Clinical trial results:
An Open-Label, One-Arm Phase II Extension Study to Evaluate Safety and Tolerability of MIV-711 in Patients with Knee Joint Osteoarthritis

Summary

EudraCT number	2016-001096-73
Trial protocol	BG
Global end of trial date	28 November 2017

Results information

Result version number	v1 (current)
This version publication date	12 December 2018
First version publication date	12 December 2018

Trial information

Trial identification

Sponsor protocol code	MIV-711-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03037489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medivir AB
Sponsor organisation address	Box 1086, Huddinge, Sweden, 141 22
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	16 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2017
Global end of trial reached?	Yes
Global end of trial date	28 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the safety and tolerability of 200 mg MIV-711 q.d. over 52 (26+26) weeks in patients with symptomatic and radiographic knee osteoarthritis (these patients were treated with 200 mg MIV-711 in the preceeding MIV-711-201 study, Group A). A secondary objective was to assess the safety and tolerability of 200 mg MIV-711 q.d. over 26 weeks in patients with symptomatic and radiographic knee OA (these patients received placebo in the preceeding MIV-711-201 study, Group B).

Protection of trial subjects:

Patients were observed 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, ECG, standard safety laboratory parameters. In addition, phone calls were made in between the dosing visits to assess safety and tolerability.
The last visit (at week 30) was a safety follow-up where all the above safety assessments were evaluated except physical examination.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 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	Germany: 14
Country: Number of subjects enrolled	Georgia: 3
Country: Number of subjects enrolled	Moldova, Republic of: 24
Country: Number of subjects enrolled	Bulgaria: 9
Worldwide total number of subjects	50
EEA total number of subjects	23

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)	32
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Bulgaria, Georgia, Germany and Moldova in patients previously enrolled in MIV-711-201 including completion of Visit 8 either by:
• Receiving MIV-711 200 mg and had non-significant clinical worsening on the primary endpoint
OR by
• Receiving placebo and had a clinically significant worsening on the primary endpoint

Pre-assignment

Screening details:

All patients in Study MIV 711 201 (Eudract No. 2015-003230-26) at the participating sites included in Study MIV-711-202 were given the opportunity to participate provided that they met the eligibility criteria. They were permitted to remain on their current analgesic regimen.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Study Group A was recruited from patients treated with 200 mg MIV-711 QD in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the NRS of ≤2 compared to baseline. Patients in Study Group A continued the same dosing for 26 additional 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	Group B

Arm description:

Study Group B was recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus baseline. Patients in Study Group B were treated with 200 mg MIV-711 QD for the next 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.

Number of subjects in period 1	Group A	Group B
Started	46	4
Completed	46	4

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

Study Group A was recruited from patients treated with 200 mg MIV-711 QD in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the NRS of ≤2 compared to baseline. Patients in Study Group A continued the same dosing for 26 additional 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	Group B

Arm description:

Study Group B was recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus baseline. Patients in Study Group B were treated with 200 mg MIV-711 QD for the next 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.

Number of subjects in period 2	Group A	Group B
Started	46	4
Completed	39	4
Not completed	7	0
Consent withdrawn by subject	3	-
Adverse event, non-fatal	4	-

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
Study Group A was recruited from patients treated with 200 mg MIV-711 QD in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the NRS of ≤2 compared to baseline. Patients in Study Group A continued the same dosing for 26 additional weeks.	
Reporting group title	Group B
Reporting group description:	
Study Group B was recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus baseline. Patients in Study Group B were treated with 200 mg MIV-711 QD for the next 26 weeks.	

Reporting group values	Group A	Group B	Total
Number of subjects	46	4	50
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)	30	2	32
From 65-84 years	16	2	18
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.5	65.5	
standard deviation	± 7.52	± 5.51	-
Gender categorical Units: Subjects			
Female	31	3	34
Male	15	1	16

End points

End points reporting groups

Reporting group title	Group A

Reporting group description:

Study Group A was recruited from patients treated with 200 mg MIV-711 QD in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the NRS of ≤2 compared to baseline. Patients in Study Group A continued the same dosing for 26 additional weeks.

Reporting group title	Group B

Reporting group description:

Study Group B was recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus baseline. Patients in Study Group B were treated with 200 mg MIV-711 QD for the next 26 weeks.

Reporting group title	Group A

Reporting group description:

Study Group A was recruited from patients treated with 200 mg MIV-711 QD in Study MIV-711-201 and whose symptoms did not clinically significantly deteriorate as defined by an increase in the NRS of ≤2 compared to baseline. Patients in Study Group A continued the same dosing for 26 additional weeks.

Reporting group title	Group B

Reporting group description:

Study Group B was recruited from patients receiving placebo in Study MIV-711-201 having experienced a clinical worsening as defined by an increase in NRS of ≥2 versus baseline. Patients in Study Group B were treated with 200 mg MIV-711 QD for the next 26 weeks.

Primary: Patients with any treatment emergent adverse events (TEAEs)

End point title	Patients with any treatment emergent adverse events

End point description:

End point type	Primary

End point timeframe:

From visit 2 until safety follow-up

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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with any TEAE	21	2		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with any Serious Adverse Events (SAEs)

End point title	Patients with any Serious Adverse Events (SAEs)[2]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit

Notes:

[2] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with any SAEs	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with related TEAEs

End point title	Patients with related TEAEs[3]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit

Notes:

[3] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with any related TEAE	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with mild TEAEs

End point title	Patients with mild TEAEs[4]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit.

Notes:

[4] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with mild TEAEs	6	1		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with moderate TEAEs

End point title	Patients with moderate TEAEs[5]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit

Notes:

[5] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with moderate TEAEs	14	1		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with severe TEAEs

End point title	Patients with severe TEAEs[6]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit

Notes:

[6] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: Number of patients with severe TEAEs	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Patients with TEAEs leading to early discontinuation

End point title	Patients with TEAEs leading to early discontinuation[7]

End point description:

End point type	Primary

End point timeframe:

From visit 2 to the safety follow-up visit

Notes:

[7] - 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: No statistical analysis was done for the study. Only descriptive results are available.

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	4		
Units: No of pats with TEAEs leading to discon	4	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from visit 2 in MIV-711-202 to the safety follow-up visit.	
Adverse event reporting additional description:	
This study reports treatment-emergent AEs (TEAEs). A TEAE was difined 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	Group A
Reporting group description:	
Group A received MIV-711 200 mg once daily in the preceeding study MIV-711-201.	
Reporting group title	Group B
Reporting group description:	
Group B received placebo in the preceeding study MIV-711-201.	

Serious adverse events	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 46 (4.35%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			

subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 46 (2.17%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 46 (28.26%)	2 / 4 (50.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 46 (2.17%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Chronic gastritis			
subjects affected / exposed	2 / 46 (4.35%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Duodenal ulcer			
subjects affected / exposed	2 / 46 (4.35%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	2 / 46 (4.35%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 46 (8.70%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 46 (4.35%)	0 / 4 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported