Clinical trial results:
A Randomised, Double-blind Placebo-controlled Phase IIa Study to Evaluate Efficacy, Safety and Tolerability of MIV-711 in Knee Joint Osteoarthritis

Summary

EudraCT number	2015-003230-26
Trial protocol	GB DE BG
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	03 June 2018
First version publication date	03 June 2018

Trial information

Trial identification

Sponsor protocol code	MIV-711-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02705625
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medivir AB
Sponsor organisation address	Box 1086, Huddinge, Sweden, 14122
Public contact	MIV-711 Clinical Study Information , Medivir AB, clinicaloperations@medivir.com
Scientific contact	MIV-711 Clinical Study Information , Medivir AB, clinicaloperations@medivir.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	22 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2017
Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of MIV-711 on target knee average pain over 26 weeks as measured by an 11-point numerical rating scale (1 week recall) in patients with symptomatic and radiographic knee osteoarthritis

Protection of trial subjects:

Patients were observered in the clinics during the study visits.
During the whole treatment period, the following safety assessments were performed at each visit; collection of adverse events and concomitant medications, vital signs, physical examination (full or targeted), ECG, standard safety laboratory parameters.
The last visit (at week 30) was a safety follow-up where all the above safety assessments were evaluated except physical examination.
In addition, a phone call was made after all dosing visits to assess safety and tolerability.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Moldova, Republic of: 92
Country: Number of subjects enrolled	Georgia: 34
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Bulgaria: 38
Country: Number of subjects enrolled	Germany: 70
Worldwide total number of subjects	244
EEA total number of subjects	118

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	162
From 65 to 84 years	82
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with chronic knee pain and Kellgren and Lawrence (K-L) classification Grade 2 or 3 were included in the study.
The study was conducted in 6 study centres in 6 countries, Bulgaria, Georgia, Germany, Moldova, Romania and United Kingdom.

Pre-assignment

Screening details:

The study population was adults aged between 40 and 80 with symptomatic and radiographic knee Osteoarthritis.
The patient's usual analgesic regimen (in case of use) must have remained the same for 4 weeks prior to the signature of the informed consent form.
The study had a screening period of approximately 4 weeks.

Period 1

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

Blinding implementation details:

All IMPs were supplied in identical packaging and were similar in color, smell, taste and appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline MIV-711 100 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MIV-711
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The included excipients were microcrystalline cellulose, Starcap 1500, magnesium stearate and anhydrous colloidal silica.

Arm title	Baseline MIV-711 200 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MIV-711
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The included excipients were microcrystalline cellulose, Starcap 1500, magnesium stearate and anhydrous colloidal silica.

Arm title	Baseline Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For the placebo formulation, the excipient composition of the MIV-711 capsule was used, but the active substance was substituted with microcrystalline cellulose and Starcap 1500.

Number of subjects in period 1	Baseline MIV-711 100 mg	Baseline MIV-711 200 mg	Baseline Placebo
Started	82	82	80
Completed	82	82	80

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	MIV-711 100 mg

Arm description:

MIV-711 100 mg once daily for 26 weeks

Arm type	Experimental
Investigational medicinal product name	MIV-711
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The included excipients were microcrystalline cellulose, Starcap 1500, magnesium stearate and anhydrous colloidal silica.

Arm title	MIV-711 200 mg

Arm description:

MIV-711 200 mg once daily for 26 weeks

Arm type	Experimental

Investigational medicinal product name	MIV-711
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The included excipients were microcrystalline cellulose, Starcap 1500, magnesium stearate and anhydrous colloidal silica.

Arm title	Placebo

Arm description:

Placebo once daily for 26 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

For the placebo formulation, the excipient composition of the MIV-711 capsule was used, but the active substance was substituted with microcrystalline cellulose and Starcap 1500.

Number of subjects in period 2	MIV-711 100 mg	MIV-711 200 mg	Placebo
Started	82	82	80
Completed	74	72	69
Not completed	8	10	11
NON COMPLIANCE BY SUBJECT	-	1	-
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	1	4	5
NON-COMPLIANCE	-	-	1
Adverse event, non-fatal	6	5	2
OVERDOSING	-	-	1
Lost to follow-up	-	-	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline MIV-711 100 mg
Reporting group description: -	
Reporting group title	Baseline MIV-711 200 mg
Reporting group description: -	
Reporting group title	Baseline Placebo
Reporting group description: -	

Reporting group values	Baseline MIV-711 100 mg	Baseline MIV-711 200 mg	Baseline Placebo
Number of subjects	82	82	80
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)	53	55	54
From 65-84 years	29	27	26
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.2	62	62.0
standard deviation	± 6.58	± 7.30	± 6.67
Gender categorical Units: Subjects			
Female	64	59	65
Male	18	23	15

Reporting group values	Total		
Number of subjects	244		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	162		
From 65-84 years	82		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	188		
Male	56		

End points

End points reporting groups

Reporting group title	Baseline MIV-711 100 mg
Reporting group description: -	
Reporting group title	Baseline MIV-711 200 mg
Reporting group description: -	
Reporting group title	Baseline Placebo
Reporting group description: -	
Reporting group title	MIV-711 100 mg
Reporting group description:	
MIV-711 100 mg once daily for 26 weeks	
Reporting group title	MIV-711 200 mg
Reporting group description:	
MIV-711 200 mg once daily for 26 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily for 26 weeks	

Primary: NRS average target knee pain score at Week 26

End point title	NRS average target knee pain score at Week 26

End point description:

Change from Visit 2 (Baseline) to Visit 8 (Week 26) in NRS average target knee pain score.
NRS (Numeric rating scale) ranges from 0 indicating -"no pain", to 10 indicating - "pain as bad as it could be".

End point type	Primary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	72	69	
Units: score				
arithmetic mean (standard deviation)	-1.7 (± 2.01)	-1.5 (± 1.95)	-1.3 (± 2.15)	

Statistical analyses

Statistical analysis title	Change in NRS average target knee pain score.

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline NRS was included

as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.4055 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.0761
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.703
upper limit	0.55

Notes:

[1] - For the primary endpoint, the Type I error for the tests of the two doses was protected by performing a fixed-sequence multiple-testing procedure in the following order:
Step 1: 200 mg versus placebo
Step 2: 100 mg versus placebo
The second step was only considered as confirmatory provided the previous step was significant at a one-sided 5%-level ($p<0.05$).
If the previous step was not significant, the analysis of the following step was considered descriptive.
[2] - The p-values reported is from Step 1 (comparing 200 mg versus placebo).
The corresponding p-value from Step 2 (comparing 100 mg versus placebo) was 0.1458.

Secondary: MRI bone area of the target knee at Week 26

End point title	MRI bone area of the target knee at Week 26

End point description:

Change from Visit 2 (Baseline) to Visit 8 (Week 26) in MRI (Magnetic Resonance Imaging;) bone area of the target knee in mm^2.

End point type	Secondary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	69	66	
Units: mm2				
arithmetic mean (standard deviation)	8.1290 (± 31.10846)	8.2142 (± 29.39941)	23.22343 (± 32.68365)	

Statistical analyses

Statistical analysis title	Change in knee joint MRI bone area

Statistical analysis description:

A linear mixed model based on the mITT population was used.

The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline knee joint MRI bone area was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0036 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.3
upper limit	-4.02

Notes:

[3] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in knee joint MRI bone area at Week 26.
[4] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: bone area increase is lower in the active treatment arm compared to placebo.

Statistical analysis title	Change in knee joint MRI bone area

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline knee joint MRI bone area was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 100 mg v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0023 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	-4.83

Notes:

[5] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in knee joint MRI bone area at Week 26.
[6] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: bone area increase is lower in the active treatment arm compared to placebo.

Secondary: CTX-I at Week 26

End point title	CTX-I at Week 26

End point description:	
Biomarkers for bone resorption (serum CTX-I)	
End point type	Secondary
End point timeframe:	
Week 26 compared to baseline	

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	71	69	
Units: ug/L				
arithmetic mean (standard deviation)	-0.1209 (± 0.16733)	-0.2575 (± 0.19931)	0.0000 (± 0.16165)	

Statistical analyses

Statistical analysis title	Change in CTX-I

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline CTX-I score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.254
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.302
upper limit	-0.206

Notes:

[7] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in CTX-I score at Week 26.
[8] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: CTX-I score is lower in the active treatment arm compared to placebo.

Statistical analysis title	Change in CTX-I

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline CTX-I score was included as a covariate for adjustment.

An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	Placebo v MIV-711 100 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.193
upper limit	-0.0983

Notes:

[9] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in CTX-I score at Week 26.

[10] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: CTX-I score is lower in the active treatment arm compared to placebo.

Secondary: CTX-II/Creatinine at Week 26

End point title	CTX-II/Creatinine at Week 26
End point description:	
Cartilage degradation (urine CTX-II)	
End point type	Secondary
End point timeframe:	
Week 26 compared to baseline	

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	72	68	
Units: ng/mmol				
arithmetic mean (standard deviation)	-138.0 (± 198.68)	-242.5 (± 266.56)	28.4 (± 225.69)	

Statistical analyses

Statistical analysis title	Change in CTX-II/Creatinine

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline CTX-II score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo

Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-270
Confidence interval	
level	95 %
sides	2-sided
lower limit	-339
upper limit	-201

Notes:

[11] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in CTX-II score at Week 26.

[12] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: CTX-II score is lower in the active treatment arm compared to placebo.

Statistical analysis title	Change in CTX-II/Creatinine

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline CTX-II score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	Placebo v MIV-711 100 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.0001 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-193
Confidence interval	
level	95 %
sides	2-sided
lower limit	-262
upper limit	-124

Notes:

[13] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in CTX-II score at Week 26.

[14] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: CTX-II score is lower in the active treatment arm compared to placebo.

Secondary: MRI of Cartilage Thickness (Femur) at Week 26

End point title	MRI of Cartilage Thickness (Femur) at Week 26

End point description:

MRI of cartilage thickness in the Central Medial Femur Region of the target knee

End point type	Secondary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	69	66	
Units: mm				
arithmetic mean (standard deviation)	0.0077 (± 0.19258)	-0.0171 (± 0.24113)	-0.0658 (± 0.21904)	

Statistical analyses

Statistical analysis title	Change in MRI of cartilage thickness (Femur)

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline MRI of cartilage thickness was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.1253 [16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0436
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.118

Notes:

[15] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in MRI of cartilage thickness (Femur Region) at Week 26.

[16] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: MRI of cartilage thinning (Femur Region) is lower in the active treatment arm compared to placebo.

Statistical analysis title	Change in MRI of cartilage thickness (Femur)

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline MRI of cartilage thickness was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	Placebo v MIV-711 100 mg
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0225 [18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0761
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.00173
upper limit	0.15

Notes:

[17] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in MRI of cartilage thickness (Femur Region) at Week 26.

[18] - p-values reported are unadjusted p-values for tests of significance for the upper one-tailed alternative hypothesis Ha: MRI of cartilage thinning (Femur Region) is lower in the active treatment arm compared to placebo.

Secondary: Normalised WOMAC, Pain Score

End point title	Normalised WOMAC, Pain Score

End point description:

End point type	Secondary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	72	69	
Units: score				
arithmetic mean (standard deviation)	-16.6 (± 19.35)	-13.0 (± 18.6)	-9.8 (± 21.89)	

Statistical analyses

Statistical analysis title	Change in normalised WOMAC Pain score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-
time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline WOMAC Pain score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.2887 [20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.02
upper limit	4.48

Notes:

[19] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in WOMAC Pain score at Week 26.

[20] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Pain score is higher in the active treatment arm compared to placebo.

Statistical analysis title	Change in normalised WOMAC Pain score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-
time, baseline analgesic (Yes/No) and random effect for clinical site. Baseline WOMAC Pain score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 100 mg v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0753 [22]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	1.67

Notes:

[21] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in WOMAC Pain score at Week 26.

[22] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Pain score is higher in the active treatment arm compared to placebo.

Secondary: Normalised WOMAC, Difficulty Score

End point title	Normalised WOMAC, Difficulty Score

End point description:

End point type	Secondary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	72	69	
Units: score				
arithmetic mean (standard deviation)	-16.39 (± 20.937)	-13.95 (± 20.668)	-9.9 (± 21.862)	

Statistical analyses

Statistical analysis title	Change in normalised WOMAC Difficulty score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic (Yes/No) and random effect for clinical site. Baseline WOMAC Difficulty score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.2898 [24]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.38
upper limit	4.7

Notes:

[23] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in WOMAC Difficulty score at Week 26.
[24] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Difficulty score is higher in the active treatment arm compared to placebo.

Statistical analysis title	Change in normalised WOMAC Difficulty score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic (Yes/No) and random effect for clinical site. Baseline WOMAC Difficulty score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	Placebo v MIV-711 100 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.1262 [26]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	2.72

Notes:

[25] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in WOMAC Difficulty score at Week 26.

[26] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Difficulty score is higher in the active treatment arm compared to placebo.

Secondary: Normalised WOMAC, Stiffness Score

End point title	Normalised WOMAC, Stiffness Score

End point description:

End point type	Secondary

End point timeframe:

Week 26 compared to baseline

End point values	MIV-711 100 mg	MIV-711 200 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	72	69	
Units: score				
arithmetic mean (standard deviation)	-17 (± 24.69)	-14.5 (± 22.71)	-9.8 (± 24.71)	

Statistical analyses

Statistical analysis title	Change in normalised WOMAC Stiffness score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-time, baseline analgesic (Yes/No) and random effect for clinical site. Baseline WOMAC Stiffness score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	MIV-711 200 mg v Placebo

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.2 [28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	4.1

Notes:

[27] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 200 mg versus placebo with respect to mean change from baseline in WOMAC Stiffness score at Week 26.
[28] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Stiffness score is higher in the active treatment arm compared to placebo.

Statistical analysis title	Change in normalised WOMAC Stiffness score

Statistical analysis description:

A linear mixed model based on the mITT population was used.
The model included fixed factors for treatment, time (measured in weeks), the interaction for treatment-by-
time, baseline analgesic user (Yes/No), and random effect for clinical site. Baseline WOMAC Stiffness score was included as a covariate for adjustment.
An unstructured covariance matrix was used to model the covariance pattern in the mixed effects model.

Comparison groups	Placebo v MIV-711 100 mg
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0861 [30]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	2.17

Notes:

[29] - One model is fit for all comparison groups (MIV-711 200 mg, MIV-711 100 mg and placebo). This analysis reports the contrast that compares 100 mg versus placebo with respect to mean change from baseline in WOMAC Stiffness score at Week 26.
[30] - p-values reported are unadjusted p-values for tests of significance for the lower one-tailed alternative hypothesis Ha: Reduction in WOMAC Stiffness score is higher in the active treatment arm compared to placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from baseline to safety follow-up visit

Adverse event reporting additional description:

This study reports treatment-emergent AEs (TEAEs). A TEAE was defined as an AE that begins or that worsens in severity after at least one dose of IMP has been administered.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	MIV-711 100 mg
Reporting group description: -	
Reporting group title	MIV-711 200 mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	MIV-711 100 mg	MIV-711 200 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 82 (3.66%)	2 / 82 (2.44%)	1 / 80 (1.25%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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
Contusion			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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
Cardiac failure			
subjects affected / exposed	0 / 82 (0.00%)	0 / 82 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prinzmetal angina			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyelonephritis chronic			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	0 / 80 (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

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

Non-serious adverse events	MIV-711 100 mg	MIV-711 200 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 82 (54.88%)	43 / 82 (52.44%)	43 / 80 (53.75%)
Investigations			

Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 82 (0.00%)	4 / 80 (5.00%)
occurrences (all)	1	0	4
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 82 (0.00%)	1 / 82 (1.22%)	4 / 80 (5.00%)
occurrences (all)	0	1	4
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 82 (6.10%)	5 / 82 (6.10%)	6 / 80 (7.50%)
occurrences (all)	6	5	8
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	7 / 82 (8.54%)	6 / 82 (7.32%)	7 / 80 (8.75%)
occurrences (all)	7	6	8
Back pain			
subjects affected / exposed	1 / 82 (1.22%)	6 / 82 (7.32%)	3 / 80 (3.75%)
occurrences (all)	1	6	3
Arthralgia			
subjects affected / exposed	5 / 82 (6.10%)	2 / 82 (2.44%)	2 / 80 (2.50%)
occurrences (all)	5	2	4
Muscle spasms			
subjects affected / exposed	6 / 82 (7.32%)	0 / 82 (0.00%)	1 / 80 (1.25%)
occurrences (all)	7	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 82 (9.76%)	7 / 82 (8.54%)	6 / 80 (7.50%)
occurrences (all)	8	9	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2016	The purposes of this amendment were: • to update the protocol with all revisions to date including amendments made at the request of country health authorities and to update patient and study-related spects such as assessments, objectives, and inclusion/exclusion criteria that were found necessary upon further internal review. Minor typographic and grammar errors were corrected but are not detailed in this amendment summary, as they do not affect the conduct of the study.
20 July 2016	The purposes of this amendment were: • to include details about the option for all patients enrolled in the current study at the participating sites included in Extension Study MIV-711-202 to have the opportunity to participate in the extension protocol provided that they meet the eligibility criteria • to confirm that females must be non-pregnant at study screening • to delete the following: "At a patient's request, their data collected up to the point of withdrawal can also be withdrawn from the study and will not be used in the final analysis" • to clarify which concomitant steroids can be used during the study • to add a new subsection on Kellgren and Lawrence grade scoring • to provide further detail on magnetic resonance imaging (MRI) procedures • to provide clarity on visit numbers for Study MIV-711-201 and MIV-711-202 • to amend details of some of the footnotes in study schedule • to provide further detail on the safety follow-up visit • to provide an update on the planned analysis methods employed for the voluntarily consented pharmacogenomics samples • to update the wording pertaining to the potential phototoxicity that could not be excluded at the start of study MIV-711-201 but that meanwhile has been discarded following cell based assays as outlined in the updated Investigator Brochure. Even though no signs of phototoxicity potential could be seen in the in vitro cell assay, it is desirable to maintain assay conditions all through the study, hence the suggested wording change Minor typographic, formatting and grammar errors were corrected but are not detailed in this amendment summary, as they do not affect the conduct of the study or the safety of subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported