Clinical trial results:
Open-Label, Phase 4 Study, Investigating the Incidence of Extra-Articular Manifestations in Subjects With Ankylosing Spondylitis Treated With Golimumab; Protocol No. MK-8259-012

Summary

EudraCT number	2012-002458-21
Trial protocol	NL
Global end of trial date	30 April 2015

Results information

Result version number	v2 (current)
This version publication date	04 August 2016
First version publication date	04 May 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	MK-8259-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01668004
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	30 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to determine the difference in the annual incidence rate of uveitis attacks in participants with ankylosing spondylitis (AS) before start initial anti-TNF therapy and after treatment with golimumab (GLM).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2012
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	Netherlands: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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)	94
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 104 participants were screened; 3 participants were screen failures who did not enroll.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	GLM 50 mg

Arm description:

GLM given subcutaneously at a dose of 50 mg once monthly for up to 12 months

Arm type	Experimental
Investigational medicinal product name	Golimumab
Investigational medicinal product code	
Other name	Simponi®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

GLM 50 mg subcutaneously once monthly.

Number of subjects in period 1	GLM 50 mg
Started	101
Treated	101
Completed	76
Not completed	25
Consent withdrawn by subject	2
Adverse event, non-fatal	7
Non-compliance with treatment	2
Lost to follow-up	5
Lack of efficacy	9

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	101	101	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	94	94	
From 65-84 years	7	7	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	44.4		
standard deviation	± 12.9	-	
Gender, Male/Female Units: Participants			
Female	35	35	
Male	66	66	
Time since diagnosis Units: Years			
arithmetic mean	10.8		
standard deviation	± 11.8	-	
Age at onset of disease Units: Years			
arithmetic mean	33.1		
standard deviation	± 11.8	-	
Height Units: cm			
arithmetic mean	175.82		
standard deviation	± 9.62	-	
Weight Units: kg			
arithmetic mean	82.63		
standard deviation	± 18	-	
Abdominal circumference Units: cm			
arithmetic mean	95.5		
standard deviation	± 15.5	-	

End points

End points reporting groups

Reporting group title	GLM 50 mg

Reporting group description:

GLM given subcutaneously at a dose of 50 mg once monthly for up to 12 months

Subject analysis set title	Before initial anti-TNF/GLM treatment
Subject analysis set type	Per protocol

Subject analysis set description:

Historical observation period: Retrospective record review over the 12 months prior to the initial anti-TNF treatment (anti-TNF experienced participants) or the first GLM dose (anti-TNF naïve participants).

Subject analysis set title	After GLM treatment start
Subject analysis set type	Per protocol

Subject analysis set description:

GLM observation period: Prospective follow-up of participants given GLM subcutaneously at a dose of 50 mg once monthly for up to 12 months

Primary: Occurence Rate of Uveitis Attacks in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point title	Occurence Rate of Uveitis Attacks in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point description:

Uveitis is an extra-articular manifestation of ankylosing spondylitis (AS) involving inflammation of the eye. The occurrence rate (assessed as present/absent) of uveitis attacks was determined over two 1-year long periods regardless of whether the event started during the assessed year: 1) the historical observation period consisting of the year before initial anti-TNF treatment (for anti-TNF experienced participants) or prior to first GLM dose (for anti-TNF naïve participants); and 2) the GLM observation period consisting of the year after first GLM dose. All participants who received at least 3 months of GLM in the study and at least 3 months of follow-up data available for analysis of the endpoint.

End point type	Primary

End point timeframe:

Twelve Months Prior to Enrollment to Study Month 12

End point values	Before initial anti-TNF/GLM treatment	After GLM treatment start		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	93	93		
Units: Ratio				
number (not applicable)	0.08	0.08		

Statistical analyses

Statistical analysis title	Treatment Comparison

Statistical analysis description:

Treatment comparison of uveitis occurrence rate assessed 1 year before initial anti-TNF/GLM treatment and 1 year after start of GLM treatment

Comparison groups	Before initial anti-TNF/GLM treatment v After GLM treatment start

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 1
Method	Mcnemar

Notes:

[1] - Number of subjects included in analysis: N=93

Primary: Annual Incidence Rate of New Uveitis Attacks in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point title	Annual Incidence Rate of New Uveitis Attacks in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point description:

Uveitis is an extra-articular manifestation of AS involving inflammation of the eye. The annual incidence rate of new uveitis attacks was determined over two 1-year long periods: 1) the historical observation period consisting of the year before initial anti-TNF treatment (for anti-TNF experienced participants) or prior to first GLM dose (for anti-TNF naïve participants); & 2) the GLM observation period consisting of the year after first GLM dose. All participants were counted as contributing a full year of GLM exposure even if discontinuing early. Due to ongoing uveitis cases at time of period entry, participants did not have the same risk of new events during the one year periods. Participants with ongoing uveitis at start of GLM who had the adverse event for the entire treatment period were counted as having the 'new attack' before & no "new attack" after GLM treatment start. All participants receiving at least 3 months of GLM with at least 3 months of follow-up data were included

End point type	Primary

End point timeframe:

Twelve Months Prior to Enrollment to Study Month 12

End point values	Before initial anti-TNF/GLM treatment	After GLM treatment start		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	92[2]	92[3]		
Units: Events per 100 participant years				
number (not applicable)	9.8	2.2		

Notes:

[2] - One participant for whom the timing of uveitis events could not be determined was excluded.

[3] - One participant for whom the timing of uveitis events could not be determined was excluded.

Statistical analyses

Statistical analysis title	Statistical Comparison

Statistical analysis description:

Treatment difference (expressed as ratio) in uveitis incidence rate assessed 1 year before initial anti-TNF/GLM treatment and 1 year after start of GLM treatment

Comparison groups	Before initial anti-TNF/GLM treatment v After GLM treatment start

Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Generalized estimating equation
Parameter estimate	Treatment Ratio
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.86
upper limit	5.25

Notes:

[4] - Number of subjects included in analysis: N=92

Secondary: Annual Incidence Rate of New-Onset or Flares of Inflammatory Bowel Disease (IBD) and Psoriasis in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point title	Annual Incidence Rate of New-Onset or Flares of Inflammatory Bowel Disease (IBD) and Psoriasis in Participants Before Anti-TNF/GLM Treatment and After the Start of GLM Treatment

End point description:

IBD (Crohn's disease or ulcerative colitis) and psoriaris are extra-articular manifestations of AS involving the intestinal tract and skin, respectively. The annual incidence rates of new-onset or flares of IBD and psoriasis were to be determined separately (i.e., for each condition) over two 1-year long periods: 1) the historical observation period consisting of the year before initial anti-TNF treatment (for anti-TNF experienced participants) or prior to first GLM dose (for anti-TNF naïve participants); and 2) the GLM observation period consisting of the year after first GLM dose. The incidence rates for new onset or flares of IBD and psoriasis could not be evaluated due to limitations of the data collected; occurrence of flares was not collected (specifically, history of IBD and/or psoriasis could not be distinguished from flares of IBD and/or psoriasis) and, therefore, results could not be determined.

End point type	Secondary

End point timeframe:

Twelve Months Prior to Enrollment to Study Month 12

End point values	Before initial anti-TNF/GLM treatment	After GLM treatment start		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: Events per 100 participant years				

Notes:

[5] - Results not provided due to limitations of data collected.

[6] - Results not provided due to limitations of data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50) Responders Following Treatment With GLM

End point title	Percentage of Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI 50) Responders Following Treatment With

	GLM

End point description:

The percentage of participants with a BASDAI 50 response (defined as a 50% improvement or as an absolute improvement of 2 points in their BASDAI physical function score) at three months was determined. The BASDAI consists of total of six visual analog scales (VAS): five VAS (0 to 10 cm; increasing severity) measuring severity of fatigue, spinal pain, peripheral joint pain or swelling, localized tenderness, and severity of morning stiffness and one VAS (0 to 10 cm; increasing duration up to 2 hours) measuring duration of morning stiffness. The morning stiffness scores are averaged and summed with the scores for the remaining four items resulting in a composite score (0-50); the final BASDAI score (0-10) is derived by dividing by 5. All participants who received at least 3 months of GLM in the study and at least 3 months of follow-up data available for analysis of the endpoint (BASDAI 50).

End point type	Secondary

End point timeframe:

Baseline (BL), Study Month 3

End point values	GLM 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Percentage of participants				
number (not applicable)	33			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Ankylosing Spondylitis Disease Activity Score (ASDAS) Responders Following Treatment With GLM

End point title	Percentage of Ankylosing Spondylitis Disease Activity Score (ASDAS) Responders Following Treatment With GLM

End point description:

The percentage of participants with ASDAS clinically important improvement (ASDAS-CII; ≥ 1.1 units) & major improvement (ASDAS-MI; ≥ 2.0 units) at 3 months were determined. The ASDAS incorporates three items from the BASDAI (spinal pain, duration of morning stiffness, & peripheral joint pain or swelling) each assessed on a VAS (0 to 10 cm; increasing severity) as well as patient global assessment of disease activity (VAS; 0 to 10 cm; increasing severity) & a laboratory measure of inflammation (CRP level [mg/L] or ESR [mm/hr]). ASDAS was calculated using the formula: 0.12*Spinal Pain + 0.06*Duration of Morning Stiffness + 0.11*Patient Global + 0.07*Peripheral Pain/Swelling + 0.58*ln(CRP (mg/L) +1). A decrease in ASDAS at 3 months relative to BL signifies an improvement in physical function; ASDAS-MI signifies a comparatively greater improvement in physical function than ASDAS-CII. All participants receiving at least 3 months of GLM with at least 3 months of follow-up data

End point type	Secondary

End point timeframe:

BL, Study Month 3

End point values	GLM 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	84			
Units: Percentage of participants				
number (not applicable)				
ASDAS-CII (≥ 1.1 units)	40.5			
ASDAS-MI (≥ 2.0 units)	19			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to one year

Adverse event reporting additional description:

All safety analyses were performed on the All Treated Set defined as all patients who received at least one dose of golimumab in the study. Only safety data during the GLM period was collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	GLM 50 mg

Reporting group description:

GLM given subcutaneously at a dose of 50 mg once monthly for up to 12 months

Serious adverse events	GLM 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 101 (6.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Fistula repair			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal ulcer haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GLM 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 101 (20.79%)		
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 101 (12.87%)		
occurrences (all)	19		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 101 (10.89%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2013	Amendment 1 included changes to procedure for collection of retrospective 12 month data, pregnancy test procedure, and Pain and Patient Global Disease Activity assessment procedure.
05 August 2013	Amendment 2 included changes to echocardiography and other heart-related procedures performed within two weeks after first study drug administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported