Clinical trial results:
A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Adult Participants with Recent Onset Chronic Cough

Summary

EudraCT number	2019-002308-42
Trial protocol	DE GB PL ES
Global end of trial date	03 November 2021

Results information

Result version number	v1 (current)
This version publication date	21 October 2022
First version publication date	21 October 2022

Trial information

Trial identification

Sponsor protocol code	7264-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04193202
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, 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	03 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 November 2021
Global end of trial reached?	Yes
Global end of trial date	03 November 2021
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 and safety of gefapixant in participants with recent onset chronic cough (duration >8 weeks after onset of cough symptoms) for <12 months and a diagnosis of refractory or unexplained chronic cough. The primary hypothesis is that gefapixant is superior to placebo in improving cough-related quality of life measured as change from baseline in the Leicester Cough Questionnaire (LCQ) total score at Week 12.

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	21 May 2020
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	Canada: 5
Country: Number of subjects enrolled	Colombia: 58
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Guatemala: 45
Country: Number of subjects enrolled	Peru: 44
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Ukraine: 95
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	419
EEA total number of subjects	56

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)	339
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 498 participants were screened, and 419 were randomized in the study. All non-randomized participants were screen failures.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Gefapixant

Arm description:

Participants receive gefapixant at a dose of 45 mg administered as an oral tablet twice daily for 12 weeks.

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:

45 mg twice daily administration

Arm title	Placebo

Arm description:

Participants receive placebo matching gefapixant, administered as an oral tablet twice daily for 12 weeks.

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 twice daily administration

Number of subjects in period 1	Gefapixant	Placebo
Started	208	211
Treated	206	209
Completed	192	201
Not completed	16	10
Adverse event, serious fatal	-	1
Physician decision	1	1
Consent withdrawn by subject	11	5
Adverse event, non-fatal	2	1
Protocol deviation	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Gefapixant
Reporting group description:	
Participants receive gefapixant at a dose of 45 mg administered as an oral tablet twice daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants receive placebo matching gefapixant, administered as an oral tablet twice daily for 12 weeks.	

Reporting group values	Gefapixant	Placebo	Total
Number of subjects	208	211	419
Age categorical Units: Participants			
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)	166	173	339
From 65-84 years	42	38	80
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	52.6	52.5	
standard deviation	± 13.8	± 13.7	-
Sex: Female, Male Units: Participants			
Female	136	135	271
Male	72	76	148
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	22	28	50
Asian	3	2	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	0	3
White	151	152	303
More than one race	29	29	58
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	71	76	147
Not Hispanic or Latino	136	134	270
Unknown or Not Reported	1	1	2

Baseline Leicester Cough Questionnaire (LCQ)			
The LCQ is a 19-item, cough-specific health related qualify of life (HRQoL) questionnaire. Each item on the LCQ assesses symptoms using a scale ranging from 1 to 7. The LCQ contains three domains on physical, psychological, and social functioning, and each domain score is calculated as the mean score of the items (range: 1 to 7) within the domain. The LCQ total score is the sum of the 3 domains, with a range from 3 to 21 .Higher scores indicate better HRQoL. The population analyzed included 202 participants in the Gefapixant group and 200 in the Placebo group.			
Units: Scores on a scale			
arithmetic mean	10.8	11.3	
standard deviation	± 3.1	± 2.8	-

End points

End points reporting groups

Reporting group title	Gefapixant
Reporting group description:	
Participants receive gefapixant at a dose of 45 mg administered as an oral tablet twice daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants receive placebo matching gefapixant, administered as an oral tablet twice daily for 12 weeks.	

Primary: Change from baseline in the Leicester Cough Questionnaire (LCQ) total score at Week 12

End point title	Change from baseline in the Leicester Cough Questionnaire (LCQ) total score at Week 12
End point description:	
Participants will be asked to complete the LCQ to assess the impact of their cough severity on health related quality of life (HRQoL) over the past 2 weeks. The LCQ is a 19-item, cough-specific HRQoL questionnaire. Each item on the LCQ assesses symptoms using a 7-point scale ranging from 1 to 7. The LCQ contains three domains on physical, psychological, and social functioning, and each domain score is calculated as the mean score of the items (range: 1 to 7) within the domain. The LCQ total score is the sum of the 3 domains, with a range from 3 (lowest total score) to 21 (highest total score). Higher scores indicate better HRQoL. The change from baseline in LCQ total score is calculated. The population analyzed included all randomized participants who had taken at least one dose of study intervention, and had LCQ total score values at both baseline and week 12.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	199	199		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	4.34 (3.84 to 4.83)	3.59 (3.09 to 4.09)		

Statistical analyses

Statistical analysis title	Treatment difference in Gefapixant vs. Placebo
Statistical analysis description:	
The estimated difference is the treatment difference in model based mean change from baseline at Week 12	
Comparison groups	Gefapixant v Placebo

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034 [1]
Method	Longitudinal ANCOVA
Parameter estimate	Estimated difference
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.44

Notes:

[1] - The model included terms for treatment group, visit, interaction of treatment by visit, gender, and baseline LCQ total score.

Secondary: Change from baseline in the Cough Severity Visual Analog Scale (VAS) score at Week 12

End point title	Change from baseline in the Cough Severity Visual Analog Scale (VAS) score at Week 12

End point description:

Participants will be asked to complete the VAS questionnaire to assess the severity of their cough over the past 24-hours. The Cough Severity VAS is a single-item questionnaire asking the participant to rate the severity of their cough on a 100-point scale ranging from 0 ("No Cough") to 100 ("Extremely Severe Cough"). Higher scores indicate greater severity of cough. The change from baseline in VAS score is calculated. The population analyzed included all randomized participants who had taken at least one dose of study intervention, and had VAS total score values at both baseline and week 12. Participants were analyzed in the group as randomized.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201	205		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	-31.79 (-35.37 to -28.20)	-24.87 (-28.41 to -21.32)		

Statistical analyses

Statistical analysis title	Treatment difference in gefapixant vs. placebo

Statistical analysis description:

The estimated difference is the treatment difference in model based mean change from baseline at Week 12.

Comparison groups	Gefapixant v Placebo

Number of subjects included in analysis	406
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.006 [3]
Method	Longitudinal ANCOVA
Parameter estimate	Estimated Difference
Point estimate	-6.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.88
upper limit	-1.97

Notes:

[2] - The model included terms for treatment group, visit, interaction of treatment by visit, gender, and baseline mean weekly cough severity VAS score.
[3] - Nominal p value, not controlled for multiplicity

Secondary: Percentage of participants with one or more adverse events (AEs)

End point title	Percentage of participants with one or more adverse events (AEs)

End point description:

An AE is defined as 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. The percentage of participants with one or more AEs is presented. The population included all randomized participants who received at least 1 dose of study intervention. Participants were analyzed in the group as treated.

End point type	Secondary

End point timeframe:

Up to approximately 14 weeks

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	209		
Units: Percentage of Participants				
number (not applicable)	65.5	43.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who discontinue study drug due to an AE

End point title	Percentage of participants who discontinue study drug due to an AE

End point description:

An AE is defined as 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. The percentage of participants who discontinue study drug due to an AE is presented. The population included all randomized participants who received at least 1 dose of study intervention. Participants were analyzed in the group as treated.

End point type	Secondary

End point timeframe:

Up to approximately 12 weeks

End point values	Gefapixant	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	209		
Units: Percentage of Participants				
number (not applicable)	11.2	1.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 114 days

Adverse event reporting additional description:

The deaths (all causes) population includes all randomized participants. The total number of participants exposed was 208 in the Gefapixant group and 211 in the Placebo group. Serious and other adverse events population includes all participants who received at least 1 dose of study intervention. Participants were analyzed in the group as treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Gefapixant

Reporting group description: -

Serious adverse events	Placebo	Gefapixant	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 209 (1.91%)	3 / 206 (1.46%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 209 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Tonsillar cyst			

subjects affected / exposed	1 / 209 (0.48%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 209 (0.48%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 209 (0.48%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 209 (0.96%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 209 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Gefapixant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 209 (10.53%)	105 / 206 (50.97%)	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 209 (0.00%)	24 / 206 (11.65%)	
occurrences (all)	0	24	
Headache			
subjects affected / exposed	14 / 209 (6.70%)	11 / 206 (5.34%)	
occurrences (all)	15	12	
Hypogeusia			

subjects affected / exposed	1 / 209 (0.48%)	22 / 206 (10.68%)	
occurrences (all)	1	22	
Dysgeusia			
subjects affected / exposed	7 / 209 (3.35%)	66 / 206 (32.04%)	
occurrences (all)	7	70	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2019	Amendment #1: Correction to entry criteria and other clarifications
20 March 2020	Amendment #2: Addition of procedures/assessments required for specialized urine crystal analysis.
05 January 2021	Amendment #3: Removal of procedures/assessments for specialized urine crystal analysis added in Protocol Amendment 02 and other clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported