Clinical trial results:
A Phase 2a, Proof of Concept, Randomized, Double-blind, Placebo-controlled Clinical Trial, to Evaluate the Efficacy and Safety of MK-7264 in Women with Moderate to Severe Endometriosis-related Pain

Summary

EudraCT number	2018-001098-26
Trial protocol	ES PL
Global end of trial date	30 June 2020

Results information

Result version number	v1 (current)
This version publication date	01 July 2021
First version publication date	01 July 2021

Trial information

Trial identification

Sponsor protocol code	MK-7264-034

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03654326
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 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2020
Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy, safety, and tolerability of gefapixant (MK-7264) in premenopausal female participants with moderate to severe endometriosis-related pain. The primary hypothesis: gefapixant is superior to placebo in reducing the average daily pelvic pain score (cyclic and non-cyclic, combined) during Treatment Cycle 2.

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	11 September 2018
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	Australia: 4
Country: Number of subjects enrolled	Chile: 6
Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Puerto Rico: 20
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Ukraine: 21
Country: Number of subjects enrolled	United States: 48
Worldwide total number of subjects	187
EEA total number of subjects	29

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)	187
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a baseline menstrual cycle (approximately 4 weeks) prior to randomization to either gefapixant or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant

Arm description:

Participants received a gefapixant 45 mg tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.

Arm type	Experimental
Investigational medicinal product name	Gefapixant
Investigational medicinal product code	
Other name	MK-7264
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Gefapixant 45 mg tablet twice a day for approximately 8 weeks (2 menstrual cycles).

Investigational medicinal product name	Naproxen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Naproxen sodium 275 mg tablets taken orally as rescue medication for endometriosis-related pain, at dose prescribed by sites' principal investigator

Arm title	Placebo

Arm description:

Participants received a placebo matching gefapixant tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.

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

Dosage and administration details:

Placebo-matching gefapixant tablet twice a day for approximately 8 weeks (2 menstrual cycles).

Investigational medicinal product name	Naproxen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Naproxen sodium 275 mg tablets taken orally as rescue medication for endometriosis-related pain, at dose prescribed by sites' principal investigator

Number of subjects in period 1	Gefapixant	Placebo
Started	94	93
Completed	88	87
Not completed	6	6
Consent withdrawn by subject	5	3
Physician decision	-	1
Unable to adhere to study schedule	-	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Gefapixant
Reporting group description:	
Participants received a gefapixant 45 mg tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo matching gefapixant tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.	

Reporting group values	Gefapixant	Placebo	Total
Number of subjects	94	93	187
Age categorical Units: Subjects			
Adults (18-64 years)	94	93	187
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	34.5	34.8	
standard deviation	± 6.6	± 7.3	-
Sex: Female, Male Units: Participants			
Female	94	93	187
Male	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	35	31	66
Not Hispanic or Latino	59	62	121
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	3	7
White	88	86	174
More than one race	1	4	5
Unknown or Not Reported	0	0	0
Average Daily Pelvic Pain Score			
Pelvic pain severity was measured using a 0-10 numeric rating scale (NRS), with 0 representing no pain and 10 representing extremely severe pain. The average of the daily pelvic pain scores entered in participants' electronic diaries (eDiaries) was calculated for the baseline cycle (approximately 28 days).			
Units: Scores on a Scale			
arithmetic mean	6.5	6.5	
standard deviation	± 1.0	± 1.0	-

End points

End points reporting groups

Reporting group title	Gefapixant
Reporting group description:	
Participants received a gefapixant 45 mg tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.	
Reporting group title	Placebo
Reporting group description:	
Participants received a placebo matching gefapixant tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.	

Primary: Change From Baseline in Average Daily Pelvic Pain Score During Treatment Cycle 2

End point title	Change From Baseline in Average Daily Pelvic Pain Score During Treatment Cycle 2
End point description:	
Pelvic pain (cyclic pain associated with menses, and non-cyclic pain not associated with menses) severity score was measured using a 0-10 numeric rating scale (NRS), with 0 representing no pain and 10 representing extremely severe pain. The averages of the daily pelvic pain scores (cyclic and non-cyclic, combined) entered in participants' electronic diaries (eDiaries) were calculated for Baseline and Treatment Cycle 2 (approximately Week 4 to Week 8). A negative change indicates a decrease in pain severity from baseline. The population analyzed included all randomized participants who received at least one dose of double-blind study intervention and had at least one day of eDiary entries during the post-randomization treatment cycle.	
End point type	Primary
End point timeframe:	
Baseline and Treatment Cycle 2 (Week 4 to Week 8; each cycle is approximately 28 days)	

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	93		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-2.2 (-2.79 to -1.62)	-1.7 (-2.30 to -1.13)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean
Comparison groups	Gefapixant v Placebo

Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066 [1]
Method	ANCOVA
Parameter estimate	Difference in Least Squares Mean
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.01
upper limit	0.03

Notes:

[1] - Based on the longitudinal analysis of covariance (ANCOVA) model including factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates

Primary: Percentage of Participants Who Experienced an Adverse Event

End point title	Percentage of Participants Who Experienced an Adverse Event

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. Per protocol, this analysis included AEs reported up to 14 days after end of study intervention (up to approximately 10 weeks). The population analyzed included all randomized participants who received at least one dose of study intervention.

End point type	Primary

End point timeframe:

Up to approximately 10 weeks

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	93		
Units: Percentage of Participants				
number (not applicable)	53.2	35.5		

Statistical analyses

Statistical analysis title	Difference in Percentage of Participants
Comparison groups	Gefapixant v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Difference in % vs Placebo
Point estimate	17.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.4
upper limit	31.3

Notes:

[2] - Based on Miettinen & Nurminen method

Primary: Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event

End point title	Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention. The population analyzed included all randomized participants who received at least one dose of study intervention.

End point type	Primary

End point timeframe:

Up to approximately 8 weeks

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	93		
Units: Percentage of Participants				
number (not applicable)	3.2	0		

Statistical analyses

Statistical analysis title	Difference in Percentage of Participants
Comparison groups	Gefapixant v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in % vs Placebo
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	9

Notes:

[3] - Based on Miettinen & Nurminen method.

Secondary: Change From Baseline in Average Daily Cyclic Pelvic Pain Score During

Treatment Cycle 2

End point title	Change From Baseline in Average Daily Cyclic Pelvic Pain Score During Treatment Cycle 2

End point description:

Cyclic pelvic pain (associated with menses) severity score was measured using a 0-10 NRS, with 0 representing no pain and 10 representing extremely severe pain. The average of the daily cyclic pelvic pain scores entered in participants' eDiaries was calculated for Baseline and Treatment Cycle 2 (Week 4 to Week 8). A negative change indicates a decrease in pain severity from baseline. The population analyzed included all randomized participants who received at least one dose of double-blind study intervention, had at least one day of eDiary entry during the post-randomization treatment cycle, and had available cyclic pelvic pain score data.

End point type	Secondary

End point timeframe:

Baseline and Treatment Cycle 2 (Week 4 to Week 8; each cycle is approximately 28 days)

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	90		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-2.0 (-2.55 to -1.35)	-1.3 (-1.94 to -0.73)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean
Comparison groups	Gefapixant v Placebo
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in Least Squares Mean
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.18
upper limit	-0.06

Notes:

[4] - The difference in least squares mean was based on the longitudinal analysis of covariance (ANCOVA) model including factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates

Secondary: Change From Baseline in Average Daily Non-Cyclic Pelvic Pain Score During Treatment Cycle 2

End point title	Change From Baseline in Average Daily Non-Cyclic Pelvic Pain Score During Treatment Cycle 2

End point description:

Non-cyclic pelvic pain (not associated with menses) severity score was measured using a 0-10 NRS, with 0 representing no pain and 10 representing extremely severe pain. The average of the non-cyclic daily pelvic pain scores entered in participants' eDiaries was calculated for the Baseline and Treatment Cycle 2 (Week 4 to Week 8). A negative change indicates decrease in pain severity from baseline. The population analyzed included all randomized participants who received at least one dose of double-blind

study intervention, had at least one day of eDiary entry during the post-randomization treatment cycle, and had available non-cyclic pelvic pain score data.

End point type	Secondary

End point timeframe:

Baseline and Treatment Cycle 2 (Week 4 to Week 8; each cycle is approximately 28 days)

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	91	90		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-2.3 (-2.90 to -1.69)	-1.8 (-2.40 to -1.18)		

Statistical analyses

Statistical analysis title	Difference in Least Squares Mean
Comparison groups	Gefapixant v Placebo
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Difference in Least Squares Mean
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.04
upper limit	0.03

Notes:

[5] - The difference in least squares mean was based on the longitudinal analysis of covariance (ANCOVA) model including factors for average pelvic pain scores at baseline cycle, stratum, treatment, cycle, interaction of stratum-by-cycle, and the interaction of treatment-by-cycle as covariates

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: Up to approximately 24 weeks
Serious adverse events and non-serious adverse events: Up to approximately 12 weeks

Adverse event reporting additional description:

All randomized participants who received at least one dose of study intervention.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Gefapixant

Reporting group description:

Participants received a gefapixant 45 mg tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.

Reporting group title	Placebo

Reporting group description:

Participants received a placebo matching gefapixant tablet twice a day for approximately 8 weeks (2 menstrual cycles). Naproxen sodium 275 mg tablets were also provided to participants, as needed, for endometriosis-related pain.

Serious adverse events	Gefapixant	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 94 (0.00%)	0 / 93 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Gefapixant	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 94 (38.30%)	12 / 93 (12.90%)	
Nervous system disorders			
Ageusia			
subjects affected / exposed	9 / 94 (9.57%)	1 / 93 (1.08%)	
occurrences (all)	9	1	
Dysgeusia			

subjects affected / exposed	15 / 94 (15.96%)	2 / 93 (2.15%)	
occurrences (all)	16	2	
Headache			
subjects affected / exposed	4 / 94 (4.26%)	7 / 93 (7.53%)	
occurrences (all)	4	7	
Hypogeusia			
subjects affected / exposed	5 / 94 (5.32%)	0 / 93 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 94 (6.38%)	0 / 93 (0.00%)	
occurrences (all)	6	0	
Dry mouth			
subjects affected / exposed	6 / 94 (6.38%)	2 / 93 (2.15%)	
occurrences (all)	6	2	

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