Clinical trial results:
Multi-centre, double-blind, placebo- and reference-controlled, randomised trial to prove the efficacy and safety of Silexan (WS®1265) in patients with a major depressive episode of mild to moderate severity

Summary

EudraCT number	2020-000688-22
Trial protocol	DE PL
Global end of trial date	29 June 2023

Results information

Result version number	v1 (current)
This version publication date	18 April 2024
First version publication date	18 April 2024

Trial information

Trial identification

Sponsor protocol code	750203.01.002

Additional study identifiers

ISRCTN number	ISRCTN36202964
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Willmar Schwabe GmbH & Co. KG
Sponsor organisation address	Willmar-Schwabe-Str. 4, Karlsruhe, Germany, 76227
Public contact	Anna Wacker, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005628, Anna.Wacker@schwabe.de
Scientific contact	Anna Wacker, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005628, Anna.Wacker@schwabe.de

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	17 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2023
Global end of trial reached?	Yes
Global end of trial date	29 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate superiority of 80 mg/day Silexan once daily vs placebo with respect to the change of the MADRS total score between baseline and week 8 when treating Major Depressive Disorders (MDD) of mild to moderate intensity, regardless of adherence to the treatment regime and under the hypothetical condition that treatments which ease depressive symptoms are not available for patients who discontinue from the randomised treatment.

Protection of trial subjects:

Possibility to withdraw consent by patient. Monitoring of adverse events and laboratory parameters.

Background therapy: -

Evidence for comparator:

The comparator Sertraline to be used in this study is a Selective Serotonin Reuptake Inhibitor (SSRIs) indicated for the treatment of MDD. For our outpatient population with mild to moderate MDD we intend to implement a dosage of 50 mg Sertraline. This dose has shown effectiveness (Fabre et al. 1995) and is related with a relatively lower adverse event rate, compared to higher dosages. For the outpatient sample being examined in this study we deem it crucial to have a low adverse event and hence dropout rate.

Actual start date of recruitment	01 October 2020
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	Poland: 129
Country: Number of subjects enrolled	Germany: 448
Worldwide total number of subjects	577
EEA total number of subjects	577

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)	530
From 65 to 84 years	46
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 577 subjects were screened for eligibility. Of these, 77 subjects were not randomised, 2 subjects were randomised but did not take any dose of IMP

Pre-assignment period milestones

Number of subjects started	577
Number of subjects completed	498

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 13
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	In-Exclusion criteria not fulfilled: 53
Reason: Number of subjects	Lost to Follow-Up: 1
Reason: Number of subjects	Other: 9
Reason: Number of subjects	Randomised without intake of IMP: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Silexan 80 mg

Arm description:

1 x 1 capsule with a daily total of 80 mg Silexan (WS® 1265) and 1 x 1 capsule Sertraline placebo/day

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

Dosage and administration details:

1 x 1 capsule Silexan + 1 x 1 capsule Sertraline placebo

Arm title	Sertraline 50 mg

Arm description:

1 x 1 capsule with a daily total of 50 mg Sertraline and 1 x 1 capsule Silexan placebo/day

Arm type	Active comparator

Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 x 1 capsule Sertraline + 1 x 1 capsule Silexan placebo

Arm title	Placebo

Arm description:

1 x 1 capsule Silexan placebo and 1 x 1 capsule Sertraline placebo/day

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

Dosage and administration details:

1 x 1 capsule Silexan placebo and 1 x 1 capsule Sertraline placebo

Number of subjects in period 1[1]	Silexan 80 mg	Sertraline 50 mg	Placebo
Started	170	171	157
Completed	154	151	141
Not completed	16	20	16
Consent withdrawn by subject	1	3	3
Adverse event, non-fatal	8	10	5
Other	4	2	2
Lost to Follow-Up	1	3	4
In-Exclusion criteria not fulfilled	-	-	2
Lack of efficacy	2	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two subjects of the Placebo-group were randomised but did not take any dose of the IMP

Baseline characteristics

Reporting groups	
Reporting group title	Silexan 80 mg
Reporting group description:	
1 x 1 capsule with a daily total of 80 mg Silexan (WS® 1265) and 1 x 1 capsule Sertraline placebo/day	
Reporting group title	Sertraline 50 mg
Reporting group description:	
1 x 1 capsule with a daily total of 50 mg Sertraline and 1 x 1 capsule Silexan placebo/day	
Reporting group title	Placebo
Reporting group description:	
1 x 1 capsule Silexan placebo and 1 x 1 capsule Sertraline placebo/day	

Reporting group values	Silexan 80 mg	Sertraline 50 mg	Placebo
Number of subjects	170	171	157
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)	159	159	138
From 65-84 years	11	12	19
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.7	44.7	46.6
standard deviation	± 14.52	± 14.36	± 15.66
Gender categorical Units: Subjects			
Female	118	110	99
Male	52	61	58

Reporting group values	Total		
Number of subjects	498		
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)	456		

From 65-84 years	42		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	327		
Male	171		

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised participants who took at least one dose of the IMP (participants were analysed as treated).

Reporting group values	Full analysis set		
Number of subjects	498		
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)	456		
From 65-84 years	42		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	45.7		
standard deviation	± 14.83		
Gender categorical			
Units: Subjects			
Female	327		
Male	171		

End points

End points reporting groups

Reporting group title	Silexan 80 mg
Reporting group description:	
1 x 1 capsule with a daily total of 80 mg Silexan (WS® 1265) and 1 x 1 capsule Sertraline placebo/day	
Reporting group title	Sertraline 50 mg
Reporting group description:	
1 x 1 capsule with a daily total of 50 mg Sertraline and 1 x 1 capsule Silexan placebo/day	
Reporting group title	Placebo
Reporting group description:	
1 x 1 capsule Silexan placebo and 1 x 1 capsule Sertraline placebo/day	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised participants who took at least one dose of the IMP (participants were analysed as treated).	

Primary: Change from Baseline in MADRS total score - Silexan and Placebo

End point title	Change from Baseline in MADRS total score - Silexan and Placebo[1]
End point description:	
MADRS total score change from baseline to week 8 (Comparison between Silexan and Placebo)	
End point type	Primary
End point timeframe:	
Baseline and Week 8	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	-12.12 (-13.26 to -10.98)	-9.95 (-11.13 to -8.77)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model including the baseline value as a covariate and factors for trial site and treatment Full Analysis Set based on multiple imputations with n=100	
Comparison groups	Silexan 80 mg v Placebo

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	-0.58

Notes:

[2] - one-sided

Secondary: Change from Baseline in MADRS total score - Sertraline and Placebo

End point title	Change from Baseline in MADRS total score - Sertraline and Placebo[3]

End point description:

MADRS total score change from baseline to week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	-12.61 (-13.74 to -11.49)	-10.02 (-11.19 to -8.85)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.17
upper limit	-1.02

Notes:

[4] - two-sided

Secondary: At least 50% reduction of MADRS total score (responder) - Silexan and Placebo

End point title	At least 50% reduction of MADRS total score (responder) - Silexan and Placebo[5]

End point description:

At least 50% reduction of MADRS total score from baseline to week 8 (responder) (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

At week 8

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Patients	91	65		

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0337 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.55

Notes:

[6] - two-sided

Secondary: At least 50% reduction of MADRS total score (responder) - Sertraline and Placebo

End point title	At least 50% reduction of MADRS total score (responder) - Sertraline and Placebo[7]

End point description:

At least 50% reduction of MADRS total score from baseline to week 8 (responder) (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

At Week 8

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Patients	92	65		

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0311 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.61

Notes:

[8] - two-sided

Secondary: MADRS total score < 10 (remitter) - Silexan and Placebo

End point title	MADRS total score < 10 (remitter) - Silexan and Placebo[9]

End point description:

MADRS total score < 10 at week 8 (remitter) (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

At Week 8

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Patients	75	51		

Statistical analyses

Statistical analysis title	Logistic regression
Statistical analysis description:	
Full Analysis Set based on multiple imputations with n=100	
Comparison groups	Silexan 80 mg v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0315 [10]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	2.63

Notes:

[10] - two-sided

Secondary: MADRS total score < 10 (remitter) - Sertraline and Placebo

End point title	MADRS total score < 10 (remitter) - Sertraline and Placebo[11]
End point description:	
MADRS total score < 10 at week 8 (remitter) (Comparison between Sertraline and Placebo)	
End point type	Secondary
End point timeframe:	
At Week 8	

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Patients	77	51		

Statistical analyses

Statistical analysis title	Logistic regression
Statistical analysis description:	
Full Analysis Set based on multiple imputations with n=100	
Comparison groups	Sertraline 50 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0246 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.72

Notes:

[12] - two-sided

Secondary: Change from Baseline in CGI (Item 1, severity) - Silexan and Placebo

End point title	Change from Baseline in CGI (Item 1, severity) - Silexan and Placebo[13]

End point description:

CGI (Item 1, severity) change from baseline to week 8 (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

Baseline to Week 8

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	-0.95 (-1.11 to -0.80)	-0.78 (-0.94 to -0.62)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1114 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.39
upper limit	0.04

Notes:

[14] - two-sided

Secondary: Change from Baseline in CGI (Item 1, severity) - Sertraline and Placebo

End point title	Change from Baseline in CGI (Item 1, severity) - Sertraline and Placebo[15]

End point description:

CGI (Item 1, severity) change from baseline to week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Baseline to Week 8

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	-1.04 (-1.19 to -0.89)	-0.79 (-0.94 to -0.63)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo
Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.04

Notes:

[16] - two-sided

Secondary: Clinical global impression (CGI) Item 2 (change) - Silexan and Placebo

End point title	Clinical global impression (CGI) Item 2 (change) - Silexan and Placebo[17]

End point description:

Clinical global impression (CGI) Item 2 (change) at week 8 (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

Week 8

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	2.51 (2.32 to 2.70)	2.72 (2.52 to 2.91)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1271 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.47
upper limit	0.06

Notes:

[18] - two-sided

Secondary: Clinical global impression (CGI) Item 2 (change) - Sertraline and Placebo

End point title	Clinical global impression (CGI) Item 2 (change) - Sertraline and Placebo[19]

End point description:

Clinical global impression (CGI) Item 2 (change) at week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Week 8

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	2.37 (2.18 to 2.56)	2.74 (2.55 to 2.94)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0058 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	-0.11

Notes:

[20] - two-sided

Secondary: Change from Baseline in Patient health questionnaire (PHQ-9) total score - Silexan and Placebo

End point title	Change from Baseline in Patient health questionnaire (PHQ-9) total score - Silexan and Placebo[21]

End point description:

Patient health questionnaire (PHQ-9) total score change from baseline to week 8 (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	-5.10 (-5.77 to -4.42)	-4.26 (-4.95 to -3.57)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0768 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	0.09

Notes:

[22] - two-sided

Secondary: Change from Baseline in Patient health questionnaire (PHQ-9) total score - Sertraline and Placebo

End point title	Change from Baseline in Patient health questionnaire (PHQ-9) total score - Sertraline and Placebo[23]

End point description:

Patient health questionnaire (PHQ-9) total score change from baseline to week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Baseline to Week 8

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	-5.42 (-6.05 to -4.79)	-4.18 (-4.83 to -3.53)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.36

Notes:

[24] - two-sided

Secondary: Change from Baseline in Beck depression inventory (BDI-II) total score - Silexan and Placebo

End point title	Change from Baseline in Beck depression inventory (BDI-II) total score - Silexan and Placebo[25]

End point description:

Beck depression inventory (BDI-II) total score change from baseline to week 8 (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	-10.06 (-11.36 to -8.76)	-8.48 (-9.82 to -7.13)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0847 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.38
upper limit	0.02

Notes:

[26] - two-sided

Secondary: Change from Baseline in Beck depression inventory (BDI-II) total score - Sertraline and Placebo

End point title	Change from Baseline in Beck depression inventory (BDI-II) total score - Sertraline and Placebo[27]

End point description:

Beck depression inventory (BDI-II) total score change from baseline to week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	-10.84 (-12.13 to -9.54)	-8.41 (-9.75 to -7.07)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Sertraline 50 mg v Placebo

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083 [28]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.23
upper limit	-0.63

Notes:

[28] - two-sided

Secondary: Change from Baseline in Sheehan disability (SDS) total score - Silexan and Placebo

End point title	Change from Baseline in Sheehan disability (SDS) total score - Silexan and Placebo[29]

End point description:

Sheehan disability (SDS) total score change from baseline to week 8 (Comparison between Silexan and Placebo)

End point type	Secondary

End point timeframe:

Baseline to Week 8

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Silexan 80 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	170	157		
Units: Points				
least squares mean (confidence interval 95%)	-6.07 (-7.03 to -5.10)	-3.67 (-4.68 to -2.65)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Silexan 80 mg v Placebo

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	-1.04

Notes:

[30] - two-sided

Secondary: Change from Baseline in Sheehan disability (SDS) total score - Sertraline and Placebo

End point title	Change from Baseline in Sheehan disability (SDS) total score - Sertraline and Placebo[31]

End point description:

Sheehan disability (SDS) total score change from baseline to week 8 (Comparison between Sertraline and Placebo)

End point type	Secondary

End point timeframe:

Baseline and Week 8

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pairwise comparisons between active treatment groups and placebo are presented

End point values	Sertraline 50 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	157		
Units: Points				
least squares mean (confidence interval 95%)	-4.35 (-5.39 to -3.31)	-3.54 (-4.60 to -2.47)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA model including the baseline value as a covariate and factors for trial site and treatment
Full Analysis Set based on multiple imputations with n=100

Comparison groups	Placebo v Sertraline 50 mg

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2671 [32]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.26
upper limit	0.63

Notes:

[32] - two-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
9 weeks	
Adverse event reporting additional description:	
Multi-centre, double-blind, placebo- and reference-controlled, randomised trial to prove the efficacy and safety of Silexan (WS1265) in patients with a major depressive episode of mild to moderate severity	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	Sertraline
Reporting group description:	
Compare medication	
Reporting group title	Silexan
Reporting group description:	
Study medication	
Reporting group title	Placebo
Reporting group description:	
Placebo treatment	
Reporting group title	No active treatment
Reporting group description:	
No active treatment	

Serious adverse events	Sertraline	Silexan	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 171 (3.51%)	7 / 170 (4.12%)	4 / 157 (2.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 171 (0.00%)	0 / 170 (0.00%)	1 / 157 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 157 (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
Atrial fibrillation			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 157 (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
Nervous system disorders			
Acute disseminated encephalomyelitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 157 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Panic attack			
subjects affected / exposed	0 / 171 (0.00%)	1 / 170 (0.59%)	0 / 157 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			
subjects affected / exposed	2 / 171 (1.17%)	2 / 170 (1.18%)	2 / 157 (1.27%)
occurrences causally related to treatment / all	2 / 2	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	1 / 171 (0.58%)	0 / 170 (0.00%)	0 / 157 (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

Serious adverse events	No active treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 498 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Acute disseminated encephalomyelitis			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Obstructive pancreatitis			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			

subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 498 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sertraline	Silexan	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 171 (21.64%)	46 / 170 (27.06%)	22 / 157 (14.01%)
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 171 (8.77%)	5 / 170 (2.94%)	10 / 157 (6.37%)
occurrences (all)	16	6	11
Gastrointestinal disorders			
Eructation			
subjects affected / exposed	0 / 171 (0.00%)	28 / 170 (16.47%)	1 / 157 (0.64%)
occurrences (all)	0	29	1
Nausea			
subjects affected / exposed	9 / 171 (5.26%)	4 / 170 (2.35%)	6 / 157 (3.82%)
occurrences (all)	9	5	6
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 171 (5.26%)	4 / 170 (2.35%)	3 / 157 (1.91%)
occurrences (all)	9	4	3
Nasopharyngitis			
subjects affected / exposed	10 / 171 (5.85%)	15 / 170 (8.82%)	4 / 157 (2.55%)
occurrences (all)	10	15	4

Non-serious adverse events	No active treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 498 (1.41%)		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 0 / 498 (0.00%) 0		
Gastrointestinal disorders Eructation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 0 / 498 (0.00%) 0 1 / 498 (0.20%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 498 (0.40%) 2 4 / 498 (0.80%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2021	Reduction of the number of German trial sites that participate in the trial and adjusting of the maximal number of patients that should be recruited by a single site. Refence document for the assessment of the expectedness of an adverse event was set to the current version of the Fachinformation for Lasea®. Positive German ethics committee vote: 07. May 2021 / Approval of the German competent authority: 13. April 2021.
18 October 2021	Adapting of timelines due to slower recruitment during corona pandemic and the actions that might be taken in case of a new lockdown, taking in consideration the EMA Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) pandemic (Version 4 from 04.02.2021). Change of project leader of the sponsor. Change to a multinational clinical trial by additional participation of Polish centres, involvement of a second contract research organisation to conduct the trial in Poland, and adaptation of the maximum number of patients per site. Including a section 'Regional Variability'. Randomisation process was described for Poland. Updating the expected percentage for an intercurrent event to take into account the greater number of patients discontinuing treatment due to an adverse event, which was found after analysing about 100 randomised patients. Subgroup analysis by country was added. Positive German ethics committee vote: 15. December 2021 / Approval of the German competent authority: 30. November 2021. This amended protocol version was also submitted in Poland: positive Polish ethics committee vote: 18. January 2022 / Approval of the Polish competent authority: 01. May 2022.

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/38558147