050
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

etanercept 2x25 mg weekly

Arm title	Arm 2
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Arm description:

Switched to ETN from SSZ

Arm type	Experimental
Investigational medicinal product name	Enbrel
Investigational medicinal product code	WAY-143050
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

etanercept 2x25 mg weekly

Number of subjects in period 2	Arm1	Arm 2
Started	35	31
Completed	19	0
Not completed	47	31
deseases	9	-
Consent withdrawn by subject	4	-
live value increase	1	-
Transferred to other arm/group	-	31
Pregnancy	10	-
Lost to follow-up	8	-
non-compliance	5	-
Lack of efficacy	10	-
Joined	31	0
Transferred in from other group/arm	31	-

Baseline characteristics

Reporting groups

Reporting group title	Arm1
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Reporting group description:

receive etanercept 2x25 mg weekly subcutaneous injection

Reporting group title	Arm2
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Reporting group description:

receive sulfasalazine up to 2 g/day (up to 3 g/ per day)

Reporting group values	Arm1	Arm2	Total
Number of subjects	40	36	76
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	40	36	76
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.6	32.9	
standard deviation	± 8.7	± 8.4	-
Gender categorical Units: Subjects			
Female	17	15	32
Male	23	21	44

End points

End points reporting groups

Reporting group title	Arm1
Reporting group description: receive etanercept 2x25 mg weekly subcutaneous injection	
Reporting group title	Arm2
Reporting group description: receive sulfasalazine up to 2 g/day (up to 3 g/ per day)	
Reporting group title	Arm1
Reporting group description: -	
Reporting group title	Arm 2
Reporting group description: Switched to ETN from SSZ	
Subject analysis set title	All Subject
Subject analysis set type	Intention-to-treat
Subject analysis set description: as described in the manuscript (see attachment:FinalStudyReport/FinalStudyReport_ESTHER.pdf	

Primary: Pain

End point title	Pain
End point description: FinalStudyReport/FinalStudyReport_ESTHER.pdf	
End point type	Primary
End point timeframe: Weeks: 48, 108, 216, 264, 432, 540	

End point values	Arm1	Arm2	Arm1	All Subject
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	35	31	66	[1]
Units: BASDAI	3	3	3	3

Notes:

[1] - see manuscript

Statistical analyses

Statistical analysis title	Long-term efficacy of etanercept
Statistical analysis description: see manuscript: Final_Study_Report_ESTHER	
Comparison groups	Arm1 v Arm2

Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	equivalence ^[2]
P-value	≤ 0.27 ^[3]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Notes:

[2] - see manuscript: Final_Study_Report_ESTHER

[3] - see manuscript: Final_Study_Report_ESTHER

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Up to Week 540 (year 10)

Adverse event reporting additional description:

see manuscript: Final_Study_Report_ESTHER, table 19 page 63-64

Assessment type

Systematic

Dictionary used

Dictionary name

MedDRA

Dictionary version

16

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: we have not recorded any non-serious events in the trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2006	Amendment 1 Justification of the study duration, Modification of the safety assessment and specification of study related procedures
02 January 2006	Amendment 2 Modification/Specification of the ICF
10 April 2006	Amendment 3 Modification of the exclusion criterion regarding previous Sulfasalazine use to: only Sulfasalazine use within 6 months before screening is an exclusion criterion
19 December 2006	Amendment 4 Study extension for 12 months up to 2 years and inclusion of x-rays
10 July 2008	Amendment 5 Study extension up to 4 years
07 July 2010	Amendment 6 Study extension up to 6 years
24 September 2011	Amendment 7 Inclusion of serum biomarkers
05 October 2012	Amendment 8 Study extension up to 8 years
30 September 2014	Amendment 9 Study extension up to 10 years

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported