Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study Of The Efficacy, Safety, And Tolerability Of Serlopitant For The Treatment Of Refractory Chronic Cough

Summary

EudraCT number	2017-003250-16
Trial protocol	GB
Global end of trial date	06 September 2018

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020

Trial information

Trial identification

Sponsor protocol code	MTI-110

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03282591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menlo Therapeutics Inc.
Sponsor organisation address	200 Cardinal Way, 2nd Floor, Redwood City, United States, CA 94063
Public contact	Chief Medical Officer, Menlo Therapeutics Inc., +1 6504861416, pkwon@menlotx.com
Scientific contact	Chief Medical Officer, Menlo Therapeutics Inc., +1 6504861416, pkwon@menlotx.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	06 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2018
Global end of trial reached?	Yes
Global end of trial date	06 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness of serlopitant for the treatment of refractory chronic cough after 12 weeks of treatment in reducing 24-hour objective cough frequency.

Secondary objectives were:
To evaluate the effectiveness of serlopitant as compared to placebo after 4 and 8 weeks of treatment in reducing 24-hour objective cough frequency.
To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8, and 12 weeks of treatment in reducing awake objective cough frequency.
To evaluate the effectiveness of serlopitant as compared to placebo after 4, 8, and 12 weeks of treatment in reducing sleep objective cough frequency.
To evaluate the effectiveness of serlopitant in:
Reducing the cough severity measured by a Visual Analog Scale (VAS)
Improving cough-specific quality of life (Leicester Cough Questionnaire)
To assess the safety and tolerability of repeated oral doses of serlopitant in subjects with treatment-refractory chronic cough.

Protection of trial subjects:

Safety was analyzed for all randomized subjects who received at least one dose of study medication. Treatment-emergent adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 and summarized. Summary statistics were provided for actual values and change from Baseline for clinical laboratory evaluations and vital signs. Shifts from Baseline clinical laboratory values based upon the normal range were tabulated. The observed vital signs and electrocardiogram data and change from Baseline were summarized by visit and treatment group descriptively. Criteria were defined for potentially clinically important findings of vital signs and results were summarized. The count and percentage of subjects with QTc interval corrected by Fredericia's formula (QTcF) > 450, 480, and 500 msec and a change from Baseline of > 30 and 60 msec were summarized by visit and treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2017
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	United States: 144
Country: Number of subjects enrolled	United Kingdom: 41
Worldwide total number of subjects	185
EEA total number of subjects	41

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)	89
From 65 to 84 years	96
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was started on the 3rd October 2017 and took place in the UK and USA.

Pre-assignment

Screening details:

During the screening period, subjects underwent eligibility evaluation and had their baseline cough monitoring conducted. Subjects must have been willing to comply with restrictions on allowable concomitant therapies for the duration of the study.

Period 1

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

Blinding implementation details:

The placebo was formulated to be indistinguishable from the active study product(s). Study materials were packaged and issued in a manner designed to maintain the blind for subjects and all study personnel involved in the direction and execution of study procedures, study assessments, and collection of data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Serlopitant 5 mg

Arm description:

Subjects received Serlopitant 5 mg.

Arm type	Active comparator
Investigational medicinal product name	Serlopitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily oral doses of Serlopitant 5 mg for 84 days.

Arm title	Placebo

Arm description:

Subjects received placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo for Serlopitant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received daily oral doses of Placebo for Serlopitant for 84 days.

Number of subjects in period 1	Serlopitant 5 mg	Placebo
Started	92	93
Completed	81	84
Not completed	11	9
Consent withdrawn by subject	2	3
Adverse event, non-fatal	2	3
Death	1	-
Excluded therapy	-	1
Lack of efficacy	6	2

Baseline characteristics

Reporting groups	
Reporting group title	Serlopitant 5 mg
Reporting group description:	
Subjects received Serlopitant 5 mg.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo.	

Reporting group values	Serlopitant 5 mg	Placebo	Total
Number of subjects	92	93	185
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	62.7	62.8	
full range (min-max)	28 to 79	26 to 80	-
Gender categorical			
Units: Subjects			
Female	71	71	142
Male	21	22	43
Race			
Units: Subjects			
Asian	1	1	2
Black of African American	4	4	8
White	86	88	174
Other	1	0	1
Ethnicity			
Units: Subjects			
Hispanic	5	1	6
Non-hispanic	87	92	179
Country			
Units: Subjects			
USA	71	72	143
UK	21	21	42

Duration of Chronic Cough Units: Years			
arithmetic mean	14.5	15.7	
standard deviation	± 10.88	± 11.63	-
BMI Units: kg/m2			
arithmetic mean	29.0	28.7	
standard deviation	± 5.10	± 5.32	-

End points

End points reporting groups

Reporting group title	Serlopitant 5 mg
Reporting group description: Subjects received Serlopitant 5 mg.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo.	

Primary: Change from Baseline in 24-Hour Cough Frequency

End point title	Change from Baseline in 24-Hour Cough Frequency
End point description:	
End point type	Primary
End point timeframe: For the primary endpoint analysis of change from Baseline in 24-hour cough frequency after 12 weeks (Day 84) of treatment.	

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: LS Mean Change				
arithmetic mean (standard error)	-0.18 (± 0.09)	-0.45 (± 0.08)		

Statistical analyses

Statistical analysis title	Change from Baseline in 24-hr Cough Frequency
Statistical analysis description: Mixed Model Repeated Measures Analysis of Change from Baseline in 24-hr Cough Frequency (coughs/hr) Based on Log Transformed Data (Full Analysis Set)	
Comparison groups	Serlopitant 5 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9942 [1]
Method	Mixed models analysis

Notes:

[1] - 1-sided p-value (Serlopitant vs. Placebo) 0.9942
Baseline 0.0018
Treatment 0.0302
Visit 0.2830
Country 0.0764
Sex 0.7259
Treatment-by-visit-interaction 0.2760

Secondary: Change from Baseline in awake objective cough frequency

End point title	Change from Baseline in awake objective cough frequency

End point description:

End point type	Secondary

End point timeframe:

Change from Baseline in awake objective cough frequency after 12 weeks (Day 84) of treatment

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: LS Mean Change				
arithmetic mean (standard error)				
LS Mean Change	-0.19 (± 0.09)	-0.46 (± 0.09)		

Statistical analyses

Statistical analysis title	Change from Baseline in Awake Cough Frequency

Statistical analysis description:

Mixed Model Repeated Measures Analysis of Change from Baseline in Awake Cough Frequency (coughs/hr) Based on Log Transformed Data (Full Analysis Set)

Comparison groups	Serlopitant 5 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.991 [2]
Method	Mixed models analysis

Notes:

[2] - 1-sided p-value (Serlopitant vs. Placebo) 0.9910
Baseline 0.0015
Treatment 0.0487
Visit 0.1434
Country 0.0779
Sex 0.5517
Treatment-by-Visit Interaction 0.1884

Secondary: Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour

End point title	Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour

End point description:

End point type	Secondary

End point timeframe:

Proportion of subjects with ≥ 30% reduction in 24-hour objective cough frequency per hour

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: LS Mean Response Rate				
arithmetic mean (standard error)	0.38 (± 0.06)	0.48 (± 0.06)		

Statistical analyses

Statistical analysis title	Responder Analysis of 24hr Cough Frequency

Statistical analysis description:

Responder Analysis (>=30% Reduction) of 24-hr Cough Frequency - Generalized Mixed Model (Full Analysis Set)

Comparison groups	Placebo v Serlopitant 5 mg
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8886 [3]
Method	Mixed models analysis

Notes:

[3] - 1-sided p-value for Odds Ratio 0.8886
Treatment 0.0527
Visit 0.3957
Country 0.0029
Sex 0.3719
Treatment-by-Visit Interaction 0.6067

Secondary: Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour

End point title	Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour

End point description:

End point type	Secondary

End point timeframe:

Proportion of subjects with ≥ 30% reduction in awake objective cough frequency per hour at Week 12 (Day 84)

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: LS Mean Response Rate				
arithmetic mean (standard error)	0.37 (± 0.06)	0.42 (± 0.06)		

Statistical analyses

Statistical analysis title	Responder Analysis of Awake Cough Frequency

Statistical analysis description:

Responder Analysis (>=30% Reduction) of Awake Cough Frequency - Generalized Mixed Model (Full Analysis Set)

Comparison groups	Serlopitant 5 mg v Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7348 [4]
Method	Mixed models analysis

Notes:

[4] - 1-sided p-value for Odds Ratio 0.7348
Treatment 0.1518
Visit 0.4407
Country 0.0021
Sex 0.1075
Treatment-by-Visit Interaction 0.4671

Secondary: Change from Baseline in Cough Severity Visual Analogue Scale (VAS)

End point title	Change from Baseline in Cough Severity Visual Analogue Scale (VAS)

End point description:

End point type	Secondary

End point timeframe:

Change from Baseline in Cough Severity Visual Analogue Scale (VAS) at Week 12 (Day 84)

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	88		
Units: LS Mean				
arithmetic mean (standard error)	-14.2 (± 2.99)	-9.9 (± 3.04)		

Statistical analyses

Statistical analysis title	Change from Baseline in Cough Severity VAS

Statistical analysis description:

Mixed Model Repeated Measures Analysis of Change from Baseline in Cough Severity Visual Analogue Scale (VAS) (Full Analysis Set)

Comparison groups	Serlopitant 5 mg v Placebo

Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9081 [5]
Method	Mixed models analysis

Notes:

[5] - 1-sided p-value (Serlopitant vs. Placebo) 0.9081
Baseline 0.0003
Treatment 0.1561
Visit 0.5537
Country 0.0017
Sex 0.5114
Treatment-by-Visit Interaction 0.0912

Secondary: Safety and tolerability of repeated oral doses of serlopitant

End point title	Safety and tolerability of repeated oral doses of serlopitant

End point description:

End point type	Secondary

End point timeframe:

During the study treatment period.

End point values	Serlopitant 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	92		
Units: Adverse events	65	52		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event occurrence during the study was recorded on source documentation and electronic case report form at the site, in accordance with protocol instructions.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Serlopitant 5mg
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Serlopitant 5mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 92 (3.26%)	3 / 92 (3.26%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (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			

Pulmonary embolism			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 92 (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: 2 %

Non-serious adverse events	Serlopitant 5mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 92 (70.65%)	52 / 92 (56.52%)	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 92 (3.26%)	0 / 92 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 92 (6.52%)	8 / 92 (8.70%)	
occurrences (all)	6	8	
Dizziness			
subjects affected / exposed	4 / 92 (4.35%)	1 / 92 (1.09%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 92 (5.43%)	6 / 92 (6.52%)	
occurrences (all)	5	6	
Oedema peripheral			
subjects affected / exposed	2 / 92 (2.17%)	1 / 92 (1.09%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 92 (5.43%)	3 / 92 (3.26%)	
occurrences (all)	5	3	
Dry mouth			
subjects affected / exposed	3 / 92 (3.26%)	2 / 92 (2.17%)	
occurrences (all)	3	2	
Abdominal distension			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	2 / 92 (2.17%)	2 / 92 (2.17%)	
occurrences (all)	2	2	
Gastrooesophageal reflux disease			

subjects affected / exposed	2 / 92 (2.17%)	2 / 92 (2.17%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 92 (4.35%)	0 / 92 (0.00%)	
occurrences (all)	4	0	
Cough			
subjects affected / exposed	3 / 92 (3.26%)	6 / 92 (6.52%)	
occurrences (all)	3	6	
Asthma			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Paranasal sinus discomfort			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Productive cough			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 92 (2.17%)	1 / 92 (1.09%)	
occurrences (all)	2	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 92 (2.17%)	0 / 92 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 92 (3.26%)	3 / 92 (3.26%)	
occurrences (all)	3	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 92 (7.61%)	6 / 92 (6.52%)	
occurrences (all)	7	6	
Urinary tract infection			

subjects affected / exposed	6 / 92 (6.52%)	3 / 92 (3.26%)	
occurrences (all)	6	3	
Bronchitis			
subjects affected / exposed	5 / 92 (5.43%)	1 / 92 (1.09%)	
occurrences (all)	5	1	
Sinusitis			
subjects affected / exposed	4 / 92 (4.35%)	4 / 92 (4.35%)	
occurrences (all)	4	4	
Acute sinusitis			
subjects affected / exposed	3 / 92 (3.26%)	0 / 92 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	2 / 92 (2.17%)	2 / 92 (2.17%)	
occurrences (all)	2	2	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 92 (2.17%)	3 / 92 (3.26%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2017	Version 2.0: Section 5.6 Study drug discontinuation was updated to comply with 21 August 2017 FDA Clinical Information Request. One of the discontinuation criterion were revised so that a subject will be discontinued from study drug if experiencing a National Cancer Institute Common Terminology Criteria for Adverse Events Grade 2 or higher treatment emergent adverse event that is assessed as likely related to study drug. Changed the language from Grade 3 to Grade 2: "The subject experiences a National Cancer Institute Common Terminology Criteria for Adverse Events Grade 2 or higher treatment emergent adverse event that is assessed as likely related to study drug".
08 March 2018	Version 3.0: A secondary endpoint was amended from 'Change from Baseline in 24-hour objective cough frequency at the Follow-Up visit (Day 112)' to 'Change from Baseline and change from Day 84 in 24-hour objective cough frequency at the Follow-Up visit (Day 112)'. This Secondary Efficacy Endpoint was inadvertently omitted in version 2.0 of the protocol. It is important to compare the change in 24-hour objective cough frequency at the end of treatment (Day 84) to the Follow-Up visit (Day 112). The study design was also amended to remove restrictions on food intake when taking the study drug following a recent food effect study with serlopitant (MTI-111) which demonstrated that the increase in Cmax and AUC0-inf of 28% and 37%, respectively, under fed condition, is not clinically significant. Therefore, serlopitant may be taken with or without food.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported