



## Clinical trial results:

**A multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase II trial to investigate the efficacy and safety of 30 mcg and 100 mcg AS902330 given as one cycle of three intra-articular knee injections once a week for three weeks as an adjunct treatment to patients following microfracture surgery for cartilage injury of the knee.**

### Summary

EudraCT number	2012-001431-31
Trial protocol	BE
Global end of trial date	10 September 2013

### Results information

Result version number	v2 (current)
This version publication date	04 July 2016
First version publication date	04 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li><li>Update in population of trial subjects section</li></ul>

### Trial information

#### Trial identification

Sponsor protocol code	EMR700692-007
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01689337
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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	10 September 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 September 2013
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The trial's primary objectives were as follows:

To evaluate the effect of AS902330 intra-articular (i.a.) knee injections as adjunct to microfracture (MFx) surgery on the composition of the refilled cartilage in the target knee, as measured by delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) T1 relaxation time at 6 months after MFx surgery.

To evaluate the safety profile of AS902330 when administered i.a into the knee as adjunct to MFx surgery in subjects with cartilage injury of the knee.

Protection of trial subjects:

Patient protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 2013
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	United States: 1
Worldwide total number of subjects	1
EEA total number of subjects	0

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)	1

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First/last subject (informed consent): Apr 2013/Aug 2013; Study completion date: September 2013.

### Pre-assignment

Screening details:

A total of 4 subjects were screened and gave signed informed consent to participate in the study. Three subjects were screen failure, therefore only one subject was randomized.

### Period 1

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

### Arms

<b>Arm title</b>	Sprifermin (AS902330), 100 mcg
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Arm description:

Sprifermin (AS902330) was administered at a dose of 100 microgram (mcg) as intra-articular injection once every week for 3 weeks, starting from 2 weeks after microfracture (MFX) surgery.

Arm type	Experimental
Investigational medicinal product name	Sprifermin
Investigational medicinal product code	
Other name	AS902330, recombinant human FGF-18, rhFGF-18
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Sprifermin (AS902330) was administered at a dose of 100 microgram (mcg) as intra-articular injection once every week for 3 weeks, starting from 2 weeks after microfracture (MFX) surgery.

<b>Number of subjects in period 1</b>	Sprifermin (AS902330), 100 mcg
Started	1
Completed	1

## Baseline characteristics

### Reporting groups

Reporting group title	Overall
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Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	1	1	
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)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	1	1	

## End points

### End points reporting groups

Reporting group title	Sprifermin (AS902330), 100 mcg
Reporting group description: Sprifermin (AS902330) was administered at a dose of 100 microgram (mcg) as intra-articular injection once every week for 3 weeks, starting from 2 weeks after microfracture (MFx) surgery.	

### Primary: Composition of the Refilled Cartilage Measured by Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) Using T1 Relaxation Time at Month 6 Post-MFx Surgery

End point title	Composition of the Refilled Cartilage Measured by Delayed Gadolinium-Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) Using T1 Relaxation Time at Month 6 Post-MFx Surgery <sup>[1]</sup>
End point description: The dGEMRIC is an imaging technique that estimates the proteoglycan (and glycosaminoglycan) content of joint cartilage using spin-lattice relaxation time T1 after penetration of gadolinium contrast agent. Composition of the refilled cartilage was to be reported.	
End point type	Primary
End point timeframe: 6 months post-MFx surgery	

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: Efficacy analysis was not performed as only one subject was enrolled in the study.

End point values	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: Subjects				

Notes:

[2] - Efficacy analysis was not performed as only one subject was enrolled in the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Composition of the Refilled Cartilage Measured by dGEMRIC Using T1 Relaxation Time Beyond Month 6 Post-MFx Surgery

End point title	Composition of the Refilled Cartilage Measured by dGEMRIC Using T1 Relaxation Time Beyond Month 6 Post-MFx Surgery
End point description: The dGEMRIC is an imaging technique that estimates the proteoglycan (and glycosaminoglycan) content of joint cartilage using spin-lattice relaxation time T1 after penetration of gadolinium contrast agent. Composition of the refilled cartilage was to be reported.	
End point type	Secondary
End point timeframe: Every 6 months up to 5 years beyond 6 months post-MFx surgery	

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: Subjects				

Notes:

[3] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Subject-reported Outcome Measure: Knee Injury and Osteoarthritis Outcome Score (KOOS) Sub-scores for Pain and Activities of Daily Living (ADL)

End point title	Change From Baseline in Subject-reported Outcome Measure: Knee Injury and Osteoarthritis Outcome Score (KOOS) Sub-scores for Pain and Activities of Daily Living (ADL)
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End point description:

The KOOS Version LK1.0 is a knee-specific self-administered questionnaire used to assess pain, function, quality of life, and ADL. It consists of 42 items grouped into 5 subscales: pain, other symptoms (including swelling, restricted range of motion, and mechanical symptoms), function in ADL, function in sport and recreation (FSR), and impact on quality of life (QOL) (knee-related QOL, including awareness of the knee condition and changes in lifestyle). The subscales are scored separately; each yields a score between 0 and 100, with 0 representing extreme knee problems and 100 representing absence of problems. Total KOOS score is the average of all 5 subscale scores; ranging from 0 to 100; where 0 represents extreme knee problems and 100 represents absence of knee problems. Change from baseline in pain and ADL sub-scores was to be calculated by the respective scores at the specific time point minus the scores at baseline.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[4]</sup>			
Units: Subjects				

Notes:

[4] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Subject-reported Outcome Measure: Total KOOS Score, Three KOOS Sub-scores and Total KOOS Minus FSR Sub-score

End point title	Change From Baseline in Subject-reported Outcome Measure: Total KOOS Score, Three KOOS Sub-scores and Total KOOS Minus FSR Sub-score
End point description:	
<p>The KOOS Version LK1.0 is a knee-specific self-administered questionnaire used to assess pain, function, quality of life, and ADL. It consists of 42 items grouped into 5 subscales: pain, other symptoms (including swelling, restricted range of motion, and mechanical symptoms), function in ADL, FSR, and impact on QOL (knee-related QOL, including awareness of the knee condition and changes in lifestyle). The subscales are scored separately; each yields a score between 0 and 100, with 0 representing extreme knee problems and 100 representing absence of problems. Total KOOS score is the average of all 5 subscale scores; ranging from 0 to 100; where 0 represents extreme knee problems and 100 represents absence of knee problems. Change from baseline in total KOOS score; other symptoms, knee-related QOL, and FSR sub-scores; and total KOOS minus FSR sub-score was to be calculated by the respective scores at the specific time point minus the scores at baseline.</p>	
End point type	Secondary
End point timeframe:	
Every 6 months up to 5 years	

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[5]</sup>			
Units: Subjects				

Notes:

[5] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Composition of the Refilled Cartilage Using T2 Mapping

End point title	Composition of the Refilled Cartilage Using T2 Mapping
End point description:	
<p>The transverse relaxation time T2 mapping is an MRI technique that is able to evaluate collagen organization and orientation within cartilage. Composition of the refilled cartilage was to be reported.</p>	
End point type	Secondary
End point timeframe:	
Every 6 months up to 5 years	

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[6]</sup>			
Units: Subjects				

Notes:

[6] - Efficacy analysis was not performed as only one subject was enrolled in the study.



## Statistical analyses

No statistical analyses for this end point

### Secondary: Volume of the Refilled Cartilage

End point title	Volume of the Refilled Cartilage
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End point description:

Volume of the refilled cartilage was to be measured by MRI.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[7]</sup>			
Units: Subjects				

Notes:

[7] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) Score

End point title	Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) Score
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End point description:

The MOCART score is used to describe the constitution of the cartilage repair tissue and the surrounding structures.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[8]</sup>			
Units: Subjects				

Notes:

[8] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Six-minute Walk Test

End point title	Six-minute Walk Test
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End point description:

Six (6)-minute walk test is used to measure gait function and for pre- and post-operative evaluation in cartilage injury repair. Maximum comfortable distance (in meters) that a subject can walk in 6 minutes was to be reported.

End point type	Secondary
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End point timeframe:

Every 3 months up to 5 years beyond Month 6 post-MFx surgery

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[9]</sup>			
Units: Subjects				

Notes:

[9] - Efficacy analysis was not performed as only one subject was enrolled in the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)
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End point description:

An AE was defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. An SAE is an AE that results in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect.

End point type	Secondary
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End point timeframe:

Baseline up to Month 60

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
SAEs	0			
AEs	6			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Subject-reported Outcome Measure: Numeric Rating Scale (NRS) Score

End point title	Change From Baseline in Subject-reported Outcome Measure: Numeric Rating Scale (NRS) Score
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End point description:

Knee pain was to be rated by the subject using an 11-point NRS of pain intensity. The NRS is scaled from 0 (no pain) to 10 (worst possible pain). Change from baseline in NRS score was to be calculated by the score at the specific time point minus the score at baseline.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

End point values	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[10]</sup>			
Units: Units on scale				

Notes:

[10] - Efficacy analysis was not performed as only one subject was enrolled in the study.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Subject-reported Outcome Measure: Lower Extremity Activity Scale (LEAS) Score

End point title	Change From Baseline in Subject-reported Outcome Measure: Lower Extremity Activity Scale (LEAS) Score
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End point description:

The LEAS is an 18-level single-question self-administered scale that has been validated as a clinical outcome measure for the assessment of subjects' actual activity levels. The LEAS is scaled from 1 to 18, with 18 indicating levels of highest activity. Change from baseline in LEAS score was to be calculated by the score at the specific time point minus the score at baseline.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[11]</sup>			
Units: Units on scale				

Notes:

[11] - Efficacy analysis was not performed as only one subject was enrolled in the study.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in the Physician-reported Outcome Measure: Lysholm Knee Scale Score

End point title	Change From Baseline in the Physician-reported Outcome Measure: Lysholm Knee Scale Score
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End point description:

The Lysholm knee scale is a physician-reported outcome measure to assess knee function after ligament injury. It is scaled from 0 to 100 with higher scores representing better function. Change from baseline in Lysholm knee scale score was to be calculated by the score at the specific time point minus the score at baseline.

End point type	Secondary
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End point timeframe:

Every 6 months up to 5 years

<b>End point values</b>	Sprifermin (AS902330), 100 mcg			
Subject group type	Reporting group			
Number of subjects analysed	0 <sup>[12]</sup>			
Units: Units on scale				
number (not applicable)				

Notes:

[12] - Efficacy analysis was not performed as only one subject was enrolled in the study

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 6 months

Adverse event reporting additional description:

An adverse event (AE) was defined as any new untoward medical occurrences/worsening of pre-existing medical condition, whether or not related to study drug.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

Reporting group title	Sprifermin (AS902330), 100 mcg
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Reporting group description:

Sprifermin (AS902330) will be administered at a dose of 100 microgram (mcg) as intra-articular injection once every week for 3 weeks, starting from 2 weeks after MFx surgery.

Serious adverse events	Sprifermin (AS902330), 100 mcg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Sprifermin (AS902330), 100 mcg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Infections and infestations			
Pyrexia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Streptococcal pharyngitis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Efficacy analysis was not performed as only one subject was enrolled in the study. The study was terminated due to low recruitment.
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Notes: