Clinical trial results:
The Safety and Efficacy of COMP360 in Participants with Treatment-Resistant Depression (P-TRD)

Summary

EudraCT number	2017-003288-36
Trial protocol	GB CZ DE PT NL IE DK ES
Global end of trial date	27 September 2021

Results information

Result version number	v1 (current)
This version publication date	22 April 2023
First version publication date	22 April 2023

Trial information

Trial identification

Sponsor protocol code	COMP 001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03775200
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	COMPASS Pathfinder Limited
Sponsor organisation address	3rd Floor, 1 Ashley Road, Altrincham, Cheshire, United Kingdom, WA14 2DT
Public contact	Guy Goodwin, COMPASS Pathways, Ltd, +44 7443 136539, info@compasspathways.com
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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 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of COMP360 (25 mg and 10 mg) compared to 1 mg, administered under supportive conditions to adult participants with TRD, in improving depressive symptoms, as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline. Baseline was defined as the assessment score obtained on Day -1. The primary timepoint was Week 3. The MADRS was also analysed for the change from baseline to Day 2, and Weeks 1, 6, 9, and 12.

Protection of trial subjects:

During the screening period, participants who are on antidepressant medications will be expected to complete the taper at least 2 weeks prior to Baseline (V2). Participants will be given a choice of the tapering rate. During the tapering period all participants will be supported by the study clinician. The designated study team member will be in frequent contact with the participants to monitor for withdrawal and worsening of depression symptoms. All participants will be evaluated for safety at the clinic weekly for a minimum of 3 weeks prior to COMP360 administration to ensure safe discontinuation of current antidepressant therapy required by the protocol. Participants' companions (friend or family member) will be educated about the signs of worsening of depression and suicidality, and instructed on ways to contact the study team in case of significant worsening of depression. The COMP360 administration session will be supported by a trained therapist who will be present with the participant at all times until discharge. Rescue medications are allowed during the study as described in the protocol. Efficacy and safety assessments including Adverse Events are performed throughout the study up to the end of study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 January 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	United States: 96
Country: Number of subjects enrolled	Netherlands: 50
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Denmark: 8

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Ireland: 11
Worldwide total number of subjects	233
EEA total number of subjects	98

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)	226
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were outpatients recruited from general practitioners and specialised psychiatric services. All participants were then seen weekly for at least 3 weeks prior to the COMP360 Session (V3) to ensure the safe discontinuation of current antidepressant therapy. Rescreening of participants considered not eligible was allowed.

Pre-assignment period milestones

Number of subjects started	428[1]
Number of subjects completed	233

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Inclusion/exclusion criteria: 156
Reason: Number of subjects	Lost to follow-up: 1
Reason: Number of subjects	Not specified: 38

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients listed as started is the number of patients screened, whereas the number of patients enrolled is the number of patients who were randomized.

Period 1

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

Blinding implementation details:

Bottles (each containing 5 capsules for a single dose administration) for each participant will be assigned according to unique identifiers by IWRS programmed with blind-breaking instructions. Study assessments were performed by investigators who were blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	COMP360 25mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	COMP360
Investigational medicinal product code	
Other name	Psilocybin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

COMP360 25mg single dose treatment: 5 × 5 mg capsules

Arm title	COMP360 10mg

Arm description: -

Arm type	Experimental

Investigational medicinal product name	COMP360
Investigational medicinal product code	
Other name	Psilocybin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

COMP360 10mg single dose treatment: 2 × 5 mg capsules and 3 × placebo capsules

Arm title	COMP360 1mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	COMP360
Investigational medicinal product code	
Other name	Psilocybin
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

COMP360 1 mg single dose treatment: 1 × 1 mg capsule and 4 × placebo capsules

Number of subjects in period 1	COMP360 25mg	COMP360 10mg	COMP360 1mg
Started	79	75	79
Completed	74	66	69
Not completed	5	9	10
Consent withdrawn by subject	2	6	6
Physician decision	-	-	1
Adverse event, non-fatal	2	2	-
Lost to follow-up	1	-	2
Lack of efficacy	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	COMP360 25mg
Reporting group description: -	
Reporting group title	COMP360 10mg
Reporting group description: -	
Reporting group title	COMP360 1mg
Reporting group description: -	

Reporting group values	COMP360 25mg	COMP360 10mg	COMP360 1mg
Number of subjects	79	75	79
Age categorical Units: Subjects			
From 18-34 years	24	29	31
From 35-64 years	52	44	46
From 65-84 years	3	2	2
Age continuous Units: years			
arithmetic mean	40.2	40.6	38.7
standard deviation	± 12.19	± 12.76	± 11.71
Gender categorical Units: Subjects			
Female	35	34	43
Male	44	41	36
Prior Psilocybin Experience Units: Subjects			
Yes	5	5	4
No	74	70	75
Number of Failed Treatment for Current Episode Units: Subjects			
One	0	1	1
Two	66	62	63
Three	8	9	11
Four	4	2	3
Unknown	1	1	1
MADRS Baseline Severity Categories Units: Subjects			
Subthreshold (<= 10)	0	1	1
Mild (11 to 19)	0	1	1
Moderate (20 to 30)	33	19	18
Severe (>= 31)	46	54	59
HAM-D 17 Baseline Severity Categories Units: Subjects			
Moderate (18-23)	57	49	59
Severe (>= 24)	22	26	20
Length of Current Depressive Episode (Months)			

Units: Subjects			
<1 year	12	10	10
≥1 year to <2 years	33	28	33
≥2 years	34	37	36
BMI			
Units: kg/m2			
arithmetic mean	26.52	28.26	27.26
standard deviation	± 6.134	± 8.203	± 6.025
Baseline MADRS Total Score			
Units: Points			
arithmetic mean	31.9	33.0	32.7
standard deviation	± 5.41	± 6.31	± 6.24
Baseline HAM-D 17 Total Score			
Units: Points			
arithmetic mean	21.8	22.4	22.2
standard deviation	± 3.04	± 2.77	± 2.93
Number of Lifetime Depression Episodes			
Units: Episodes			
arithmetic mean	7.3	7.8	5.7
standard deviation	± 8.58	± 9.09	± 4.35

Reporting group values	Total		
Number of subjects	233		
Age categorical			
Units: Subjects			
From 18-34 years	84		
From 35-64 years	142		
From 65-84 years	7		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	112		
Male	121		
Prior Psilocybin Experience			
Units: Subjects			
Yes	14		
No	219		
Number of Failed Treatment for Current Episode			
Units: Subjects			
One	2		
Two	191		
Three	28		
Four	9		
Unknown	3		
MADRS Baseline Severity Categories			
Units: Subjects			
Subthreshold (<= 10)	2		
Mild (11 to 19)	2		

Moderate (20 to 30)	70		
Severe (>= 31)	159		
HAM-D 17 Baseline Severity Categories Units: Subjects			
Moderate (18-23)	165		
Severe (>= 24)	68		
Length of Current Depressive Episode (Months) Units: Subjects			
<1 year	32		
≥1 year to <2 years	94		
≥2 years	107		
BMI Units: kg/m2 arithmetic mean standard deviation	- -		
Baseline MADRS Total Score Units: Points arithmetic mean standard deviation	- -		
Baseline HAM-D 17 Total Score Units: Points arithmetic mean standard deviation	- -		
Number of Lifetime Depression Episodes Units: Episodes arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	Main Efficacy Analysis Set (Full Analysis Set-FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All participants randomised who receive study drug and have at least 1 post-dose efficacy assessment. Outputs based on this analysis set will use the treatment the study participant was randomised to.

Subject analysis set title	Secondary Efficacy Analysis Set (Per Protocol Analysis Set)
Subject analysis set type	Per protocol

Subject analysis set description:

All participants in the FAS who do not have a protocol deviation (PD) that is thought to significantly affect the integrity of the participant's efficacy data.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomised participants who receive study drug. Outputs based on this analysis set will use the actual treatment received by the study participant.

Subject analysis set title	Randomised Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomised participants, whether or not they receive study drug.

Reporting group values	Main Efficacy Analysis Set (Full Analysis Set-FAS)	Secondary Efficacy Analysis Set (Per Protocol Analysis Set)	Safety Analysis Set
Number of subjects	233	210	233
Age categorical Units: Subjects			
From 18-34 years	84		84
From 35-64 years	142		142
From 65-84 years	7		7
Age continuous Units: years			
arithmetic mean	39.8		39.8
standard deviation	± 12.19	±	± 12.19
Gender categorical Units: Subjects			
Female	112		112
Male	121		121
Prior Psilocybin Experience Units: Subjects			
Yes	14		14
No	219		219
Number of Failed Treatment for Current Episode Units: Subjects			
One	2		2
Two	191		191
Three	28		28
Four	9		9
Unknown	3		3
MADRS Baseline Severity Categories Units: Subjects			
Subthreshold (<= 10)	2		2
Mild (11 to 19)	2		2
Moderate (20 to 30)	70		70
Severe (>= 31)	159		159
HAM-D 17 Baseline Severity Categories Units: Subjects			
Moderate (18-23)	165		165
Severe (>= 24)	68		68
Length of Current Depressive Episode (Months) Units: Subjects			
<1 year	32		32
≥1 year to <2 years	94		94
≥2 years	107		107
BMI Units: kg/m2			
arithmetic mean	27.34		27.34
standard deviation	± 6.858	±	± 6.858
Baseline MADRS Total Score Units: Points			
arithmetic mean	32.5		32.5

standard deviation	± 5.99	±	± 5.99
Baseline HAM-D 17 Total Score Units: Points			
arithmetic mean	22.2		22.2
standard deviation	± 2.92	±	± 2.92
Number of Lifetime Depression Episodes Units: Episodes			
arithmetic mean	6.9		6.9
standard deviation	± 7.63	±	± 7.63

Reporting group values	Randomised Analysis Set		
Number of subjects	233		
Age categorical Units: Subjects			
From 18-34 years	84		
From 35-64 years	142		
From 65-84 years	7		
Age continuous Units: years			
arithmetic mean	39.8		
standard deviation	± 12.19		
Gender categorical Units: Subjects			
Female	112		
Male	121		
Prior Psilocybin Experience Units: Subjects			
Yes	14		
No	219		
Number of Failed Treatment for Current Episode Units: Subjects			
One	2		
Two	191		
Three	28		
Four	9		
Unknown	3		
MADRS Baseline Severity Categories Units: Subjects			
Subthreshold (<= 10)	2		
Mild (11 to 19)	2		
Moderate (20 to 30)	70		
Severe (>= 31)	159		
HAM-D 17 Baseline Severity Categories Units: Subjects			
Moderate (18-23)	165		
Severe (>= 24)	68		
Length of Current Depressive Episode (Months) Units: Subjects			
<1 year	32		
≥1 year to <2 years	94		

≥2 years	107		

BMI			
Units: kg/m2			
arithmetic mean	27.34		
standard deviation	± 6.858		
Baseline MADRS Total Score			
Units: Points			
arithmetic mean	32.5		
standard deviation	± 5.99		
Baseline HAM-D 17 Total Score			
Units: Points			
arithmetic mean	22.2		
standard deviation	± 2.92		
Number of Lifetime Depression Episodes			
Units: Episodes			
arithmetic mean	6.9		
standard deviation	± 7.63		

End points

End points reporting groups

Reporting group title	COMP360 25mg
Reporting group description: -	
Reporting group title	COMP360 10mg
Reporting group description: -	
Reporting group title	COMP360 1mg
Reporting group description: -	
Subject analysis set title	Main Efficacy Analysis Set (Full Analysis Set-FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants randomised who receive study drug and have at least 1 post-dose efficacy assessment. Outputs based on this analysis set will use the treatment the study participant was randomised to.	
Subject analysis set title	Secondary Efficacy Analysis Set (Per Protocol Analysis Set)
Subject analysis set type	Per protocol
Subject analysis set description:	
All participants in the FAS who do not have a protocol deviation (PD) that is thought to significantly affect the integrity of the participant's efficacy data.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised participants who receive study drug. Outputs based on this analysis set will use the actual treatment received by the study participant.	
Subject analysis set title	Randomised Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomised participants, whether or not they receive study drug.	

Primary: Change in MADRS total score from Baseline (Day -1) to 3 weeks post COMP360.

End point title	Change in MADRS total score from Baseline (Day -1) to 3 weeks post COMP360.
End point description:	
End point type	Primary
End point timeframe:	
Baseline (Day -1) to 3 weeks post COMP360.	

End point values	COMP360 25mg	COMP360 10mg	COMP360 1mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	75	79	
Units: Points				
least squares mean (confidence interval 95%)	-12.0 (-14.6 to -9.3)	-7.9 (-10.6 to -5.2)	-5.4 (-8.1 to -2.7)	

Statistical analyses

Statistical analysis title	Hypothetical Estimand (25mg vs 1mg)

Statistical analysis description:

Mixed Model for Repeated Measures model includes treatment, visit, pooled study site, treatment*visit, baseline (day -1) MADRS total score and an unstructured correlation. Data after the start of new treatment for depression or withdrawal (lack of efficacy or adverse event) was imputed 100 times under MNAR. Remaining missing data were imputed under MAR using MCMC methods with a non-informative prior. The imputed datasets were analysed using the MMRM model and estimates pooled using Rubin's rules

Comparison groups	COMP360 25mg v COMP360 1mg
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (final values)
Point estimate	-6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	-2.9
Variability estimate	Standard error of the mean
Dispersion value	1.86

Statistical analysis title	Hypothetical Estimand (10mg vs 1mg)

Statistical analysis description:

Mixed Model for Repeated Measures model includes treatment, visit, pooled study site, treatment*visit, baseline (day -1) MADRS total score and an unstructured correlation. Data after the start of new treatment for depression or withdrawal (lack of efficacy or adverse event) was imputed 100 times under MNAR. Remaining missing data were imputed under MAR using MCMC with a non-informative prior. The imputed datasets were analysed using the MMRM model and estimates pooled using Rubin's rules.

Comparison groups	COMP360 1mg v COMP360 10mg
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.184
Method	Mixed models analysis
Parameter estimate	LS Mean Difference (final values)
Point estimate	-2.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	1.2
Variability estimate	Standard error of the mean
Dispersion value	1.87

Secondary: The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from Baseline) at Week 3 post COMP360

End point title	The proportion of participants with a response (defined as a ≥ 50% improvement in MADRS total score from Baseline) at Week 3 post COMP360

End point description:

A MADRS responder is a participant with a ≥ 50% reduction in baseline MADRS total score at Week 3 post COMP 360.

End point type	Secondary

End point timeframe:

Week 3 post COMP360

End point values	COMP360 25mg	COMP360 10mg	COMP360 1mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	63	60	
Units: Subjects	29	14	14	

Statistical analyses

Statistical analysis title	Composite Estimand (25mg vs 1mg)

Statistical analysis description:

A GLMM using a binomial distribution and a logit link was fit. The model included treatment, pooled study site, visit, treatment*visit, baseline (day -1) MADRS total score as covariates and an unstructured correlation. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-responders. Missing MADRS values imputed using MAR methods for the primary endpoint were dichotomised. Results were pooled using Rubin's rules

Comparison groups	COMP360 25mg v COMP360 1mg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Generalised Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	6.6

Statistical analysis title	Composite Estimand (10mg vs 1mg)

Statistical analysis description:

A GLMM using a binomial distribution and a logit link was fit. The model included treatment, pooled study site, visit, treatment*visit, baseline (day -1) MADRS total score as covariates and an unstructured correlation. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-responders. Missing MADRS values imputed using MAR methods for the primary endpoint were dichotomised. Results were pooled using Rubin's rules.

Comparison groups	COMP360 1mg v COMP360 10mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.709
Method	Generalised Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3

Secondary: The proportion of participants with remission (defined as a MADRS total score ≤ 10) at Week 3 post COMP360

End point title	The proportion of participants with remission (defined as a MADRS total score ≤ 10) at Week 3 post COMP360

End point description:

Remitters are defined as having a MADRS total score ≤ 10 at Week 3 post COMP360.

End point type	Secondary

End point timeframe:

Week 3 post COMP360

End point values	COMP360 25mg	COMP360 10mg	COMP360 1mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	63	60	
Units: Subjects	23	7	6	

Statistical analyses

Statistical analysis title	Composite Estimand (25mg vs 1mg)

Statistical analysis description:

A GLMM using a binomial distribution and a logit link was fit. The model included treatment, pooled study site, visit, treatment*visit, baseline (day -1) MADRS total score as covariates and an unstructured correlation. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-remitters. Missing MADRS values imputed using MAR methods for the primary endpoint were dichotomised. Results were pooled using Rubin's rules.

Comparison groups	COMP360 25mg v COMP360 1mg
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Generalised Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	12.8

Statistical analysis title	Composite Estimand (10mg vs 1mg)

Statistical analysis description:

A GLMM using a binomial distribution and a logit link was fit. The model included treatment, pooled study site, visit, treatment*visit, baseline (day -1) MADRS total score as covariates and an unstructured correlation. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-remitters. Missing MADRS values imputed using MAR methods for the primary endpoint were dichotomised. Results were pooled using Rubin's rules.

Comparison groups	COMP360 1mg v COMP360 10mg
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723
Method	Generalised Linear Mixed Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.9

Secondary: The proportion of participants who have a sustained response at Week 12

End point title	The proportion of participants who have a sustained response at Week 12

End point description:

Sustained responders are participants meeting the MADRS response criteria (a ≥ 50% reduction from baseline in MADRS total score) at any visit up to and including week 3 and also at all visits after week 3 until week 12.

End point type	Secondary

End point timeframe:

At Week 12

End point values	COMP360 25mg	COMP360 10mg	COMP360 1mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46	44	44	
Units: Subjects	16	4	8	

Statistical analyses

Statistical analysis title	Composite Estimand (25mg vs 1mg)

Statistical analysis description:

A logistic regression with treatment and baseline (day -1) MADRS total score as covariates was fit. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-responders. Sustained responder status for all other participants was derived from the multiple imputed dataset as obtained for the main analysis of the Composite Strategy estimand of the MADRS responder endpoint. Results were pooled across imputations using Rubin's rules.

Comparison groups	COMP360 25mg v COMP360 1mg
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	5.4

Statistical analysis title	Composite Estimand (10mg vs 1mg)

Statistical analysis description:

A logistic regression with treatment and baseline (day -1) MADRS total score as covariates was fit. Participants starting new treatment for depression or withdrawing (lack of efficacy or adverse event) were imputed as non-responders. Sustained responder status for all other participants was derived from the multiple imputed dataset as obtained for the main analysis of the Composite Strategy estimand of the MADRS responder endpoint. Results were pooled across imputations using Rubin's rules.

Comparison groups	COMP360 1mg v COMP360 10mg

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	2

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From ICG sign-off to last study event

Adverse event reporting additional description:

Any AEs occurring before the start of treatment (ie, before the dose of the IP on Day 0 [V3]) was recorded in the medical history. Any AE ongoing at V10 (EOS/ET) was followed until resolution or no longer considered clinically significant by the investigator.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	COMP360 25mg
Reporting group description: -	
Reporting group title	COMP360 10mg
Reporting group description: -	
Reporting group title	COMP360 1mg

Reporting group description: -

Serious adverse events	COMP360 25mg	COMP360 10mg	COMP360 1mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 79 (6.33%)	6 / 75 (8.00%)	1 / 79 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	0 / 79 (0.00%)	1 / 75 (1.33%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 75 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Intentional self-injury			

subjects affected / exposed	2 / 79 (2.53%)	2 / 75 (2.67%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 79 (2.53%)	2 / 75 (2.67%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal behaviour			
subjects affected / exposed	3 / 79 (3.80%)	0 / 75 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjustment disorder with anxiety			
subjects affected / exposed	1 / 79 (1.27%)	0 / 75 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	1 / 79 (1.27%)	0 / 75 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 79 (0.00%)	1 / 75 (1.33%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	COMP360 25mg	COMP360 10mg	COMP360 1mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 79 (75.95%)	51 / 75 (68.00%)	50 / 79 (63.29%)
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 79 (34.18%)	16 / 75 (21.33%)	20 / 79 (25.32%)
occurrences (all)	34	22	30
Dizziness			

subjects affected / exposed	6 / 79 (7.59%)	1 / 75 (1.33%)	1 / 79 (1.27%)
occurrences (all)	6	1	1
Paraesthesia			
subjects affected / exposed	3 / 79 (3.80%)	4 / 75 (5.33%)	1 / 79 (1.27%)
occurrences (all)	3	4	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 79 (15.19%)	5 / 75 (6.67%)	7 / 79 (8.86%)
occurrences (all)	12	5	8
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	18 / 79 (22.78%)	7 / 75 (9.33%)	4 / 79 (5.06%)
occurrences (all)	19	7	4
Abdominal pain upper			
subjects affected / exposed	4 / 79 (5.06%)	2 / 75 (2.67%)	1 / 79 (1.27%)
occurrences (all)	4	2	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 79 (10.13%)	11 / 75 (14.67%)	14 / 79 (17.72%)
occurrences (all)	8	11	16
Anxiety			
subjects affected / exposed	7 / 79 (8.86%)	13 / 75 (17.33%)	3 / 79 (3.80%)
occurrences (all)	7	16	3
Depression			
subjects affected / exposed	4 / 79 (5.06%)	5 / 75 (6.67%)	5 / 79 (6.33%)
occurrences (all)	4	5	5
Euphoric mood			
subjects affected / exposed	4 / 79 (5.06%)	5 / 75 (6.67%)	4 / 79 (5.06%)
occurrences (all)	4	5	5
Depressed mood			
subjects affected / exposed	3 / 79 (3.80%)	5 / 75 (6.67%)	4 / 79 (5.06%)
occurrences (all)	3	5	5
Suicidal ideation			
subjects affected / exposed	5 / 79 (6.33%)	3 / 75 (4.00%)	4 / 79 (5.06%)
occurrences (all)	5	3	5
Mood altered			

subjects affected / exposed	7 / 79 (8.86%)	3 / 75 (4.00%)	1 / 79 (1.27%)
occurrences (all)	8	3	1
Irritability			
subjects affected / exposed	4 / 79 (5.06%)	2 / 75 (2.67%)	1 / 79 (1.27%)
occurrences (all)	4	2	1
Panic reaction			
subjects affected / exposed	4 / 79 (5.06%)	1 / 75 (1.33%)	1 / 79 (1.27%)
occurrences (all)	4	1	1
Thinking abnormal			
subjects affected / exposed	0 / 79 (0.00%)	4 / 75 (5.33%)	0 / 79 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 79 (7.59%)	0 / 75 (0.00%)	3 / 79 (3.80%)
occurrences (all)	6	0	4
Myalgia			
subjects affected / exposed	5 / 79 (6.33%)	2 / 75 (2.67%)	1 / 79 (1.27%)
occurrences (all)	5	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 October 2017	Version 2.0
03 April 2018	Version 3.0
22 July 2019	Version 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36322843