Clinical trial results:
BETTER-B (Feasibility)
BETter TreatmEnts for Refractory Breathlessness: A feasibility study of the use of mirtazapine for refractory breathlessness

Summary

EudraCT number	2015-004064-11
Trial protocol	GB
Global end of trial date	13 December 2017

Results information

Result version number	v2 (current)
This version publication date	17 March 2019
First version publication date	11 January 2019
Version creation reason	• Correction of full data set Amendment required to number of patients completing the trial and corresponding minor updates to endpoint tables.

Trial information

Trial identification

Sponsor protocol code	BETTER-B (Feasibility)

Additional study identifiers

ISRCTN number	ISRCTN32236160
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Professor Irene Higginson, Professor of Palliative Care, King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilit, +44 207 848 5516, irene.higginson@kcl.ac.uk
Scientific contact	Professor Irene Higginson, Professor of Palliative Care, King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilit, +44 207 848 5516, irene.higginson@kcl.ac.uk
Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Professor Irene Higginson, Professor of Palliative Care, King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilit, +44 207 848 5516, irene.higginson@kcl.ac.uk
Scientific contact	Professor Irene Higginson, Professor of Palliative Care, King's College London, Cicely Saunders Institute, Department of Palliative Care, Policy & Rehabilit, +44 207 848 5516, irene.higginson@kcl.ac.uk

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	13 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2017
Global end of trial reached?	Yes
Global end of trial date	13 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether a randomised, double-blind, placebo-controlled large-scale trial of mirtazapine for refractory breathlessness is feasible in terms of recruitment, as assessed by the number of patients recruited across 3 hospitals over a 12-month period.

Protection of trial subjects:

Patients are free to withdraw consent for study treatment and/or consent to participate in the study at any time and without the prejudice to further treatment. Patients who withdraw from study treatment, but are willing to continue to participate in the follow-up visits should be followed according to the procedures outlined in the protocol.
The role of the trial steering committee for this trial was to provide independent oversight of ethical and safety aspects of the trial.

Background therapy: -

Evidence for comparator:

Breathlessness is a complex, multifactorial experience and is reported as a subjective measure, and refractory breathlessness is a feature of advanced disease where participants may suffer from adverse events due to their underlying condition(s). Therefore, in order to gain a measure of the benefits and harms of an intervention in a trial, a placebo control is needed.

Actual start date of recruitment	01 September 2016
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 Kingdom: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	10
From 65 to 84 years	48
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Recruitment took place in three UK centres with each site open for a total of 12 months. King's College Hospital opened on 17/08/2016, Nottingham opened on 13/10/2016 and Castle Hill Hospital opened on the 24/11/2016. King's College Hospital had a pause in recruitment between the 12/04/2017 and 03/07/2017 due to short term resource issues.

Pre-assignment

Screening details:

Male or female aged ≥ 18 years old. Diagnosed with: Cancer, or Chronic obstructive pulmonary disease (COPD), or Interstitial lung disease (ILD), or Chronic heart failure (New York Heart Association (NYHA) class III or IV) Breathlessness severity: Modified MRC dyspnoea scale grade 3 or 4.

Pre-assignment period milestones

Number of subjects started	64
Number of subjects completed	64

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Mirtazapine

Arm description:

For participants randomised to receive mirtazapine, the daily dose will be 15mg (one capsule) for the first 14 days; participants will be assessed for possible dose escalation at the trial assessment visit for day 14 and if appropriate, their daily dose will be escalated to 30mg (two capsules) on days 15 through to 28. Where dose escalation is not appropriate, the participant will continue to take a daily dose of 15mg (one capsule) on days 15 through to 28.

Arm type	Experimental
Investigational medicinal product name	Mirtazapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

15 mg for the first 14 days and either 15 mg or 30 mg from day 15 to day 28 mg milligram(s)

Arm title	Placebo

Arm description:

For participants randomised to receive placebo the daily dose will be 1 capsule for the first 14 days; participants will be assessed for possible dose escalation on day 14 and if appropriate, their daily dose will be escalated to 2 capsules on days 15 through to 28. Where dose escalation is not appropriate, the participant will continue to take a daily dose of 1 capsule on days 15 through to 28.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1 capsule for the first 14 days; participants will be assessed for possible dose escalation on day 14 and if appropriate, their daily dose will be escalated to 2 capsules on days 15 through to 28. Where dose escalation is not appropriate, the participant will continue to take a daily dose of 1 capsule on days 15 through to 28.

Number of subjects in period 1	Mirtazapine	Placebo
Started	30	34
Completed	24	28
Not completed	6	6
Adverse event, serious fatal	1	-
Participant Choice	5	6

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial period
Reporting group description:	
Mirtazapine and placebo	

Reporting group values	Overall trial period	Total	
Number of subjects	64	64	
Age categorical			
Mirtazapine			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	48	48	
85 years and over	6	6	
Age continuous			
Units: years			
arithmetic mean	71.7		
standard deviation	± 8.45	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	47	47	

End points

End points reporting groups

Reporting group title	Mirtazapine

Reporting group description:

For participants randomised to receive mirtazapine, the daily dose will be 15mg (one capsule) for the first 14 days; participants will be assessed for possible dose escalation at the trial assessment visit for day 14 and if appropriate, their daily dose will be escalated to 30mg (two capsules) on days 15 through to 28. Where dose escalation is not appropriate, the participant will continue to take a daily dose of 15mg (one capsule) on days 15 through to 28.

Reporting group title	Placebo

Reporting group description:

For participants randomised to receive placebo the daily dose will be 1 capsule for the first 14 days; participants will be assessed for possible dose escalation on day 14 and if appropriate, their daily dose will be escalated to 2 capsules on days 15 through to 28. Where dose escalation is not appropriate, the participant will continue to take a daily dose of 1 capsule on days 15 through to 28.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

This includes all participants who have received at least one dose of the placebo. Only patients for whom written informed consent was not received and those who recieved Mirtazapine are excluded.

Primary: Recruitment

End point title	Recruitment[1]

End point description:

Average number of patients recruited per non-calendar month by site

End point type	Primary

End point timeframe:

Length of time sites open to recruitment

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: The primary endpoint is the number of patients recruited across 3 hospitals over a 12month period. This has been chosen to determine whether a larger scale trial of the same design is feasible, when expanded to additional centres.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Participants				
number (not applicable)				
KCL Average	1.7			
KCL No. of patients recruited	20			
KCL No. of months open to recruitment	12.0			
Nottingham City Average	1.3			
Nottingham City No. of patients recruited	13			
Nottingham City No. of months open to recruitment	10.3			
Castle Hill Average	2.8			
Castle Hill No. of patients recruited	31			
Castle Hill No. of months open to recruitment	11.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Screening outcomes

End point title	Screening outcomes

End point description:

Outcomes for patients who were screened

End point type	Secondary

End point timeframe:

Duration sites open to recruitment

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	409[2]			
Units: Participants				
Randomised	64			
Not approached due to ineligibility	142			
Approached, subsequently found to be ineligible	110			
Consented, subsequently found to be ineligible	7			
Approached, declined to participate	83			
Died	1			
Unable to be contacted	2			

Notes:

[2] - This is the number of patients screened for eligibility

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance- day 7

End point title	Treatment compliance- day 7

End point description:

Number of participants with at least 1 dose omission or reduction in the timeframe.

End point type	Secondary

End point timeframe:

Day 1- 7

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants	3	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance- day 14

End point title	Treatment compliance- day 14

End point description:

Number of participants with at least 1 dose omission or reduction in the timeframe.

End point type	Secondary

End point timeframe:

Day 8- 14

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	34		
Units: Participants	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance- day 21

End point title	Treatment compliance- day 21

End point description:

Number of participants with at least 1 dose omission or reduction in the timeframe.

End point type	Secondary

End point timeframe:

Day 15- 21

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	31		
Units: Participants	6	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance- day 28

End point title	Treatment compliance- day 28

End point description:

Number of participants with at least 1 dose omission or reduction in the timeframe.

End point type	Secondary

End point timeframe:

Day 22- 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: Participants	7	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Blinding

End point title	Blinding

End point description:

All participants and research assessors remained blinded during the trial

End point type	Secondary

End point timeframe:

Duration of trial

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants	30	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Participants remaining on study for 28 days

End point title	Participants remaining on study for 28 days

End point description:

Number of participants who were still on treatment at day 28.

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants	23	27		

Statistical analyses

No statistical analyses for this end point

Secondary: Dose escalation

End point title	Dose escalation

End point description:

Participants who had a dose escalation at day 28

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants				
Yes	10	11		
No	13	15		
N/A participant did not continue treatment	7	7		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Missing trial outcomes

End point title	Missing trial outcomes

End point description:

There were no participants with missing data for the primary trial outcome (recruitment).

End point type	Secondary

End point timeframe:

Duration sites open to recruitment

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Average breathlessness at day 28

End point title	Average breathlessness at day 28

End point description:

Severity of breathlessness at the assessment visit for day 28 as assessed by the NRS

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29[3]		
Units: Score				
arithmetic mean (standard deviation)	4.7 (± 1.96)	4.9 (± 1.77)		

Notes:

[3] - Data for 1 of these participants is missing

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of breathlessness at days 7, 14 and 21

End point title	Severity of breathlessness at days 7, 14 and 21

End point description:

Severity of breathlessness at the assessment visits/calls for days 7, 14 and 21, as assessed by NRS

End point type	Secondary

End point timeframe:

Days 7, 14 and 21

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[4]	34[5]		
Units: Score				
arithmetic mean (standard deviation)				
Day 7	5.0 (± 1.43)	5.3 (± 1.66)		
Day 14	4.9 (± 1.68)	5.2 (± 1.84)		
Day 21	5.1 (± 1.97)	5.0 (± 1.92)		

Notes:

[4] - Data is missing for 1 participant on day 7

[5] - Data is missing for 1 participant on days 7, 14 and 21

Statistical analyses

No statistical analyses for this end point

Secondary: Change in AKPS from baseline at days 14 and 28

End point title	Change in AKPS from baseline at days 14 and 28

End point description:

Change in AKPS from baseline to days 14 and 28. Decreasing numbers indicate a reduced performance status.

Note that at day 14 one participant's AKPS is missing in the placebo arm. At day 28 one participant's AKPS is missing in the mirtazapine arm and one participant's AKPS is missing in the placebo arm.

End point type	Secondary

End point timeframe:

Baseline to day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Score				
arithmetic mean (standard deviation)				
Day 14	-1.0 (± 4.70)	-0.6 (± 4.29)		
Day 28	-1.1 (± 3.93)	-0.7 (± 4.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: mMRC change from baseline at days 14 and 28

End point title	mMRC change from baseline at days 14 and 28

End point description:

Change in mMRC from baseline to days 14 and 28. An increased score indicates increased breathlessness.

Note that at day 14 two participant's mMRC is missing in the placebo arm. At day 28 one participant's mMRC is missing in the mirtazapine arm and one participant's mMRC is missing in the placebo arm.

End point type	Secondary

End point timeframe:

From baseline to day 28.

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Score				
arithmetic mean (standard deviation)				
Day 14	-0.6 (± 0.78)	-0.3 (± 0.97)		
Day 28	-0.6 (± 0.79)	-0.4 (± 1.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Opioid medication

End point title	Opioid medication

End point description:

Number of patients receiving one or more opioid medications at days 7, 14, 21 and 28.

Note that for days 14 and 28 there is one missing value for a participant in the placebo arm.

End point type	Secondary

End point timeframe:

Days 7, 14, 21 and 28.

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Participants				
Day 7	12	10		
Day 14	11	11		
Day 21	11	10		
Day 28	11	10		

Statistical analyses

No statistical analyses for this end point

Secondary: SPPB Change from baseline to day 28

End point title	SPPB Change from baseline to day 28

End point description:

Change in Short Physical Performance Battery (SPPB) from baseline at day 28. For change in score from baseline at day 28 positive scores indicate improvement and negative scores indicate a decline.

Note there are 2, 8, 2 and 8 participants' scores missing for chair stand, balance, gait and summary respectively for the mirtazapine arm. Similarly, there are 4, 8, 4 and 8 participants' scores missing for chair stand, balance, gait and summary respectively for the placebo arm.

End point type	Secondary

End point timeframe:

Baseline to day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Score				
arithmetic mean (standard deviation)				
Chair stand score	0.2 (± 1.10)	0.2 (± 1.27)		
Balance score	0.1 (± 1.00)	0.0 (± 1.17)		
Gait score	0.1 (± 0.89)	0.2 (± 1.08)		
Summary score	0.2 (± 1.83)	0.2 (± 1.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: GSES change from baseline at day 28

End point title	GSES change from baseline at day 28

End point description:

Change in GSES scores from baseline at day 28. A decrease in the change from baseline indicates a decrease in the strength of a participants self-efficacy belief.

Note that two participants are missing data for this from the placebo arm.

End point type	Secondary

End point timeframe:

Baseline to day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	34		
Units: Score				
arithmetic mean (standard deviation)	1.5 (± 4.95)	0.6 (± 3.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Mobility

End point title	EQ-5D-5L Mobility

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
I have no problems walking about	3	2		
I have slight problems walking about	6	7		
I have moderate problems walking about	13	10		
I have severe problems walking about	4	10		
I am unable to walk about	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Self-care

End point title	EQ-5D-5L Self-care

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
I have no problems washing or dressing myself	9	5		
I have slight problems washing or dressing myself	8	10		
I have moderate problems washing or dressing	7	13		
I have severe problems washing or dressing myself	3	1		
I am unable to wash or dress myself	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Usual activities

End point title	EQ-5D-5L Usual activities

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
I have no problems doing my usual activities	4	4		
I have slight problems doing my usual activities	6	5		
I have moderate problems doing my usual activities	10	10		
I have severe problems doing my usual activities	4	7		
I am unable to do my usual activities	4	2		
Missing	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Pain/Discomfort

End point title	EQ-5D-5L Pain/Discomfort

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
I have no pain or discomfort	21	19		
I have slight pain or discomfort	4	8		
I have moderate pain or discomfort	1	2		
I have severe pain or discomfort	2	0		
I have extreme pain or discomfort	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Anxiety/Depression

End point title	EQ-5D-5L Anxiety/Depression

End point description:

End point type	Secondary

End point timeframe:
Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
I am not anxious or depressed	19	17		
I am slightly anxious or depressed	4	9		
I am moderately anxious or depressed	5	3		
I am severely anxious or depressed	0	0		
I am extremely anxious or depressed	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: EQ-5D-5L Your health today (score)

End point title	EQ-5D-5L Your health today (score)

End point description:

End point type	Secondary

End point timeframe:
Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Score				
arithmetic mean (standard deviation)	63.4 (± 21.2)	60.8 (± 19.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: IPOS Overall total score

End point title	IPOS Overall total score

End point description:

The overall IPOS score is useful in understanding the overall symptoms, concerns, and status of the patient at a specific point in time. A higher score indicates a participant is experiencing a greater severity of symptoms/concerns than a participant with a lower score. The overall IPOS score is the sum of the scores from each of the 17 IPOS questions.

End point type	Secondary

End point timeframe:

Days 14 and 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[6]	32[7]		
Units: Score				
arithmetic mean (standard deviation)				
Day 14	19.2 (± 6.51)	20.5 (± 7.88)		
Day 28	17.2 (± 8.02)	17.8 (± 7.55)		

Notes:

[6] - At day 28 only 28 participants in the mirtazapine arm were still enrolled on the trial

[7] - At day 28, 29 participants were still enrolled in the placebo arm of the trial

Statistical analyses

No statistical analyses for this end point

Secondary: HADS anxiety score day 14

End point title	HADS anxiety score day 14

End point description:

End point type	Secondary

End point timeframe:

Day 14

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: Participants				
Normal	19	19		
Mild	7	9		
Moderate	3	3		
Severe	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS anxiety score day 28

End point title	HADS anxiety score day 28

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
Normal	26	20		
Mild	1	8		
Moderate	1	1		
Severe	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS depression score day 14

End point title	HADS depression score day 14

End point description:

End point type	Secondary

End point timeframe:

Day 14

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: Participants				
Normal	18	17		
Mild	10	7		
Moderate	1	8		
Severe	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: HADS depression score day 28

End point title	HADS depression score day 28

End point description:

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Participants				
Normal	17	17		
Mild	7	8		
Moderate	4	3		
Severe	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: CRQ Day 14

End point title	CRQ Day 14

End point description:

Higher scores represent better participant outcomes.

Note that for dyspnoea- patients with all 5 score completed there is data from 6 and 11 participants missing in the mirtazapine and placebo arms respectively. Similarly, for dyspnoea - patients with atleast 50% data there is data from 4 participants missing in each arm.

End point type	Secondary

End point timeframe:

Day 14

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	32		
Units: Score				
arithmetic mean (standard deviation)				
Dyspnoea - Patients with all 5 scores complete	2.7 (± 1.03)	2.6 (± 0.89)		

Dyspnoea - Patients with atleast 50% data	2.7 (± 1.06)	2.6 (± 0.92)		
Fatigue	3.7 (± 1.13)	3.5 (± 1.25)		
Emotional	5.0 (± 1.16)	4.5 (± 1.11)		
Mastery	4.8 (± 1.48)	4.3 (± 1.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: CRQ Day 28

End point title	CRQ Day 28

End point description:

Higher scores represent better participant outcomes.

Note that for dyspnoea- patients with all 5 score completed there is data from 6 and 9 participants missing in the mirtazapine and placebo arms respectively. Similarly, for dyspnoea - patients with atleast 50% data there is data from 4 and 6 participants missing in the mirtazapine and placebo arms respectively.

End point type	Secondary

End point timeframe:

Day 28

End point values	Mirtazapine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	29		
Units: Score				
arithmetic mean (standard deviation)				
Dyspnoea - Patients with all 5 scores completed	3.1 (± 1.11)	2.8 (± 0.96)		
Dyspnoea - Patients with atleast 50% data	3.1 (± 1.04)	2.9 (± 1.04)		
Fatigue	3.8 (± 1.26)	4.0 (± 1.22)		
Emotional	5.0 (± 1.17)	4.9 (± 1.25)		
Mastery	4.9 (± 1.22)	4.9 (± 1.34)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline to 7 days post treatment end	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo safety population
Reporting group description:	
This includes all participants who have received at least one dose of the placebo. Only patients who received Mirtazapine are excluded.	
Reporting group title	Mirtazapine safety population
Reporting group description:	
This includes all participants who have received at least one dose of Mirtazapine. Only patients who received the placebo are excluded.	

Serious adverse events	Placebo safety population	Mirtazapine safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 34 (14.71%)	4 / 30 (13.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain - cardiac			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal			

disorders			
Dyspnea			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal hemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (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			
Bronchial Infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: Participant withdrew from the study prior to death.		
subjects affected / exposed	1 / 34 (2.94%)	3 / 30 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
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: 0 %

Non-serious adverse events	Placebo safety population	Mirtazapine safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 34 (88.24%)	29 / 30 (96.67%)	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Edema limbs			

subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	18 / 34 (52.94%)	18 / 30 (60.00%)	
occurrences (all)	36	53	
Irritability			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	4 / 34 (11.76%)	3 / 30 (10.00%)	
occurrences (all)	8	5	
Dyspnea			
subjects affected / exposed	6 / 34 (17.65%)	6 / 30 (20.00%)	
occurrences (all)	9	9	
Hypoxia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	2 / 34 (5.88%)	3 / 30 (10.00%)	
occurrences (all)	4	11	
Sore throat			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	10 / 34 (29.41%)	8 / 30 (26.67%)	
occurrences (all)	16	16	
Confusion			
subjects affected / exposed	3 / 34 (8.82%)	5 / 30 (16.67%)	
occurrences (all)	5	7	
Insomnia			
subjects affected / exposed	10 / 34 (29.41%)	4 / 30 (13.33%)	
occurrences (all)	23	5	
Investigations			
Weight gain			
subjects affected / exposed	6 / 34 (17.65%)	5 / 30 (16.67%)	
occurrences (all)	11	9	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 34 (5.88%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	10 / 34 (29.41%)	9 / 30 (30.00%)	
occurrences (all)	12	19	
Dizziness			
subjects affected / exposed	11 / 34 (32.35%)	11 / 30 (36.67%)	
occurrences (all)	18	20	
Headache			
subjects affected / exposed	6 / 34 (17.65%)	4 / 30 (13.33%)	
occurrences (all)	8	4	
Lethargy			

subjects affected / exposed	11 / 34 (32.35%)	13 / 30 (43.33%)	
occurrences (all)	26	29	
Movements involuntary			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	16 / 34 (47.06%)	21 / 30 (70.00%)	
occurrences (all)	26	61	
Tremor			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 34 (2.94%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Diarrhea			
subjects affected / exposed	8 / 34 (23.53%)	7 / 30 (23.33%)	
occurrences (all)	10	12	
Dyspepsia			
subjects affected / exposed	1 / 34 (2.94%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Dry mouth			
subjects affected / exposed	2 / 34 (5.88%)	3 / 30 (10.00%)	
occurrences (all)	4	7	
Dysphagia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gingival pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	6 / 34 (17.65%)	9 / 30 (30.00%)	
occurrences (all)	7	14	

Oral pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 34 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Chest wall pain			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	3 / 34 (8.82%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Lung infection			
subjects affected / exposed	3 / 34 (8.82%)	3 / 30 (10.00%)	
occurrences (all)	6	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 34 (8.82%)	0 / 30 (0.00%)	
occurrences (all)	5	0	
Dehydration			

subjects affected / exposed	1 / 34 (2.94%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Other	Additional description: Increased appetite was a prespecified variable on the CRFs and is not strictly a CTCAE term		
subjects affected / exposed	11 / 34 (32.35%)	15 / 30 (50.00%)	
occurrences (all)	24	39	

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