Clinical trial results:
A Phase 3b Randomized, Double-blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Gefapixant in Women with Chronic Cough and Stress Urinary Incontinence

Summary

EudraCT number	2019-002321-29
Trial protocol	DE GB ES
Global end of trial date	02 September 2022

Results information

Result version number	v1
This version publication date	31 August 2023
First version publication date	31 August 2023

Trial information

Trial identification

Sponsor protocol code	7264-042

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04193176
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, 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	22 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 August 2022
Global end of trial reached?	Yes
Global end of trial date	02 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of gefapixant, in improving symptoms of cough-induced stress urinary incontinence (SUI) in adult female participants with refractory or unexplained chronic cough. The primary hypothesis was that gefapixant is superior to placebo in reducing the frequency of cough-induced SUI episodes over 12 weeks.

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	10 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	Argentina: 21
Country: Number of subjects enrolled	Colombia: 46
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Guatemala: 46
Country: Number of subjects enrolled	Israel: 20
Country: Number of subjects enrolled	Peru: 33
Country: Number of subjects enrolled	Russian Federation: 89
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Ukraine: 57
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	United States: 20
Worldwide total number of subjects	376
EEA total number of subjects	15

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)	276
From 65 to 84 years	100
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the 376 randomized participants, 375 participants received treatment.

Pre-assignment

Screening details:

Participant flow as per the database cutoff date of 02Sep2022.

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	Placebo

Arm description:

Participants received placebo 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:

Administered twice daily as a placebo oral tablet matching gefapixant

Arm title	Gefapixant

Arm description:

Participants received 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	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered twice daily as an oral tablet of 45 mg

Number of subjects in period 1	Placebo	Gefapixant
Started	190	186
Treated	190	185
Completed	184	176
Not completed	6	10
Consent withdrawn by subject	6	10

Baseline characteristics

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

Reporting group values	Placebo	Gefapixant	Total
Number of subjects	190	186	376
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)	133	143	276
From 65-84 years	57	43	100
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	56.6	56.2	
standard deviation	± 11.3	± 11.5	-
Sex: Female, Male			
Units: Participants			
Female	190	186	376
Male	0	0	0
Region			
Region of participants			
Units: Subjects			
North America	11	9	20
Europe	102	102	204
Asia Pacific	3	3	6
Other	74	72	146
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	18	16	34
Asian	3	6	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	3	3
White	143	137	280
More than one race	26	24	50

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	79	73	152
Not Hispanic or Latino	111	113	224
Unknown or Not Reported	0	0	0
Primary cough diagnosis			
Primary type of cough diagnosis was categorized as either refractory chronic cough or unexplained chronic cough.			
Units: Subjects			
Refractory Chronic Cough	149	141	290
Unexplained Chronic Cough	41	45	86
Weight			
Mean weight of participants			
Units: kilograms arithmetic mean standard deviation	 75.6 ± 13.1	 75.9 ± 13.3	 -
Height			
Mean height of participants			
Units: centimeters arithmetic mean standard deviation	 159.6 ± 6.9	 159.8 ± 7.0	 -
Duration of Chronic Cough			
Duration of chronic cough in years for participants with data			
Units: Years arithmetic mean standard deviation	 5.1 ± 6.6	 5.3 ± 6.5	 -
Duration of Stress Urinary Incontinence (SUI)			
Duration of stress urinary incontinence in participants			
Units: Months arithmetic mean standard deviation	 53.8 ± 80.8	 43.4 ± 58.3	 -
Body mass index			
Mean body mass index of participants			
Units: kg/m^2 arithmetic mean standard deviation	 29.7 ± 4.4	 29.7 ± 4.8	 -
Baseline Mean Weekly Cough Severity in Visual Analog Scale (VAS) in mm			
Baseline mean weekly cough severity in participants measured in Visual Analog Scale in mm.			
Units: VAS (mm) arithmetic mean standard deviation	 69.5 ± 15.6	 69.3 ± 15.8	 -
Baseline Mean Daily Cough-Induced Stress Urinary Incontinence Episodes, 7-day Average			
Baseline Mean Daily Cough-Induced Stress Urinary Incontinence Episodes, 7-day Average for participants			
Units: Number of episodes arithmetic mean standard deviation	 4.7 ± 4.1	 4.7 ± 3.0	 -

End points

End points reporting groups

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

Primary: Percent change from baseline in average daily cough-induced stress urinary incontinence (SUI) episodes at Week 12

End point title	Percent change from baseline in average daily cough-induced stress urinary incontinence (SUI) episodes at Week 12
End point description:	
Cough-induced SUI episodes were assessed using an event-driven electronic Incontinence Diary where the participant recorded the main cause of each urinary incontinence episode as coughing, another stress reason, or other cause. Episodes of incontinence were recorded for the week before baseline and treatment visit. Average daily cough induced SUI episodes were calculated as (sum of daily cough-induced SUI episodes in a week)/number of days recorded. The analysis population consisted of all randomized participants who received at least 1 dose of study intervention and had incontinence frequency of at least 4 days in the 7-day period prior to the visit at Week 12. The percent change from baseline in the average daily cough-induced SUI episodes to Week 12 are presented.	
End point type	Primary
End point timeframe:	
Baseline and week 12	

End point values	Placebo	Gefapixant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185	183		
Units: Percent Change				
least squares mean (confidence interval 95%)	-41.09 (-46.74 to -35.45)	-52.78 (-58.44 to -47.09)		

Statistical analyses

Statistical analysis title	Superiority of Gefapixant versus Placebo
Comparison groups	Placebo v Gefapixant
Number of subjects included in analysis	368
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.67
upper limit	-3.67

Secondary: Percentage of participants who discontinued study intervention due to AEs

End point title	Percentage of participants who discontinued study intervention due to AEs

End point description:

An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The analysis population consisted of all randomized participants who received at least one dose of study intervention. The number of participants who discontinued study intervention due to an adverse event are presented.

End point type	Secondary

End point timeframe:

Up to Week 12

End point values	Placebo	Gefapixant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	185		
Units: Percentage				
number (not applicable)	1.1	7.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with adverse events

End point title	Percentage of participants with adverse events

End point description:

An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The analysis population consisted of all randomized participants who received at least one dose of study intervention. The number of participants who experienced an adverse event are presented.

End point type	Secondary

End point timeframe:

Up to 27 months

End point values	Placebo	Gefapixant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	185		
Units: Percentage				
number (not applicable)	37.4	69.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All deaths and adverse events: up to 27 months

Adverse event reporting additional description:

Every participant is counted a single time for each applicable serious adverse event. A system organ class appears on this report only if one or more specific serious adverse events in that system organ class occurred.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Gefapixant

Reporting group description:

Participants received 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 received placebo administered as an oral tablet twice daily for 12 weeks.

Serious adverse events	Gefapixant	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 185 (1.62%)	2 / 190 (1.05%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	0 / 185 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal fissure			

subjects affected / exposed	1 / 185 (0.54%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 185 (0.54%)	0 / 190 (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	0 / 185 (0.00%)	1 / 190 (0.53%)	
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	Gefapixant	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 185 (56.22%)	12 / 190 (6.32%)	
Nervous system disorders			
Ageusia			
subjects affected / exposed	35 / 185 (18.92%)	1 / 190 (0.53%)	
occurrences (all)	36	1	
Hypogeusia			
subjects affected / exposed	14 / 185 (7.57%)	0 / 190 (0.00%)	
occurrences (all)	14	0	
Headache			
subjects affected / exposed	13 / 185 (7.03%)	5 / 190 (2.63%)	
occurrences (all)	14	5	
Dysgeusia			
subjects affected / exposed	57 / 185 (30.81%)	4 / 190 (2.11%)	
occurrences (all)	59	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 185 (5.41%)	2 / 190 (1.05%)	
occurrences (all)	10	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2020	Amendment 2 included the addition of procedures/assessments required for specialized urine crystal analysis.
17 December 2020	Amendment 3 included 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